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Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

Part I: Estimating Exposure to Dioxin-Like Compounds

Volume 1: Sources of Dioxin-Like Compounds in the United States

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LIST OF ACRONYMS

AHA	American Hospital Association
AISI	American Iron and Steel Institute
$AlCl_3$	Aluminum Chloride
AMSA	Association of Metropolitan Sewerage Agencies
APC	Air Pollution Control
APCD	Air Pollution Control Device
atm	Atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BAAQMD	Bay Area Air Quality Management District
BCF	Bioconcentration Factor
BDDs	Polybrominated Dibenzo-p-dioxins or PBDDS
BDFs	Polybrominated Dibenzofurans or PBDFs
BHF	Bag House Filter
Btu	British Thermal Unit
CAA	Clean Air Act
$CaCl_2$	Calcium Chloride
CARB	California Air Resources Board
CBI	Confidential Business Information
°C	Degree Celsius
CD	Compact Disk
CDDs	Polychlorinated Dibenzo-p-dioxins or PCDDs
CDFs	Polychlorinated Dibenzofurans or PCDFs
CEQ	Council on Environmental Quality
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act (also know as Superfund)
C-ESP	Cold-side Electrostatic Precipitator
CETRED	Combustion Emissions Technical Resource Document
CFR	Code of Federal Regulations
CSF	Confidential Statement of Formula
CKD	Cement Kiln Dust
Cl^-	Chloride
Cl_2	Dichloride
cm	Centimeters
CO	Carbon Monoxide
CO_2	Carbon Dioxide
CRWQCB	California Regional Water Quality Control Board
CR	Confidence Rating
CuCl	Copper (Cupric) Chloride
$CuCl_2$	Copper (Cupric) Dichloride
D	Symbol for Congener Class: Dibenzo-p-dioxin
D	Symbol for di (i.e., Two Halogen Substitution)
DBF	Dibenzofuran
DCBz	Dichlorobenzene
DCI	Data Call-In

LIST OF ACRONYMS (continued)

DCP	Dichlorophenols
DHHS	U.S. Department of Health and Human Services
DL	Detection Limit
DOC	U.S. Department of Commerce
DOE	U.S. Department of Energy
d_p	Physical Diameter
dscm	Dry Standard Cubic Meter
DSI	Dry Sorbent Injection
EAF	Electric Arc Furnaces
EDC	Ethylene Dichloride
EEI	Edison Electric Institute
EF	Emission Factor
e.g.	For example
EGB	Electro Granular Bed
EIA	Energy Information Administration
EPA	U.S. Environmental Protection Agency
EPRI	Electric Power Research Institute
ESP	Electrostatic Precipitator
F	Symbol for Congener Class: Dibenzofuran
FF	Fabric Filter
^oF	Degree Fahrenheit
FB-RDF	Fluidized Bed Refuse-Derived Fuel
FCEM	Field Chemical Emissions Measurement
$FeCl_2$	Ferric (Iron) Dichloride
$FeCl_3$	Ferric (Iron) Trichloride
FGD	Flue Gas Desulfurization
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
ft	Feet
ft^3	Cubic Feet
g	Gram
GAC	Granular Activated Carbon
GC-ECD	Gas Chromatography/Electron Capture Detector
GC-MS	Gas Chromatography/Mass Spectrometry
gplg	Grams Per Leaded Gallon
gpg	Gram Per Gallon
gr/dscf	Grains Per Dry Standard Cubic Foot
HAPs	Hazardous Air Pollutants
HCl	Hydrogen Chloride
HCBz	Hexachlorobenzene
HD	Heavy Duty
HDD	Polyhalogenated Dibenzo-p-Dioxins
HDF	Pollyhalogenated Dibenzofurans
H-ESP	Hot-side Electrostatic Precipitator
Hp	Symbol for Hepta (i.e., Seven Halogen Substitution)

hr	Hour
HWI	Hazardous Waste Incineration
Hx	Symbol for Hexa (i.e., Six Halogen Substitution)
HxCB	Hexachlorobiphenyl
i.e.	That Is
ITC	U.S. International Trade Commission
IUPAC	International Union of Pure and Applied Chemistry
J	Joules
KCl	Potassium Chloride
kg	Kilogram
km	Kilometer
kW	Kilowatt
L	Liter
lb	Pound
LII	Liquid Injection Incinerator
LOQ	Limits of Quantitation
M	Symbol for Mono (i.e., One Halogen Substitution)
MACT	Maximum Achievable Control Technologies
MB	Mass Burn
MB-RC	Mass Burn Rotary Kiln
MB-REF	Mass Burn Refractory-Walled
MB-WW	Mass Burn Waterwall
MCBz	Monochlorobenzene
MCP	Monochlorophenol
$MgCl_2$	Magnesium Chloride
MgO	Magnesium Oxide
μg	Microgram
mg	Milligram
mm	Millimeter
mol	Mole (Unit of Substance)
MOD/EA	Modular Excess Air
MOD/SA	Modular Starved Air
MSW	Municipal Solid Waste
MSWI	Municipal Solid Waste Incinerator
MWI	Medical Waste Incineration
m^2	Square Meter
m^3	Cubic Meter
Na	Sodium
NA	Not Applicable
NaCl	Sodium Chloride
NaOCl	Soldium Hypochlorite
NATO	North Atlantic Treaty Organization
ng	Nanogram
NCASI	National Council of the Paper Industry for Air and Stream Improvement

LIST OF ACRONYMS (continued)

ND	Not Detected
NCEA	National Center for Environmental Assessment
NEG	Expected To Be Negligible or Non-existent
NESHAP	National Emission Standards for Hazardous Air Pollutants
$NiCl_2$	Nickel Chloride
NiO	Nickel Oxide
Nm^3	Standard Cubic Meter
NMOC	Nonmethane Organic Compounds
NR	Not Reported
NYSDEC	New York State Department of Environmental Conservation
NYSDOH	New York State Department of Health
O	Symbol for Octa (i.e., Eight Halogen Substitution)
OAQPS	Office of Air Quality Planning and Standards
O_2	Molecular Oxygen
OH	Hydroxide ion
OMS	Office of Mobile Sources
OPP	Office of Pesticide Programs
OPPT	Office of Pollution Prevention and Toxics
ORD	Office of Research and Development
OSW	Office of Solid Waste
Pa	Pascals (i.e., Unit of Pressure)
PAH	Polycyclic Aromatic Hydrocarbons
Pb	Lead
PBDDs	Polybrominated Dibenzo-p-dioxins or BDDs
PBDFs	Polybrominated Dibenzofurans or BDFs
PBS	Packed Bed Scrubber
PCA	Portland Cement Association
PCBs	Polychlorinated Biphenyls
PCDDs	Polychlorinated Dibenzo-p-dioxins or CDDs
PCDFs	Polychlorinated Dibenzofurans or CDFs
PCP	Pentachlorophenol
PCP-Na	Pentachlorophenate
PCT	Polychlorinated Terphenyl
Pe	Symbol for Penta (i.e., Five Halogen Substitution)
PeCB	Pentachlorobiphenyl
PeCBz	Pentachlorobenzene
pg	Picogram
PL	Public Law
PM	Particulate Matter
POM	Polycyclic Organic Matter
POTW	Publicly Owned Treatment Works
ppb	Parts Per Billion
ppm	Parts Per Million
ppmv	Parts Per Million (Volume Basis)

LIST OF ACRONYMS (continued)

ppq	Parts Per Quadrillion
ppt	Parts Per Trillion
ppt/v	Parts Per Trillion (Volume Basis)
PUF	Polyurethane Foam Plug
PVC	Polyvinyl Chloride
QA/QC	Quality Assurance/Quality Control
QWASI	Quantitative Water Sediment Interaction
RCRA	Resource Conservation and Recovery Act
RDF	Refuse-Derived Fuel
RT	Residence Time
SAB	Science Advisory Board
sec	Second
SIC	Standard Industrial Code
$SiCl_4$	Silium Tetrachloride
SIPs	State Implementation Plans
SNUR	Significant New Use Rule
SO_2	Sulfur Dioxide
sq	Square
T	Symbol for Tetra (i.e., Four Halogen Substitution)
TCBz	Trichlorobenzene
TCDD	2,3,7,8-tetrachlorobidenzo-p-dioxin
TCDF	2,3,.7,8-tetrachlorobidenzofuran
TCLP	Toxicity Characteristic Leachate Procedure
TeCB	Tetrachlorobiphenyls
TeCP	Tetrachlorophenols
TEF	Toxicity Equivalency Factor
TEQ	Toxicity Equivalents
TEQ/yr	Toxicity Equivalents Per Year
$TiCl_4$	Titanium Tetrachloride
Tr	Symbol for Tri (i.e., Three Halogen Substitution)
TrCBs	Trichlorobiphenyls
TrCP	Trichlorophenols
TRI	Toxics Release Inventory
TSCA	Toxics Substances Control Act
2,4-D	2,4-Dichlorophenoxyacetic Acid
2,4-DB	4-(2,4-Dichlorophenoxy) Butyric Acid
2,4-DCP	2,4-Dichlorophenol
2,4-DP	2-(2,4-Dichlorophenoxy) Propionic Acid
2,4,5-T	2,4,5-Trichlorophenoxy (Phenoxy Herbicides)
2378	Halogen Substitutions in the 2,3,7,8 Positions
μg	Microgram
UK	United Kingdom
UNC	Uncontrolled
USDA	U.S. Department of Agriculture

USITC	U.S. International Trade Commissiion
USWAG	Utility Solid Wastes Activity Group
UV	Ultraviolet
VCM	Vinyl Chloride Monomer
v/v	Volume per Volume
WHO	World Health Organization
wk^{-1}	Per Week
WS	Wet Scrubber
yr	Year

SYMBOLS:

@	At
/	Per
μ	Micro
%	Percent
$\prec$	Less than
$\succ$	Greater than
$\preceq$	Less than or equal to
$\succeq$	Greater than or equal to
$\sim$	Difference

1.0. BACKGROUND AND SUMMARY

1.1. BACKGROUND

This reassessment is comprised of three reports:

Part 1. *Estimating Exposure to Dioxin-Like Compounds* (U.S. EPA, 2000b) (which expanded upon a 1988 draft exposure report titled, *Estimating Exposure to 2,3,7,8-TCDD* [U.S. EPA, 1988d]);
Part 2. *Health Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 1994a; U.S. EPA, 2000c); and
Part 3. *Dioxin: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2000d).

Throughout the remainder of this document, these three parts as a whole will be abbreviated as the Reassessment Documents, and the individual parts will be referred to as the Exposure Reassessment Document, the Health Reassessment Document, and the Risk Characterization. The Exposure Reassessment Document has expanded to three volumes, as discussed below. Volumes 1 and 2 of the Exposure Reassessment Document are summarized in Section 4 of the Risk Characterization.

The process for developing the Reassessment Documents has been open and participatory. Each of the documents has been developed in collaboration with scientists from inside and outside the Federal Government. Each document has undergone extensive internal and external review, including review by EPA's Science Advisory Board (SAB). In September 1994, drafts of each document were made available for public review and comment. This included a 150-day comment period and 11 public meetings around the country to receive oral and written comments. These comments, along with those of the SAB (U.S. EPA, 1995a), have been considered in the drafting of this final document. The Dose-Response Chapter of the Health Document underwent peer review in 1997 (U.S. EPA, 1997a); an earlier version of the Integrated Summary and Risk Characterization underwent development and review in 1997 and 1998, and comments have been incorporated. In 1998, EPA released a workshop review version of the sources inventory (U.S. EPA, 1998a), one of the three volumes of the Exposure Reassessment Document. In

addition, as requested by the SAB, a chapter on Toxic Equivalency has been developed and underwent external peer review in parallel with the Integrated Summary and Risk Characterization in July 2000. The November 2000, review by the SAB of the Dose-Response Chapter, the Toxic Equivalency Chapter and the Integrated Summary and Risk Characterization was the final step in this open and participatory process of reassessment. The full set of background documents and the integrative summary and risk characterization replace the previous dioxin assessments as the scientific basis for EPA decision-making.

The final Exposure Reassessment Document reflects changes made as a result of both review comments and analyses of a variety of other types of information that has come available. These include relevant information obtained from published peer-reviewed literature, EPA program offices, and other Federal agencies. This version of the Exposure Reassessment Document is current in this regard through 2000.

The purpose of the Exposure Reassessment Document is threefold: 1) to inventory the known sources of release of dioxins into the environment, 2) to develop an understanding of dioxins in the environment, including fate and transport properties, environmental and exposure media concentrations, background as well as elevated exposures, and temporal trends in exposure, and 3) provide site-specific procedures for evaluating the incremental exposures due to specific sources of dioxin-like compounds. Following this structure, the Exposure Reassessment Document is presented in three volumes:

Volume 1 - Sources of Dioxin-Like Compounds in the United States

This volume presents a comprehensive review of known sources of environmental releases of dioxin-like compounds in the United States. It includes an inventory of known source activity in terms of estimates of annual releases of dioxin-like compounds into the U.S. environment (i.e., air, water and land). This inventory is specific for two reference years, 1987 and 1995. From these data, it is possible to compare and contrast releases of dioxin-like compounds among the sources and between the reference years.

Volume 2 - Properties, Environmental Levels, and Background Exposures

This volume presents and evaluates information on the physical-chemical properties, environmental fate, environmental and exposure media levels, background and elevated human exposures, and temporal trends of dioxin-like compounds in the U.S. environment during the 20th century.

Volume 3 - Site-Specific Assessment Procedures

This volume presents procedures for evaluating the incremental impact from sources of dioxin release into the environment. The sources covered include contaminated soils, stack emissions, and point discharges into surface water. This volume includes sections on: exposure parameters and exposure scenario development; stack emissions and atmospheric transport modeling; aquatic and terrestrial fate, and food chain modeling; demonstration of methodologies; and uncertainty evaluations including exercises on sensitivity analysis and model validation, review of Monte Carlo assessments conducted for dioxin-like compounds, and other discussions.

The primary technical resource supporting the development of the inventory of sources of dioxin-like compounds discussed in Volume I (above) is the Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States (EPA/600/C-01/012. March, 2001). This database includes congener-specific CDD and CDF emissions data extracted from original engineering test reports. It has been published independently from the Reassessment and is available on Compact Disk-Read only Memory (CD-ROM), without cost, from EPA's National Service Center for Environmental Publications (NSCEP) in Cincinnati, Ohio (telephone: 1-800-490-9198, or 513-489-8190; fax: 513-489-8695). Summary files from the database will be available for downloading from the Web page of the National Center for Environmental Assessment, www.epa.gov/ncea/dioxin.htm. Instructions on how to order and obtain the CD-ROM will also be available on the Web page.

1.2. DEFINITION OF DIOXIN-LIKE COMPOUNDS

This assessment addresses specific compounds in the following chemical classes: polychlorinated dibenzo-*p*-dioxins (PCDDs or CDDs), polychlorinated dibenzofurans (PCDFs

or CDFs), polybrominated dibenzo-*p*-dioxins (PBDDs or BDDs), polybrominated dibenzofurans (PBDFs or BDFs), and polychlorinated biphenyls (PCBs), and describes this subset of chemicals as "dioxin-like." Dioxin-like refers to the fact that these compounds have similar chemical structure, similar physical-chemical properties, and invoke a common battery of toxic responses. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. The CDDs include 75 individual compounds; CDFs include 135 different compounds. These individual compounds are referred to technically as congeners. Likewise, the BDDs include 75 different congeners and the BDFs include an additional 135 congeners. Only 7 of the 75 congeners of CDDs, or of BDDs, are thought to have dioxin-like toxicity; these are ones with chlorine/bromine substitutions in, at a minimum, the 2, 3, 7, and 8 positions. Only 10 of the 135 possible congeners of CDFs or of BDFs are thought to have dioxin-like toxicity; these also are ones with substitutions in the 2, 3, 7, and 8 positions. This suggests that 17 individual CDDs/CDFs, and an additional 17 BDDs/BDFs, exhibit dioxin-like toxicity. The database on many of the brominated compounds regarding dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment.

There are 209 PCB congeners. Only 13 of the 209 congeners are thought to have dioxin-like toxicity; these are PCBs with 4 or more lateral chlorines with 1 or no substitution in the ortho position. These compounds are sometimes referred to as coplanar, meaning that they can assume a flat configuration with rings in the same plane. Similarly configured polybrominated biphenyls (PBBs) are likely to have similar properties. However, the database on these compounds with regard to dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment. Mixed chlorinated and brominated congeners of dioxins, furans, and biphenyls also exist, increasing the number of compounds potentially considered dioxin-like within the definitions of this assessment. The physical/chemical properties of each congener vary according to the degree and position of chlorine and/or bromine substitution. Very little is known about occurrence and toxicity of the mixed (chlorinated and brominated) dioxin, furan, and biphenyl congeners. Again, these compounds have not been explicitly considered in this assessment. Generally speaking, this assessment focuses on the 17 CDDs/CDFs and a few of the coplanar PCBs that are frequently encountered in

source characterization or environmental samples. While recognizing that other "dioxin-like" compounds exist in the chemical classes discussed above (e.g., brominated or chlorinated/brominated congeners) or in other chemical classes (e.g., halogenated naphthalenes or benzenes, azo- or azoxybenzenes), the evaluation of less than two dozen chlorinated congeners is generally considered sufficient to characterize environmental "dioxin."

The chlorinated dibenzodioxins and dibenzofurans are tricyclic aromatic compounds with similar physical and chemical properties. Certain of the PCBs (the so-called coplanar or mono-ortho coplanar congeners) are also structurally and conformationally similar. The most widely studied of this general class of compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This compound, often called simply "dioxin," represents the reference compound for this class of compounds. The structure of TCDD and several related compounds is shown in Figure 1-1. Although sometimes confusing, the term "dioxin" is often also used to refer to the complex mixtures of TCDD and related compounds emitted from sources, or found in the environment or in biological samples. It can also be used to refer to the total TCDD "equivalents" found in a sample. This concept of toxic equivalency is discussed below.

1.3. TOXIC EQUIVALENCY FACTORS

CDDs, CDFs, and PCBs are commonly found as complex mixtures when detected in environmental media and biological tissues, or when measured as environmental releases from specific sources. Humans are likely to be exposed to variable distributions of CDDs, CDFs, and dioxin-like PCB congeners that vary by source and pathway of exposures. This complicates the human health risk assessment that may be associated with exposures to variable mixtures of dioxin-like compounds. In order to address this problem, the concept of toxic equivalency has been considered and discussed by the scientific community, and TEFs have been developed and introduced to facilitate risk assessment of exposure to these chemical mixtures.

On the most basic level, TEFs compare the potential toxicity of each dioxin-like compound comprising the mixture to the well-studied and understood toxicity of TCDD, the most toxic member of the group. The background and historical perspective regarding this procedure is described in detail in Part II, Chapter 9, Section 9.1, 9.2, and in Agency

documents (U.S. EPA, 1987e; 1989a,b; 1991i). This procedure involves assigning individual TEFs to the 2,3,7,8-substituted CDD/CDF congeners and "dioxin-like" PCBs. To accomplish this, scientists have reviewed the toxicological databases along with considerations of chemical structure, persistence, and resistance to metabolism, and have agreed to ascribe specific, "order of magnitude" TEFs for each dioxin-like congener relative to TCDD, which is assigned a TEF of 1.0. The other congeners have TEF values ranging from 1.0 to 0.00001. Thus, these TEFs are the result of scientific judgment of a panel of experts using all of the available data and are selected to account for uncertainties in the available data and to avoid underestimating risk. In this sense, they can be described as "public health conservative" values. To apply this TEF concept, the TEF of each congener present in a mixture is multiplied by the respective mass concentration and the products are summed to represent the 2,3,7,8-TCDD Toxic Equivalence (TEQ) of the mixture, as determined by Equation (1-1):

$$TEQ \cong \sum_{i-n}\left(Congener_i \times TEF_i\right) + \left(Congener_j \times TEF_j\right) + ...\left(Congener_n \times TEF_n\right) \quad (1\text{-}1)$$

The TEF values for PCDDs and PCDFs were originally adopted by international convention (U.S. EPA, 1989a). Subsequent to the development of the first international TEFs for CDD/CDFs, these values were further reviewed and/or revised and TEFs were also developed for PCBs (Ahlborg et al., 1994; van den Berg et al., 1998). A problem arises in that past and present quantitative exposure and risk assessments may not have clearly identified which of three TEF schemes was used to estimate the TEQ. This reassessment introduces a new uniform TEQ nomenclature that clearly distinguishes between the different TEF schemes and identifies the congener groups included in specific TEQ calculations. The nomenclature uses the following abbreviations to designate which TEF scheme was used in the TEQ calculation:

1. I-TEQ refers to the International TEF scheme adopted by EPA in 1989 (U.S. EPA, 1989a). See Table 1-1.
2. TEQ-WHO_{94} refers to the 1994 WHO extension of the I-TEF scheme to include 13 dioxin-like PCBs (Ahlborg et al., 1994). See Table 1-2.

3. TEQ-WHO_{98} refers to the 1998 WHO update to the previously established TEFs for dioxins, furans, and dioxin-like PCBs (van den Berg et al., 1998). See Table 1-3.

The nomenclature also uses subscripts to indicate which family of compounds is included in any specific TEQ calculation. Under this convention, the subscript D is used to designate dioxins, the subscript F to designate furans and the subscript P to designate PCBs. As an example, "TEQ_{DF}-WHO_{98}" would be used to describe a mixture for which only dioxin and furan congeners were determined and where the TEQ was calculated using the WHO_{98} scheme. If PCBs had also been determined, the nomenclature would be "TEQ_{DFP}-WHO_{98}." Note that the designations TEQ_{DF}-WHO_{94} and I-TEQ_{DF} are interchangeable, as the TEFs for dioxins and furans are the same in each scheme. Note also that in this document, I-TEQ sometimes appears without the D and F subscripts. This indicates that the TEQ calculation includes both dioxins and furans.

This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxic equivalency to complex environmental mixtures for assessment and regulatory purposes. Sections in the Health Reassessment Document, and summarized in the Risk Characterization, describe the mode(s) of action by which dioxin-like chemicals mediate biochemical and toxicological actions. These data provide the scientific basis for the TEF/TEQ methodology. In its 20-year history, the approach has evolved, and decision criteria supporting the scientific judgment and expert opinion used in assigning TEFs has become more transparent. Numerous states, countries, and several international organizations have evaluated and adopted this approach to evaluating complex mixtures of dioxin and related compounds. It has become the accepted methodology, although the need for research to explore alternative approaches is widely endorsed. Clearly, basing risk on TCDD alone or assuming all chemicals are equally potent to TCDD is inappropriate on the basis of available data. Although uncertainties in the use of the TEF methodology have been identified (which are described in detail in the Health Reassessment Document, Chapter 9, Section 9.5), one must examine the use of this method in the broader context of the need to evaluate the potential public health impact of complex mixtures of persistent, bioaccumulative chemicals. It can be generally concluded that the use of TEF methodology for evaluating complex mixtures of dioxin-like compounds decreases the overall uncertainties in the risk assessment process as compared to alternative approaches.

Use of the latest consensus values for TEFs assures that the most recent scientific information informs this "useful, interim approach" (U.S. EPA, 1989a; Kutz et al., 1990) to dealing with complex environmental mixtures of dioxin-like compounds. As stated by the U.S. EPA Science Advisory Board (U.S. EPA, 1995a), "The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the TEFs and the availability of representative and reliable exposure data." EPA will continue to work with the international scientific community to update these TEF values to assure that the most up-to-date and reliable data are used in their derivation and to evaluate their use on a periodic basis.

A chemical is assigned a TEF value based on all the available data comparing the chemical to either TCDD or PCB 126. In addition, there are weighting criteria that place more emphasis on chronic and subchronic studies examining toxic endpoints (van den Berg et al., 1998). There is a broad range in the quantity and quality of the data available for individual congeners. For example, the TEF for PCB 126 is based on over 60 in vivo endpoints examining responses as diverse as enzyme induction, developmental toxicity, immunotoxicity, hepatic toxicity, alterations in hormones and tumor promotion, while the TEF for 3,4,4',5-tetrachlorobiphenyl (PCB 81) is based on in vitro CYP1A induction and QSAR calculations. Fortunately, PCB 81 does not significantly contribute to human TEQ exposures. There are 5 congeners that contribute approximately 80% of the total TEQ in humans: 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PCDF, and PCB 126 (See Part I, Volume 2 and Section 4.4.3 of this document). With the exception of 1,2,3,6,7,8-HxCDD, the TEFs for these chemicals are based on a number of different endpoints from multiple studies performed in different laboratories. The TEF for 1,2,3,6,7,8-HxCDD is based on a two-year bioassay in which rats were exposed to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD. The TEFs for 2,3,4,7,8-PCDF and PCB 126 are similar to the mean REP value for all in vivo endpoints and are similar to their REPs for tumor promotion. The TEF for 12378-PCDD is based largely on its REP for tumor promotion in rats. From these data, it is clear that the chemicals that contribute approximately 80% to the total human TEQ are well studied and the assigned TEFs provide reasonable estimates of the relative potency of these chemicals. In contrast, while there are some chemicals in the TEF methodology which have minimal data sets to reliably

assess their relative potency, these chemicals do not contribute substantially to the human blood TEQ.

The ability of the TEF methodology to predict the biological effects of mixtures containing dioxin-like chemicals has been evaluated in a number of experimental systems. These studies generally demonstrate that the assumption of additivity provides a reasonable estimate of the dioxin-like potential of a mixture (described in the Health Reassessment Document, Chapter 9, Section 9.4). In addition, there are examples of non-additive interactions between dioxins and non-dioxins. Both greater than additive and less than additive interactions have been observed in these studies. In general the non-additive interactions between the dioxins and non-dioxins have been observed at doses that are considerably higher than present background human exposures.

There are a number of natural chemicals that bind and activate the aryl hydrocarbon receptor (AhR) and induce some dioxin-like effects. It has been proposed by some scientists that these chemicals contribute significantly to the total TEQ exposures and that these exposures far out weigh those from PCDDs, PCDFs and PCBs (Safe, 1995). While this hypothesis is intriguing, there are several limitations to these analyses. The in vivo data on the natural aromatic hydrocarbon receptor (AhR) ligands is limited to enzyme induction and a single developmental study. Few, if any, toxicology studies demonstrating clear dioxin-like toxicities have been published. The natural AhR ligands are rapidly metabolized and result in both transient tissue concentrations and transient effects. The natural ligands also have significant biological effects that are independent of the AhR and it is not clear as to the role of the AhR in the biological effects of these chemicals. Clearly this issue requires further research in order to better understand the relative potential health effect of dioxin and related chemicals as compared to natural AhR ligands.

One of the limitations of the use of the TEF methodology in risk assessment of complex environmental mixtures is that the risk from non-dioxin-like chemicals is not evaluated in concert with that of dioxin-like chemicals. Another limition of the TEF methodology is their application to non-biological samples. The fate and distribution of PCDDs, PCDFs and PCBs are not necessarily related to their TEF. Thus, the use of the TEF for non-biological media must be done cautiously. Future approaches to the assessment of environmental mixtures should focus on the development of methods that will allow risks to be predicted when multiple mechanisms are present from a variety of contaminants.

1.4. OVERVIEW OF SOURCES AND EMISSIONS INVENTORY METHODOLOGY

In the United States, the major identified sources of environmental release have been grouped into five broad categories for the purposes of this report:

- Combustion Sources: CDD/CDFs are formed in most combustion systems. These can include waste incineration (such as municipal solid waste, sewage sludge, medical waste, and hazardous wastes), burning of various fuels (such as coal, wood, and petroleum products), other high temperature sources (such as cement kilns), and poorly or uncontrolled combustion sources (such as forest fires, building fires, and open burning of wastes).

- Metals Smelting, Refining and Processing Sources: CDD/CDFs can be formed during various types of primary and secondary metals operations including iron ore sintering, steel production, and scrap metal recovery.

- Chemical Manufacturing: CDD/CDFs can be formed as by-products from the manufacture of chlorine bleached wood pulp, chlorinated phenols (e.g., pentachlorophenol - PCP), PCBs, phenoxy herbicides (e.g., 2,4,5-T), and chlorinated aliphatic compounds (e.g., ethylene dichloride).

- Biological and Photochemical Processes: Recent studies suggest that CDD/CDFs can be formed under certain environmental conditions (e.g., composting) from the action of microorganisms on chlorinated phenolic compounds. Similarly, CDD/CDFs have been reported to be formed during photolysis of highly chlorinated phenols.

- Reservoir Sources: Reservoirs are materials or places that contain previously formed CDD/CDFs or dioxin-like PCBs and have the potential for redistribution and circulation of these compounds into the environment. Potential reservoirs include soils, sediments, biota, water and some anthropogenic materials. Reservoirs become sources when they have releases to the circulating environment.

1.4.1. Overview and Organization of Source Analysis

Only sources judged to have a reasonable likelihood for releases to the "circulating environment" were addressed in ths document. Examples of the circulating environment system boundary are as follows:

- CDD/CDFs and dioxin-like PCBs in air emissions and wastewater discharges were included; whereas, CDD/CDFs and dioxin-like PCBs in intermediate products or internal wastestreams were excluded. For example, the CDD/CDFs in a wastestream going to an on-site incinerator would not be addressed in this

document, but any CDD/CDFs in the stack emissions from the incinerator would be included.

- CDD/CDFs and dioxin-like PCBs in wastestreams applied to land in the form of "land farming" are included; whereas, those disposed in permitted landfills were excluded. Properly designed and operated landfills are considered to achieve long-term isolation from the circulating environment. Land farming, however, involves the application of wastes directly to land, clearly allowing for releases to the circulating environment.

The sources addressed in this document (as defined above) can be divided into two subclasses: 1) contemporary formation sources (sources which have essentially simultaneous formation and release) and 2) reservoir sources (materials or places that contain previously formed CDD/CDFs or dioxin-like PCBs that are re-released to environment). The contemporary formation sources are discussed in Chapters 2 through 11 and the reservoir sources are discussed in Chapter 12. The presence of CDD/CDFs in ball clay is discussed in Chapter 13. Table 1-5 provides a comprehensive list of all known or suspected sources of CDDs/CDFs in the United States. The checkmarks indicate how each source was classified in terms of the following six categories:

- Contemporary formation sources with reasonably well quantified releases (referred to in this document as the Quantitative Inventory of Sources). These sources are listed in Table 1-5 and release estimates are shown in Tables 1-7 and 1-8.
- Contemporary formation sources with preliminary release estimates. These sources are listed in Table 1-5 and release estimates are shown in Tables 1-7 and 1-8.
- Contemporary formation sources without quantified release estimates. These sources are listed in Table 1-5.
- Reservoir sources with reasonably well quantified releases. These sources are listed in Table 1-5.
- Reservoir sources with preliminary release estimates. These sources are listed in Table 1-5 and release estimates are shown in Tables 1-7 and 1-8.
- Reservoir sources without quantified releases. These sources are listed in Table 1-5.

This document includes discussions on products which contain dioxin-like compounds. Some of these, such as 2,4-D, are considered to be sources since they are clearly used in ways that result in environmental releases. These products have been

classified into one of the above six groups. Other products containing dioxin-like compounds, such as vinyl chloride products, do not appear to have environmental releases and are not considered sources. For all CDD/CDF containing products, this document summarizes the available information about the contamination levels and, where possible, makes estimates of the total amount of CDD/CDF produced annually in these products. Estimates of the CDD/CDF TEQ amounts in products are summarized in Tables 1-11 and 1-12.

Throughout this document, environmental release estimates are presented in terms of TEQs. This is done for convenience in presenting summary information and to facilitate comparisons across sources. For purposes of environmental fate modeling, however, it is important to use the individual CDD/CDF and PCB congener values, rather than TEQs. This is because the physical/chemical properties of individual CDD/CDF congeners vary and, consequently, the congeners will behave differently in the environment. For example, the relative mix of congeners released from a stack cannot be assumed to remain constant during transport through the atmosphere and deposition to various media. The full congener-specific release rates for most sources are given in an electronic database which is available as a companion to this document (Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States, EPA/600/R-01/012). In Part I-Volume 3, site-specific procedures are provided for estimating the impact of emissions on local populations and emphasizes that congener-specific emission values should be used in modeling environmental fate. Finally, it is important to understand that this series of documents does not use source release estimates to generate background population intake/risk estimates (rather these estimates are derived in Volume 2 primarily from food levels and consumption rates).

1.4.2 Quantitative Inventory of Sources

EPA's Science Advisory Board (SAB) reviewed an earlier draft of the national dioxin source emissions inventory and commented that the effort was comprehensive and inclusive of most known sources (U.S. EPA, 1995f). However, the SAB emphasized that source emissions are time-dependant, and recommended that emissions be associated with a specific time reference. In consideration of this recommendation, EPA developed in this report emission estimates for two reference years: 1987 and 1995.

EPA selected 1987 primarily because, prior to this time, little empirical data existed for making source specific emission estimates. The first study providing the type of data needed for a national inventory was EPA's National Dioxin Study (U.S. EPA, 1987a). The year 1987 also corresponds roughly with the time when significant advances occurred in emissions measurement techniques and in the development of high resolution mass spectrometry and gas chromatography necessary for analytical laboratories to achieve low level detection of CDD and CDF congeners in environmental samples. Soon after this time, a number of facilities began upgrades specifically intended to reduce CDD/CDF emissions. Consequently, 1987 is also the latest time representative of the emissions occurring before widespread installation of dioxin-specific emission controls.

EPA selected 1995 as the latest time period that could practically be addressed consistent with the time table for producing the rest of the document. The data collected in the companion document to this document on CDD/CDF and dioxin-like PCB levels in environmental media and food were used to characterize conditions in the mid-1990s. So the emissions data and media/food data in these two volumes are presented on a roughly consistent basis. Since 1995, EPA has promulgated regulations limiting CDD/CDF emissions for a number of the source categories that contribute to the inventory including municipal waste combustors, medical waste incinerators, hazardous waste incinerators, cement kilns burning hazardous waste, and pulp and paper facilities using chlorine bleached processes. Consequently, the estimate of releases in the1995 inventory should not be assumed to accurately represent post-1995 releases. EPA intends to periodically revise this inventory.

A key element of the inventory is the method of extrapolation from tested facilities to national estimates of environmental releases. Because not every U.S. facility in each of the source categories have been tested for CDD/CDF emissions and releases, an extrapolation procedure was developed to estimate national emissions for most source categories. Many of the national emission estimates were, therefore, developed using a "top down" approach. The first step in this approach is to derive from the available emission monitoring data an emission factor (or series of emission factors) deemed to be representative of the source category (or segments of a source category that differ in configuration, fuel type, air pollution control equipment, etc.). The emission factor relates mass of CDD/CDFs or dioxin-like PCBs released into the environment per some measure of

activity (e.g., kilograms of material processed per year, vehicle miles traveled per year, etc.). The emission factor is then multiplied by a national value for the activity level basis of the emission factor (e.g., total kilogram [kg] of material processed in the United States annually).

With the exception of certain releases from the bleached chemical wood pulp/paper industry, no source category has estimates developed from a true "bottom up" approach (i.e., estimates developed using site-specific emissions and activity data for all individual sources in a category and then summed to obtain a national total). Existing facility-specific emissions testing and activity level data for some source categories (e.g., municipal solid waste incinerators) supported a semi- "bottom up" approach. In this approach, facility-specific annual emissions were calculated for those facilities with adequate data. For the untested facilities in the class, a subcategory (or class) emission factor was developed by averaging the emission factors for the tested facilities in the class. This average emission factor was then multiplied by the measure of activity for the non-tested facilities in the class. Emissions were summed for the tested facilities and non-tested facilities. In summary, this procedure can be represented by the following equations:

$$E_{total} = \Sigma E_{tested,i} + \Sigma E_{untested,i}$$
$$E_{total} = \Sigma E_{tested,i} + \Sigma (EF_i * A_i)_{untested}$$

Where: E_{total} = annual emissions from all facilities (g TEQ/yr)

$E_{tested,i}$ = annual emissions from all tested facilities in class I (g TEQ/yr)

$E_{untested,i}$ = annual emissions from all untested facilities class I (g TEQ/yr)

Ef_i = mean emission factor for tested facilities in class I (g TEQ/kg)

A_i = activity measure for untested facilities class I (kg/yr)

Some source categories are made up of facilities that vary widely in terms of design and operating conditions. For these sources, as explained above, an attempt was made to create subcategories that grouped facilities with common features and then to develop separate emission factors for each subcategory. Implicit in this procedure is the assumption that facilities with similar design and operating conditions should have similar

CDD/CDF release potential. For most source categories, however, the specific combination of features that contributes most to CDD/CDF or dioxin-like PCB release is not well understood. Therefore, how to best subcategorize a source category was often problematic. For each subcategorized source category in this report, a discussion is presented about the variability in design and operating conditions, what is known about how these features contribute to CDD/CDF or dioxin-like PCB release, and the rationale for subcategorizing the category.

As discussed above, each source emission calculation required estimates of an "emission factor" and the "activity level." For each emission source, the quantity and quality of the available information for both terms vary considerably. Consequently, it is important that emission estimates be accompanied by some indicator of the uncertainties associated with their development. For this reason, a qualitative confidence rating scheme was developed as an integral part of the emission estimate in consideration of the following factors:

- *Emission Factor* - The uncertainty in the emission factor estimate depends primarily on how well the tested facilities represent the untested facilities. In general, confidence in the emission factor increases with increases in the number of tested facilities relative to the total number of facilities. Variability in terms of physical design and operating conditions within a class or subclass must also be considered. The more variability among facilities, the less confidence that a test of any single facility is representative of that class or subclass. The quality of the supporting documentation also affects uncertainty. Whenever possible, original engineering test reports were used. Peer reviewed reports from the open literature were also used for developing some emission factors. In some cases, however, draft reports that had undergone more limited review were used. In a few cases, unpublished references were used (such as personal communication with experts) and are clearly noted in the text.

- *Activity Level* - The uncertainty in the activity level estimate was judged primarily on the basis of the extent of the underlying data. Estimates derived from comprehensive surveys (including most facilities in a source category) were assigned high confidence. As the number of facilities in the survey relative to the total decreased, confidence also decreased. The quality of the supporting documentation also affects uncertainty. Peer reviewed reports from the open literature (including government and trade association survey data) were considered most reliable. In some cases, however, draft reports that had undergone more limited review were used. In a few cases, unpublished references were used (such as personal communication with experts) and are clearly noted in the text.

The confidence rating scheme, presented in Table 1-6, presents the qualitative criteria used to assign a high, medium, or low confidence rating to the emission factor and activity level terms for those source categories for which emission estimates can be reliably quantified. The overall "confidence rating" assigned to an emission estimate was determined by the confidence ratings assigned to the corresponding "activity level" term and "emission factor" term. If the lowest rating assigned to either the activity level or emission factor terms is “high,” then the category rating assigned to the emission estimate is high (also referred to as “A”). If the lowest rating assigned to either the activity level or emission factor terms is “medium,” then the category rating assigned to the emission estimate is medium (also referred to as “B”). If the lowest rating assigned to either the activity level or emission factor terms is “low,” then the category rating assigned to the emission estimate is low (also referred to as “C”). It is emphasized that this confidence rating scheme should be interpreted as subjective judgements of the relative uncertainty among sources, not statistical measures.

For many source categories, either emission factor information or activity level information were inadequate to support development of reliable quantitative release estimates for one or more media. For some of these source categories, sufficient information was available to make preliminary estimates of emissions of CDD/CDFs or dioxin-like PCBs; however, the confidence in the activity level estimates or emission factor estimates was so low that the estimates cannot be included in the sum of quantified emissions from sources with confidence ratings of A, B and C. These preliminary estimates were given an overall confidence class rating of D (see Tables 1-7 and 1-8). As preliminary estimates of source magnitude, they can be used, however, to help prioritize future research and data collection. The actual magnitude of emissions from these sources could be significantly lower or higher than these preliminary estimates. Although EPA has chosen not to include them in the more thoroughly characterized emissions of the national inventory, some of these poorly characterized sources have the potential of being major contributors of releases to the environment. As the uncertainty around these sources is reduced, they will be included in future inventory calculations. For other sources, some information exists which suggests that they may release dioxin-like compounds; however, the available data were judged to be insufficient for developing any quantitative emission estimate. These source categories were assigned a confidence category rating of “E” and

also were not included in the national inventory (See listings in Table 1-5 under the "Not Quantifiable" column).

The emission factors developed for the emissions inventory are intended to be used for estimating the total emissions for a source category rather than for individual facilities. EPA has made uncertainty determinations for each of these emission factors based, in part, on the assumption that by applying them to a group of facilities, the potential for overestimating or underestimating individual facilities will to some extent be self compensating. This means that in using these emission factors one can place significantly greater confidence in an emission estimate for a class than can be placed on an emission estimate for any individual facility. Given the limited amount of data available for deriving emission factors, and the limitations of our understanding about facility-specific conditions that determine formation and control of dioxin-like compounds, the current state of knowledge cannot support the development of emission factors that can be used to accurately estimate emissions on an individual facility-specific basis.

1.5. GENERAL FINDINGS OF THE EMISSIONS INVENTORY

Nationwide emission estimates of I-TEQ_{DF} and TEQ_{DF}-WHO_{98} for the United States inventory are presented in Tables 1-7 and 1-8, respectively, for those source categories for which emission estimates can be reliably quantified. Nationwide emission estimates for dioxin-like PCBs are presented in Chapter 11. Figures 1-2 and 1-3 are charts that visually display the range of I-TEQ_{DF} emission estimates to air that are reported in Table 1-7 with confidence ratings of A, B, or C. Figure 1-4 compares the I-TEQ_{DF} emission estimates to air for the two reference years (i.e., 1987 and 1995). Figures 1-5 and 1-6 are charts that visually display the range of TEQ_{DF}-WHO_{98} emission estimates to air that are reported in Table 1-8 with confidence ratings of A, B, or C. Figure 1-7 compares the TEQ_{DF}-WHO_{98} emission estimates to air for the two reference years.

Table 1-9 lists the I-TEQ_{DF} emission factors used to derive the emission estimates presented in Table 1-7 with confidence ratings of A, B, or C. Table 1-10 lists the TEQ_{DF}-WHO_{98} emission factors used to derive the emission estimates presented in Table 1-8 with confidence ratings of A, B, or C. The emission factors used to calculate these emission estimates were derived by setting "not detected" (ND) values in test reports as zeros. Because detection limits were not always reported in test reports, it was not possible to

consistently develop emission factors on any other basis (e.g., values set at one-half the detection limit) for all source categories. When detection limits were reported for all test reports for a given source category, emission factors were calculated and are presented in this report for both ND equals zero and ND equals one-half the detection limit.

Tables 1-7 and 1-8 also present preliminary indications of the potential magnitude of I-TEQ_{DF} and TEQ_{DF}-WHO_{98} emissions, respectively, from category D sources in reference year 1995. These estimates are based on very limited data whose representativeness is unknown. The estimates were developed primarily as a tool to direct future investigations and studies.

EPA's best estimates of releases of CDD/CDFs to air, water, and land from reasonably quantifiable sources were approximately 3,000 gram (g) I-TEQ_{DF} (3,300 g TEQ_{DF}-WHO_{98}) in 1995 and 12,800-g I-TEQ_{DF} (14,000 g TEQ_{DF}-WHO_{98}) in 1987.

The environmental releases of CDD/CDFs in the United States occur from a wide variety of sources, but are dominated by releases to the air from combustion sources. The current (i.e., 1995) inventory indicates that quantifiable emissions from combustion sources are more than an order of magnitude greater than quantifiable emissions from all other categories combined. Approximately 71% of all quantifiable environmental releases were dominated by air emissions from just three source categories in 1995: municipal waste incinerators (representing 38% of total environmental releases); backyard burning of refuse in barrels (representing 19% of total releases); and medical waste incinerators (representing 14% of total releases).

The decrease in estimated emissions of CDD/CDFs between 1987 and 1995 (approximately 77 percent) was due primarily to reductions in air emissions from municipal and medical waste incinerators, and further reductions are anticipated. For both categories, these emission reductions have occurred from a combination of improved combustion and emission controls and from the closing of a number of facilities. EPA's regulatory programs estimate that full compliance with recently promulgated regulations should result in further reductions in emissions from the 1995 levels (i.e., a reduction of more than 1,800 grams I-TEQ_{DF} by the year 2005). Specifically, the Office of Air and Radiation estimates that full compliance with Maximum Achievable Control Technology (MACT) standards under the Clean Air Act (CAA) will result in annual emissions of 12 g I-TEQ_{DF} from municipal solid waste incinerators and 6 g I-TEQ_{DF} from medical waste

incinerators by the year 2005. The Office of Solid Waste anticipates that full compliance with regulations promulgated under the combined authorities of the CAA and the Resource Conservation and Recovery Act (RCRA) will result in annual emissions from hazardous waste incinerators and cement kilns burning hazardous waste of about 4 and 8 g I-TEQ_{DF}, respectively, by 2002. The Office of Water estimates that full compliance with effluent guidelines promulgated under the Clean Water Act for the pulp and paper industry will result in annual releases to water of 5 g I-TEQ_{DF}. However, no Federal regulations are in place or currently under development for limiting CDD/CDF emissions from backyard burning of refuse in barrels. A number of states have general restrictions on the practice of backyard trash burning.

Insufficient data are available to comprehensively estimate point source releases of dioxin-like compounds to water. Sound estimates of releases to water are only available for chlorine bleached pulp and paper mills (356 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} for 1987 and 28 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} for 1995) and manufacture of ethylene dichloride (EDC)/vinyl chloride monomer (VCM) (<1 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995). Other releases to water bodies that cannot be quantified on the basis of existing data include effluents from POTWs and most industrial/commercial sources.

Based on the available information, the quantitative inventory of sources includes only a limited set of activities that result in direct environmental releases to land. The only releases to land quantified in the national inventory are land application of sewage sludge or commercial sludge products (106.5 g I-TEQ_{DF} or 79 g TEQ_{DF}-WHO_{98} in 1995), land application of pulp and paper mill wastewater sludges (2.0 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995), use of 2,4-D pesticides (18.4 g I-TEQ_{DF} or 28.9 g TEQ_{DF}-WHO_{98}), and manufacturing wastes from EDC/VCM (<1 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98}). Not included in the Inventory's definition of an environmental release is the disposal of sludges and ashes into approved and regulated landfills.

Significant amounts of dioxin-like compounds produced annually are not considered environmental releases and, therefore, are not included in the national inventory. Examples include dioxin-like compounds generated internal to a process, but destroyed before release, waste streams which are disposed of in approved landfills and are therefore outside the definition of annual environmental releases, and products which contain dioxin-like compounds but for which environmental releases, if any, cannot be estimated.

The procedures and results of the U.S. inventory may have underestimated releases from contemporary sources. A number of investigators have suggested that national inventories may underestimate emissions because of the possibility of unknown sources. This claim has been supported with mass balance analyses suggesting that deposition exceeds emissions (Rappe et al., 1991; Harrad et al. 1992b; Bruzy and Hites, 1995). The uncertainty, however, in both the emissions and deposition estimates for the United States prevents the use of this approach for reliably evaluating the issue (U.S. EPA, 1995a). As explained below, this document has instead evaluated this issue by making preliminary estimates of poorly characterized sources and listing other sources that have been reported to emit dioxin-like compounds but cannot be characterized on even a preliminary basis.

- A number of sources were not included in the inventory even though limited evidence exists indicating that these sources can emit CDD/CDFs. These sources include various components of the metals industries such as electric arc furnaces and foundries and uncontrolled or minimally controlled combustion practices (e.g., backyard trash burning and accidental fires at landfills). Tables 1-11 and 1-12 present preliminary estimates of U.S. national emissions using the emission factors reported in these other studies as though they were representative of emission factors for U.S. facilities.

- The possibility remains that truly unknown sources exist. Many of the sources that are well accepted today were only discovered in the past 10 years. For example, CDD/CDFs were found unexpectedly in the wastewater effluent from bleached pulp and paper mills in the mid 1980s. Ore sintering is now listed as one of the leading sources of CDD/CDF emissions in Germany, but was not recognized as a source until the early 1990s.

1.6. GENERAL SOURCE OBSERVATIONS

For any given time period, releases from both contemporary formation sources and reservoir sources determine the overall amount of the dioxin-like compounds that are being released to the open and circulating environment. Because existing information is incomplete with regard to quantifying contributions from contemporary and reservoir sources, it is not currently possible to estimate total magnitude of release for dioxin-like compounds into the U.S. environment from all sources. For example, in terms of 1995 releases from reasonably quantifiable sources, this document estimates releases of 3,000 g T-TEQ_{DF} (3,300 g TEQ_{DF}-WHO_{98}) for contemporary formation sources and 2,900 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} for reservoir sources. In addition, there remains a number of

unquantifiable and poorly quantified sources. No quantitative release estimates can be made for agricultural burning or for most CDD/CDF reservoirs or for any dioxin-like PCB reservoirs. The preliminary estimate of 1995 poorly characterized contemporary formation sources is 1,500 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98}.

The contribution of dioxin-like compounds to waterways from nonpoint source reservoirs is likely to be greater than the contributions from point sources. Current data are only sufficient to support preliminary estimates of nonpoint source contributions of dioxin-like compounds to water (i.e., urban storm water runoff and rural soil erosion). These estimates suggest that, on a nationwide basis, total nonpoint releases are significantly larger than point source releases.

Current releases of CDD/CDFs to the U.S. environment result principally from anthropogenic activities. This finding applies to both sources of newly formed dioxin-like compounds and reservoir sources. Four lines of evidence support this finding:

- As discussed in Volume 2, the companion document to this report, studies of sediment corings in lakes in the United States show a consistent pattern of change in CDD/CDF concentration in the sediments over time. The time period when increases are observed in CDD/CDF levels in sediments coincides with the time period when general industrial activity began increasing rapidly. CDD/CDF concentrations in sediments began to increase around the 1930s, and continued to increase until the 1960s and 1970s. Decreases appear to have occurred only during the most recent time periods (i.e., 1970s and 1980s). These trend observations are consistent among the dated sediment cores collected from over 20 freshwater and marine water bodies in various locations throughout the United States and Europe. Levels of CDD/CDF in sediments from these lakes are considered to be a reasonable indicator of the rate of environmental deposition. The period of increase generally matches the time when a variety of industrial activities began rising and the period of decline appears to correspond with growth in pollution abatement. Some of these pollution abatement actions are likely to have resulted in decreased CDD/CDF emissions (i.e., elimination of much open burning of solid waste, installation of particulate controls on combustors, phase out of leaded gasoline, and bans or restrictions on PCBs, 2,4,5-T, and PCP).
- In at least one case, soil erosion to surface waters, reservoir sources are thought to be a significant contributor to the environment. However, the principal source of CDD/CDFs in surface soils is air deposition. As discussed in the first bullet, it appears that CDD/CDFs associated with air deposition are primarily of anthropogenic origin.

- No large natural sources of CDD/CDF have been identified. EPA's current estimate of emissions from all sources of CDD/CDFs suggests that forest fires are a minor source of emissions compared to anthropogenic combustion activity. Recently

CDD/CDFs have been discovered in ball clay deposits in western Mississippi, Kentucky, and Tennessee. Although the origin of the CDD/CDFs in these clays may be natural, it has not been confirmed.

- As discussed in Volume 2, the companion document to this report, CDD/CDF levels in human tissues from the general population in industrialized countries are higher than levels observed in less-industrialized countries. Human populations in Europe and North America have significantly higher mean tissue levels (e.g., blood, adipose tissues, and breast milk) than human populations in developing countries of Asia.

Although chlorine is an essential component for the formation of CDD/CDFs in combustion systems, the empirical evidence indicates that for commercial scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of CDD/CDF stack emissions. Important factors which can affect the rate of CDD/CDF formation include the overall combustion efficiency, post-combustion flue gas temperatures and residence times, and the availability of surface catalytic sites to support CDD/CDF synthesis. Data from bench, pilot and commercial scale combustors indicate that CDD/CDF formation can occur by a number of mechanisms. Some of these data, primarily from laboratory and pilot scale combustors, have shown direct correlation between chlorine content in fuels and rates of CDD/CDF formation. Other data, primarily from commercial scale combustors, show little relation between availability of chlorine in feeds and rates of CDD/CDF formation. These studies are summarized below:

- Evidence from laboratory studies - A number of laboratory studies indicate that changes in the chlorine content of feed materials may result in changes in the amount of CDD/CDFs formed in the post-combustion region of a bench scale combustion system (Kanters and Louw, 1994; Kanters et al., 1996; De Fre and Rymen 1989; Wagner and Green, 1993).

- Evidence from pilot-scale studies - Recent evidence from a pilot-scale combustion study suggests that the amount of CDD/CDFs formed is not strongly correlated with chlorine content of the feed material when the feed material contains less than one percent chlorine; when chlorine in the feed is above one percent, the chlorine feed content appears to be directly proportional to the amount of CDD/CDFs formed (Wikstrom et al., 1996). Other pilot-scale studies indicate a strong relationship between the amount of HCl formed (from organically-bound chlorine in feeds) and the amount of CDD/CDFs formed (Bruce et al., 1991; Wagner and Green, 1993). Wagner and Green (1993) concluded that a decrease in the levels of organically-bound chlorine in the feed leads to a decrease in chlorinated organic emissions.

- Evidence from studies of full-scale systems - Combustors having poor combustion characteristics and hot-sided particulate control devices show a positive correlation between chlorine in feeds/fuels and CDD/CDF stack emissions (Thomas and Spiro 1995; U.S. EPA, 1987a). Combustors with high combustion efficiency, cool-sided particulate control devices, and advanced dioxin-specific air pollution control systems, however, do not show a strong correlation between chlorine amounts in feeds/fuels and the amount of CDDs/CDFs emitted from the stack (Rigo et al., 1995). This conclusion has been questioned in a paper by Costner (1998) who claims that many of the facilities assessed by Rigo et al. (1996) show a positive (though small) correlation between chlorine in feed and CDD/CDF emissions. Conversely, Costner (1998) also found that about half the facilities showed a weak inverse relationship. The American Society of Mechanical Engineers (ASME) has concluded that, "Whatever effect chlorine has on PCDD/CDF emissions in commercial scale systems is masked by the effect of APCS (air pollution control systems), temperature, ash chemistry, combustion conditions, measurement imprecision, and localized flow stratification (ASME, 1995)."

The conclusion that chlorine in feed is not a strong determinant of CDD/CDF emissions applies to the overall population of commercial scale combustors. For any individual commercial scale combustor, circumstances may exist in which changes in chlorine content of feed could affect CDD/CDF emissions. For uncontrolled combustion, such as open burning of household waste, the chlorine content of the waste may play a more significant role in rates of CDD/CDF formation and release than is observed at commercial scale combustors.

Dioxins are present in some ball clays, but insufficient data are available to estimate whether environmental releases occur during the mining and use. Recent studies in the U.S. and Europe have measured dioxins (principally CDDs) in some ball clays and other related clays. As discussed in Chapter 13, it is likely that the CDDs present in ball clay are of a natural origin. Ball clay is principally used in the manufacture of ceramics which involves firing the clay in high temperature kilns. This activity may cause some portion of the CDDs contained in the clay to be released into the air, but emission tests have not yet been conducted which would allow characterizing these releases.

Data are available to estimate the amounts of CDD/CDFs contained in only a limited number of commercial products. No systematic survey has been conducted to determine levels of dioxin-like compounds in commercial products. The available data does, however, allow estimates to be made of the amounts of dioxin-like compounds in bleached pulp (40 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995), POTW sludge used in fertilizers (3.5 g I-TEQ_{DF} or 2.6 g

TEQ_{DF}-WHO_{98} in 1995), pentachlorophenol-treated wood (8,400 g I-TEQ_{DF} or 4,800 g TEQ_{DF}-WHO_{98} in 1995), dioxazine dyes and pigments (<1 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995) and 2,4-D (18.4 g I-TEQ_{DF} or 28.9 g TEQ_{DF}-WHO_{98} in 1995).

No significant release of newly formed dioxin-like PCBs is occurring in the United States. Unlike CDD/CDFs, PCBs were intentionally manufactured in the United States in large quantities from 1929 until production was banned in 1977. Although it has been demonstrated that small quantities of dioxin-like PCBs can be produced during waste combustion, no strong evidence exists that the dioxin-like PCBs make a significant contribution to TEQ releases during combustion. The occurrences of dioxin-like PCBs in the U.S. environment most likely reflect past releases associated with PCB production, use, and disposal. Further support for this finding is based on observations of reductions since the 1980s in PCB concentrations in Great Lakes sediment and other areas.

It is unlikely that the emission rates of CDD/CDFs from known sources correlate proportionally with general population exposures. Although the Inventory shows the relative contribution of various sources to total emissions, it cannot be assumed that these sources make the same relative contributions to human exposure. It is quite possible that the major sources affecting CDD/CDF concentrations in food (see discussion in Section 2.6 of Volume 2) may not be those sources that represent the largest fractions of current total emissions in the United States. The geographic locations of sources relative to the areas from which much of the beef, pork, milk, and fish are produced are important to consider. That is, many of the agricultural areas that produce dietary animal fats are not located near or directly down wind of the major sources of dioxin-like compounds.

The contribution of reservoir sources to human exposure may be significant. Several factors support this finding:

- Because the magnitude of releases from current sources of newly formed PCBs are most likely negligible, human exposure to the dioxin-like PCBs is thought to be derived almost completely from reservoir sources. Key pathways involve releases from both soils and sediments to both aquatic and terrestrial food chains. As discussed in Volume 2, one third of general population TEQ_{DFP} exposure is due to PCBs. Thus, at least one third of the overall risk from dioxin-like compounds comes from reservoir sources.

- CDD/CDF releases from soil via soil erosion and runoff to waterways may be significant. These releases appear to be greater than releases to water from the primary sources included in the inventory. CDD/CDFs in waterways can

bioaccumulate in fish leading to human exposure via consumption of fish. As discussed in Volume 2, fish consumption makes up about one third of the total general population CDD/CDF TEQ exposure. This suggests that a significant portion of the CDD/CDF TEQ exposure could be due to releases from the soil reservoir. It is not known, however, how much of the soil erosion and runoff represents recently deposited CDD/CDFs from primary sources or longer term accumulation. Much of the eroded soil comes from tilled agricultural lands which would include a mix of CDD/CDFs from various deposition times. The age of CDD/CDFs in urban runoff is less clear.

- Potentially, soil reservoirs could have vapor and particulate releases which deposit on plants and enter the terrestrial food chain. The magnitude of this contribution, however, is unknown. EPA plans future studies in agricultural areas which will compare modeled air concentrations from primary sources to measured levels as a way to get further insight to this issue.

1.7. CONGENER PROFILES OF CDD/CDF SOURCES

This section summarizes congener profiles of known sources of dioxin-like compounds in the United States (Cleverly et. al, 1998). Congener profiles are the fractional distribution of CDD/CDF congeners in an environmental release, in an environmental sample, or in a biological sample. Under some circumstances, these congener profiles may assist researchers in: (1) identification of specific combustion source contributions to near field air measurements of CDD/CDFs; (2) comparing sources in terms of discerning differences in the types and amplitude of CDD/CDF congeners emitted; and (3) providing insights on formation of CDDs and CDFs in various sources and chemicals. There are numerous procedures one could elect to use to derive a congener profile, and there is no single agreed-upon convention (Cleverly et al., 1998; Lorber et al., 1996; Hagenmaier et al., 1994). In this report, congener profiles were developed primarily by calculating the ratio of specific 2,3,7,8-substituted CDDs and CDFs in the emission or product to the total (Cl_4 - Cl_8) CDDs/CDFs. With respect to combustion sources, the profiles were derived by: (a) dividing the congener-specific emission factors by the total (Cl_4 - Cl_8) CDD/CDF emission factor for each tested facility; and (b) then averaging the congener profiles developed for all tested facilities within the combustor type. For chemical processes and commercial chemicals, CDD/CDF profiles were typically generated by dividing average congener concentrations (ppt) in the chemical by the total CDD/CDF present. Profiles for selected source categories are presented in Figure 1-8.

On the basis of inspection and comparisons of the average CDD/CDF congener profiles across combustion and non-combustion sources, the following observations are made (Cleverly et al., 1998): (These generalizations are derived from this data set, and their application beyond these data is uncertain).

i. It appears that combustion sources emit all 2,3,7,8-substituted CDDs and CDFs, although in varying percentages of total CDD/CDF.

ii. In combustion source emissions, 2,3,7,8-TCDD is usually 0.1 to 1.0 percent of total CDD/CDF. The exception to this are stack emissions from industrial oil-fired boilers where the available, but limited data, indicate that 2,3,7,8-TCDD constitutes an average of 7 percent of total CDD/CDF emissions.

iii. It cannot be concluded that OCDD is the dominant congener for all combustion generated emissions of CDD/CDFs. OCDD dominates total emissions from: mass burn municipal solid waste incinerators (MSWI) that have dry scrubbers and fabric filters (DS/FF) for dioxin controls; industrial oil-fired boilers; industrial wood-fired boilers; unleaded gasoline combustion; diesel fuel combustion in trucks; and sewage sludge incinerators. The dominant congeners for other combustion sources are: 1,2,3,4,6,7,8-HpCDF in emissions from mass burn MSWIs equipped with hot-sided electrostatic precipitators (ESPs); OCDF in emissions from medical waste incineration; 1,2,3,4,6,7,8-HpCDF in hazardous waste incinerators; 2,3,4,7,8-PeCDF in cement kilns burning hazardous waste; 2,3,7,8-TCDF in cement kilns not burning hazardous waste; OCDF in industrial/utility coal-fired boilers; 1,2,3,4,6,7,8-HpCDF in secondary aluminum smelters; and 2,3,7,8-TCDF in secondary lead smelters.

iv. The 1,2,3,4,6,7,8-HpCDF appears to be the dominant congener in the following sources: secondary aluminum smelters; MSWIs equipped with hot-sided ESPs; hazardous waste incinerators; and 2,4-D salts and esters.

v. Evidence for a shift in the congener patterns potentially caused by the application of different air pollution control systems within a combustion source-type can be seen in the case of mass burn MSWIs. For mass burn MSWIs equipped with hot-sided ESPs, the most prevalent CDD/CDF congeners are: 1,2,3,4,6,7,8-HpCDF; OCDD; 1,2,3,4,6,7,8-HpCDD/1,2,3,4,7,8-HxCDF; 2,3,4,6,7,8-HxCDF/OCDF; 1,2,3,6,7,8-HxCDF. The most prevalent congeners emitted from MSWIs equipped with DS/FF are: OCDD; 1,2,3,4,6,7,8-HpCDD; 1,2,3,4,6,7,8-HpCDF; OCDF; 2,3,7,8-TCDF/1,2,3,4,7,8-HxCDD; 2,3,4,6,7,8-HxCDF.

vi. There is evidence of marked differences in the distribution of CDD/CDF congeners between cement kilns burning and not burning hazardous waste. When not burning hazardous waste as supplemental fuel, the dominant congeners appear to be 2,3,7,8-TCDF; OCDD; 1,2,3,4,6,7,8-HpCDD, and OCDF. When burning hazardous waste, the dominant congeners are: 2,3,7,8-PeCDF; 2,3,7,8-TCDF; 1,2,3,4,7,8-

HxCDF; and 1,2,3,4,6,7,8-HpCDD. When burning hazardous waste, OCDD and OCDF are minor constituents of stack emissions.

vii. The congener profile of 2,4-D salts and esters seems to mimic a combustion source profile in the number of congeners represented, and in the minimal amount of 2,3,7,8-TCDD relative to all 2,3,7,8-substituted congeners. A major difference is the prevalence of 1,2,3,7,8-PeCDD in 2,4-D (i.e., 14 percent), which is not seen in any other combustion or non-combustion sources presented here.

viii. There are similarities in the congener profiles of pentachlorophenol (PCP), diesel truck emissions, unleaded gasoline vehicle emissions, and industrial wood combustors. In these sources, OCDD dominates total emissions, but the relative ratio of 1,2,3,4,6,7,8-HpCDD to OCDD is also quite similar.

ix. The congener profiles for diesel truck exhaust and air measurements from a tunnel study of diesel traffic are quite similar.

Table 1-1. The TEF Scheme for I-TEQ_{DF}

Dioxin (D) Congener	TEF	Furan (F) Congener	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		OCDF	

Table 1-2. The TEF Scheme for Dioxin-Like PCBs, as Determined by the World Health Organization in 1994

Chemical Structure	IUPAC Number	TEF
3,3',4,4'-TeCB	PCB-77	0.0005
2,3,3',4,4'-PeCB	PCB-105	0.0001
2,3,4,4',5-PeCB	PCB-114	0.0005
2,3',4,4',5-PeCB	PCB-118	0.0001
2',3,4,4',5-PeCB	PCB-123	0.0001
3,3',4,4',5-PeCB	PCB-126	0.1
2,3,3',4,4',5-HxCB	PCB-156	0.0005
2,3,3',4,4',5'-HxCB	PCB-157	0.0005
2,3',4,4',5,5'-HxCB	PCB-167	0.00001
3,3',4,4',5,5'-HxCB	PCB-169	0.01
2,2',3,3',4,4',5-HpCB	PCB-170	0.0001
2,2',3,4,4',5,5'-HpCB	PCB-180	0.00001
2,3,3',4,4',5,5'-HpCB	PCB-189	0.0001

Table 1-3. The TEF Scheme for TEQ_{DFP}-WHO_{98}

Dioxin Congeners	TEF	Furan Congeners	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	1.0	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
OCDD	0.0001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		OCDF	0.0001

Chemical Structure	IUPAC Number	TEF
3,3',4,4'-TeCB	PCB-77	0.0001
3,4,4',5-TCB	PCB-81	0.0001
2,3,3',4,4'-PeCB	PCB-105	0.0001
2,3,4,4',5-PeCB	PCB-114	0.0005
2,3',4,4',5-PeCB	PCB-118	0.0001
2',3,4,4',5-PeCB	PCB-123	0.0001
3,3',4,4',5-PeCB	PCB-126	0.1
2,3,3',4,4',5-HxCB	PCB-156	0.0005
2,3,3',4,4',5'-HxCB	PCB-157	0.0005
2,3',4,4',5,5'-HxCB	PCB-167	0.00001
3,3',4,4',5,5'-HxCB	PCB-169	0.01
2,3,3',4,4',5,5'-HpCB	PCB-189	0.0001

Table 1-4. Nomenclature for Dioxin-Like Compounds

Term/Symbol	Definition
Congener	Any one particular member of the same chemical family (e.g., there are 75 congeners of chlorinated dibenzo-p-dioxins).
Congener Group	Group of structurally related chemicals that have the same degree of chlorination (e.g., there are eight congener groups of CDDs, monochlorinated through octochlorinated).
Isomer	Substances that belong to the same congener group (e.g., 22 isomers constitute the congener group of TCDDs).
Specific Isomer	Denoted by unique chemical notation (e.g., 2,4,8,9-tetrachlorodibenzofuran is referred to as 2,4,8,9-TCDF).
D	Symbol for congener class: dibenzo-p-dioxin
F	Symbol for congener class: dibenzofuran
M	Symbol for mono (i.e., one halogen substitution)
D	Symbol for di (i.e., two halogen substitution)
Tr	Symbol for tri (i.e., three halogen substitution)
T	Symbol for tetra (i.e., four halogen substitution)
Pe	Symbol for penta (i.e., five halogen substitution)
Hx	Symbol for hexa (i.e., six halogen substitution)
Hp	Symbol for hepta (i.e., seven halogen substitution)
O	Symbol for octa (i.e., eight halogen substitution)
CDD	Chlorinated dibenzo-p-dioxins, halogens substituted in any position
CDF	Chlorinated dibenzofurans, halogens substituted in any position
PCB	Polychlorinated biphenyls
2378	Halogen substitutions in the 2,3,7,8 positions

Source: Adapted from U.S. EPA (1989)

Table 1-5. List of Known and Suspected CDD/CDF Sources

Emission Source Category	Contemporary Formation Sources			Reservoir Sources		
	Quantifiable	Preliminary Estimate	Not Quantifiable	Quantifiable	Preliminary Estimate	Not Quantifiable
I. COMBUSTION SOURCES						
Waste Incineration						
Municipal waste incineration	✓					
Hazardous waste incineration	✓					
Boilers/industrial furnaces	✓					
Medical waste/pathological incineration	✓					
Crematoria	✓					
Sewage sludge incineration	✓					
Tire combustion	✓					
Pulp and paper mill sludge incinerators	✓					
BioGas combustion		✓				
Power/Energy Generation						
Vehicle fuel combustion - leaded[b]	✓					
- unleaded	✓					
- diesel	✓					
Wood combustion - residential	✓					
- industrial	✓					
Coal combustion - residential		✓				
- industrial/utility	✓					
Oil combustion - residential		✓				
- industrial/utility	✓					
Other High Temperature Sources						
Cement kilns (haz waste burning)	✓					
Cement kilns (non haz waste burning)	✓					
Asphalt mixing plants		✓				
Petro. refining catalyst regeneration	✓					
Cigarette combustion	✓					
Carbon reactivation furnaces	✓					
Kraft recovery boilers	✓					

Table 1-5. List of Known and Suspected CDD/CDF Sources (continued)

Emission Source Category	Contemporary Formation Sources			Reservoir Sources		
	Quantifiable	Preliminary Estimate	Not Quantifiable	Quantifiable	Preliminary Estimate	Not Quantifiable
Manufacture of ball clay products			✓			

Table 1-5. List of Known and Suspected CDD/CDF Sources (continued)

Emission Source Category	Contemporary Formation Sources			Reservoir Sources		
	Quantifiable	Preliminary Estimate	Not Quantifiable	Quantifiable	Preliminary Estimate	Not Quantifiable
Minimally Controlled or Uncontrolled Combustion Combustion of landfill gas in flares		✓				
Landfill fires		✓				
Accidental fires (structural)		✓				
Accidental fires (vehicles)		✓				
Forest, brush, and straw fires		✓				
Backyard barrel burning	✓					
Uncontrolled combustion of PCBs			✓			
II. METAL SMELTING/REFINING ***Ferrous metal smelting/refining***						
- Sintering plants	✓					
- Coke production		✓				
- Electric arc furnaces		✓				
- Ferrous foundries		✓				
Nonferrous metal smelting/refining						
- Primary aluminum			✓			
- Primary copper	✓					
- Primary magnesium		✓				
- Primary nickel			✓			
- Secondary aluminum	✓					
- Secondary copper	✓					
- Secondary lead	✓					
Scrap electric wire recovery	✓					
Drum and barrel reclamation	✓					
III. CHEMICAL MANUFACTURING ***(Releases to the Environment)*** Bleached chemical wood pulp and paper mills	✓					
Mono- to tetrachlorophenols			✓			
Pentachlorophenol			✓			
Chlorobenzenes			✓			

Table 1-5. List of Known and Suspected CDD/CDF Sources (continued)

Emission Source Category	Contemporary Formation Sources			Reservoir Sources		
	Quantifiable	Preliminary Estimate	Not Quantifiable	Quantifiable	Preliminary Estimate	Not Quantifiable
Chlorobiphenyls (leaks/spills)			✓			
Ethylene dichloride/vinyl chloride	✓					
Dioxazine dyes and pigments			✓			
2,4-Dichlorophenoxy acetic acid			✓			
Municipal wastewater treatment		✓				
Tall oil-based liquid soaps			✓			
IV. BIOLOGICAL AND PHOTOCHEMICAL PROCESSES			✓			
V. RESERVOIR SOURCES						
Natural						
- Land					✓	
- Air						✓
- Water						✓
- Sediments						✓
Anthropogenic Structures						
- PCP Treated Wood						✓

Table 1-6. Confidence Rating Scheme for U.S. Emission Estimates

Confidence Rating	Activity Level Estimate	Emission Factor Estimate
Categories/Media for Which Releases Can Be Reasonably Quantified		
High	Derived from comprehensive survey	Derived from comprehensive survey
Medium	Based on estimates of average plant activity level and number of plants or limited survey	Derived from testing at a limited but reasonable number of facilities believed to be representative of source category
Low	Based on data judged possibly nonrepresentative	Derived from testing at only a few, possibly nonrepresentative facilities or from similar source categories
Categories/Media for Which Releases Cannot Be Reasonably Quantified		
Preliminary Estimate	Based on extremely limited data, judged to be clearly nonrepresentative	Based on extremely limited data, judged to be clearly nonrepresentative
Not Quantified	No data available	1) Argument based on theory but no data, or 2) Data available indicating formation, but not in a form that allows developing an emission factor

Table 1-7. Inventory of Environmental Releases (grams/year) of I-TEQ_{DF} From Known Sources in the United States for 1995 and 1987

Emission Source Category	Confidence Rating[a] Reference Year1995				Confidence Rating[a] Reference Year 1987		
	A	B	C	D	A	B	C
Releases (g TEQ/yr) to Air							
WASTE INCINERATION							
Municipal waste incineration		1,100				7,915	
Hazardous waste incineration		5.7				5.0	
Boilers/industrial furnaces			0.38				0.77
Medical waste/pathological incineration			461				2,440
Crematoria			9.1				5.5
Sewage sludge incineration		14.7				6.0	
Tire combustion			0.11				0.11
Pulp and paper mill sludge incinerators[e]							
Biogas Combustion				>1			
POWER/ENERGY GENERATION							
Vehicle fuel combustion - leaded[b]			1.7				31.9
- unleaded			5.6				3.3
- diesel			33.5				26.3
Wood combustion - residential			62.8				89.6
- industrial		26.2				25.1	
Coal combustion - utility boilers		60.9				51.4	
Coal Combustion - residential				30.0			
Coal Combustion - commercial/Industrial				40.0			
Oil combustion - industrial/utility			9.3				15.5
Oil combustion - residential				6.0			
OTHER HIGH TEMPERATURE SOURCES							
Cement kilns (hazardous waste burning)			145.3				109.6
Lightweight aggregate kilns burning hazardous waste			3.3				2.4
Cement kilns (non hazardous waste burning)			16.6				12.7
Asphalt mixing plants				7			
Petroleum Refining Catalyst Regeneration			2.11				2.14
Cigarette combustion			0.8				1.0
Carbon reactivation furnaces			0.08				0.06
Kraft recovery boilers		2.3				2.0	
MINIMALLY CONTROLLED OR UNCONTROLLED COMBUSTION[d]							
Backyard barrel burning[f]			595				573
Combustion of Landfill Gas				7.0			
Landfill fires				1,000			
Accidental Fires (Structural)				>20			
Accidental Fires (Vehicles)				30.0			
Forest and Brush Fires				200			
METALLURGICAL PROCESSES							
Ferrous metal smelting/refining							
- Sintering plants		25.1					29.3
- Coke production				7.0			
- Electric arc furnaces				40.0			
- Foundries				20.0			

Table 1-7. Inventory of Environmental Releases (grams/year) of I-TEQ_{DF} From Known Sources in the United States for 1995 and 1987 (continued)

Emission Source Category	Confidence Rating[a] Reference Year1995				Confidence Rating[a] Reference Year 1987		
	A	B	C	D	A	B	C
Nonferrous metal smelting/refining							
- Primary copper		<0.5				<0.5	
- Secondary aluminum			27.4				15.3
- Secondary copper			266				966
- Secondary lead		1.63				1.22	
- Primary Magnesium				15.0			
Drum and barrel reclamation			0.08				0.08
CHEMICAL MANUFAC./PROCESSING SOURCES Ethylene dichloride/vinyl chloride		11.2					
TOTAL RELEASES TO AIR[c]	2,888				12,331		
Releases (g TEQ/yr) to Water							
CHEMICAL MANUF./PROCESSING SOURCES Bleached chemical wood pulp and paper mills	28.0				356		
POTW (municipal) wastewater				10			
Ethylene dichloride/vinyl chloride		0.43					
RESERVOIR SOURCES Urban runoff to surface water				190			
Rural soil erosion to surface water				2,700			
TOTAL RELEASES TO WATER[c]	28.43				356		
Releases (g TEQ/yr) to Land							
CHEMICAL MANUF./PROCESSING SOURCES Bleached chemical wood pulp and paper mill sludge	2.0				14.1		
Ethlyene dichloride/vinyl chloride		0.73					
Municipal wastewater treatment sludge	103				103		
Commercially marketed sewage sludge	3.5				3.5		
2,4-Dichlorophenoxy acetic acid	18.4				21.3		
TOTAL RELEASES TO LAND[c]	127.6				141.8		
OVERALL RELEASES (g/yr)TO THE OPEN and CIRCULATING ENVIRONMENT	**3,044 (SUM OF COLUMNS A, B, C)**				**12,829 (SUM OF COLUMNS A, B, C)**		

[1]/ The most reliable estimates of environmental releases are those sources within Categories A, B and C (see footnote 'a' for definitions).

[a] A = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **High Confidence** in the **Emission Factor** and **High Confidence** in **Activity Level**.
B = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Medium Confidence** in the **Emission Factor** and at least **Medium Confidence** in **Activity Level**.
C = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Low Confidence** in either the **Emission Factor** and/or the **Activity Level**.
D = **Preliminary Indication** of the Potential Magnitude of I-TEQ_{DF} Emissions from "Unquantified" (i.e., Category D) Sources in Reference Year 1995. **Based on extremely limited data, judged to be clearly nonrepresentative**.

[b] Leaded fuel production and the manufacture of motor vehicle engines requiring leaded fuel for highway use have been prohibited in the United States. (See Section 4.1 for details.)

[c] TOTAL reflects only the total of the estimates made in this report.

[d] This refers to conventional pollutant control, not dioxin emissions control. Very few of the sources listed in this inventory control specifically for CDD/CDF emissions.

[e] Included within estimate for Wood Combustion - industrial.

[f] This term refers to the burning of residential waste in barrels.

Table 1-8. Inventory of Environmental Releases (grams/year) of TEQ_{DF}-WHO_{98} From Known Sources in the United States for 1995 and 1987

Emission Source Category	Confidence Rating[a] Reference Year1995				Confidence Rating[a] Reference Year 1987		
	A	B	C	D	A	B	C
Releases (g TEQ/yr) to Air							
WASTE INCINERATION							
Municipal waste incineration		1,250				8,877	
Hazardous waste incineration		5.8				5.0	
Boilers/industrial furnaces			0.39				0.78
Medical waste/pathological incineration			488				2,590
Crematoria			9.1[e]				5.5[e]
Sewage sludge incineration		14.8				6.1	
Tire combustion			0.11				0.11
Pulp and paper mill sludge incinerators[f]							
Biogas Combustion				< 1			
POWER/ENERGY GENERATION							
Vehicle fuel combustion - leaded[b]			2.0				37.5
- unleaded			5.6				3.6
- diesel			33.5				27.8
Wood combustion - residential			62.8[e]				89.6[e]
- industrial		27.6				26.4	
Coal combustion - utility boilers		60.1				50.8	
Coal Combustion - residential				30			
Coal Combustion - commercial/Industrial				40			
Oil combustion - industrial/utility			10.7				17.8
Oil combustion - residential				6			
OTHER HIGH TEMPERATURE SOURCES							
Cement kilns (hazardous waste burning)			156.1				117.8
Lightweight aggregate kilns burning hazardous waste			3.3[e]				2.4[e]
Cement kilns (non hazardous waste burning)			17.8				13.7
Asphalt mixing plants				7			
Petroleum Refining Catalyst Regeneration			2.21				2.24
Cigarette combustion			0.8				1.0
Carbon reactivation furnaces			0.08[e]				0.06[e]
Kraft recovery boilers		2.3				2.0	
MINIMALLY CONTROLLED OR UNCONTROLLED COMBUSTION[d]							
Backyard barrel burning[g]			628				604
Combustion of Landfill Gas				7			
Landfill fires				1,000			
Accidental Fires (Structural)				> 20			
Accidental Fires (Vehicles)				30			
Forest and Brush Fires				200			
METALLURGICAL PROCESSES							
Ferrous metal smelting/refining							
- Sintering plants		28					32.7
- Coke production				7.0			
- Electric arc furnaces				40			
- Foundries				20			

Table 1-8. Inventory of Environmental Releases (grams/year) of TEQ_{DF}-WHO_{98} From Known Sources in the United States for 1995 and 1987 (continued)

Emission Source Category	Confidence Rating[a] Reference Year1995				Confidence Rating[a] Reference Year 1987		
	A	B	C	D	A	B	C
Nonferrous metal smelting/refining							
- Primary copper		<0.5[e]				<0.5[e]	
- Secondary aluminum			29.1				16.3
- Secondary copper			271				983
- Secondary lead		1.72				1.29	
- Primary Magnesium				15.0			
Drum and barrel reclamation			0.08				0.08
CHEMICAL MANUFAC./PROCESSING SOURCES Ethylene dichloride/vinyl chloride		11.2[e]					
TOTAL RELEASES TO AIR[c]	3,125				13,515		
Releases (g TEQ/yr) to Water							
CHEMICAL MANUF./PROCESSING SOURCES Bleached chemical wood pulp and paper mills	19.5				356		
POTW (municipal) wastewater				10			
Ethylene dichloride/vinyl chloride		0.43[e]					
RESERVOIR SOURCES Urban runoff to surface water				190			
Rural soil erosion to surface water				2,700			
TOTAL RELEASES TO WATER[c]	19.93				356		
Releases (g TEQ/yr) to Land							
CHEMICAL MANUF./PROCESSING SOURCES Bleached chemical wood pulp and paper mill sludge	1.4				14.1		
Ethlyene dichloride/vinyl chloride		0.73[e]					
Municipal wastewater treatment sludge	76.6				76.6		
Commercially marketed sewage sludge	2.6				2.6		
2,4-Dichlorophenoxy acetic acid	28.9				33.4		
TOTAL RELEASES TO LAND[c]	110.23				126.7		
OVERALL RELEASES (g/yr)TO THE OPEN and CIRCULATING ENVIRONMENT	**3,255 (SUM OF COLUMNS A, B, C)**				**13,998 (SUM OF COLUMNS A, B, C)**		

[1]/ The most reliable estimates of environmental releases are those sources within Categories A, B and C (see footnote 'a' for definitions).

[a] A = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **High Confidence** in the **Emission Factor** and **High Confidence** in **Activity Level**.
B = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Medium Confidence** in the **Emission Factor** and at least **Medium Confidence** in **Activity Level**.
C = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Low Confidence** in either the **Emission Factor** and/or the **Activity Level**.
D = **Preliminary Indication** of the Potential Magnitude of I-TEQ_{DF} Emissions from "Unquantified" (i.e., Category D) Sources in Reference Year 1995. **Based on extremely limited data, judged to be clearly nonrepresentative**.

[b] Leaded fuel production and the manufacture of motor vehicle engines requiring leaded fuel for highway use have been prohibited in the United States. (See Section 4.1 for details.)

[c] TOTAL reflects only the total of the estimates made in this report.

[d] This refers to conventional pollutant control, not dioxin emissions control. Very few of the sources listed in this inventory control specifically for CDD/CDF emissions.

[e] Congener-specific emissions data were not available; the I-TEQ_{DF} emission estimate was used as a surrogate for the TEQ_{DF}-WHO_{98} emission estimate.

[f] Included within estimate for Wood Combustion - industrial.

[g] This term refers to the burning of residential waste in barrels.

Table 1-9. I-TEQ$_{DF}$ Emission Factors Used to Develop National Emission Inventory Estimates of Releases to Air

Emission Source	I-TEQ$_{DF}$ Emission Factor		Emission Factor Units
	1995	1987	
Waste Incineration			
Municipal waste incineration	38.2[a]	573[a]	ng TEQ/kg waste combusted
Hazardous waste incineration	3.83	3.83	ng TEQ/kg waste combusted
Boilers/industrial furnaces	0.64	0.64	ng TEQ/kg waste combusted
Medical waste/pathological incineration	598[a]	1,706[a]	ng TEQ/kg waste combusted
Crematoria	17	17	μg TEQ/body
Sewage sludge incineration	6.94	6.94	ng TEQ/kg dry sludge combusted
Tire combustion	0.282	0.282	ng TEQ/kg tires combusted
Pulp and paper mill sludge incinerators	b	b	
Power/Energy Generation			
Vehicle fuel combustion - leaded[b]	45	45	pg TEQ/km driven
- unleaded	1.5	1.5	pg TEQ/km driven
- diesel	172	172	pg TEQ/km driven
Wood combustion - residential	2	2	ng TEQ/kg wood combusted
- industrial	0.56 to 13.2[c]	0.56 to 13.2[c]	ng TEQ/kg wood combusted
Coal combustion - utility	0.079	0.079	ng TEQ/kg coal combusted
Oil combustion - industrial/utility	0.20	0.20	ng TEQ/L oil combusted
Other High Temperature Sources			
Cement kilns burning hazardous waste	1.04 to 28.58[e]	1.04 to 28.58[e]	ng TEQ/kg clinker produced
Cement kilns not burning hazardous waste	0.27	0.27	ng TEQ/kg clinker produced
Petroleum refining catalyst regeneration	1.52	1.52	ng TEQ/barrel reformer feed
Cigarette combustion	0.00043 to 0.0029	0.00043 to 0.0029	ng TEQ/cigarette
Carbon reactivation furnaces	1.2	1.2	ng TEQ/kg of reactivated carbon
Kraft recovery boilers	0.029	0.029	ng TEQ/kg solids combusted
Minimally Controlled or Uncontrolled Combustion			
Backyard barrel burning	72.8	72.8	ng TEQ/kg waste combusted
Metallurgical Processes			
Ferrous metal smelting/refining			
- Sintering plants	0.55 to 4.14	0.55 to 4.14	ng TEQ/kg sinter
Nonferrous metal smelting/refining			
- Primary copper	<0.31	<0.31	ng TEQ/kg copper produced
- Secondary aluminum smelting	21.1	21.1	ng TEQ/kg scrap feed
- Secondary copper smelting	[d]	[d]	ng TEQ/kg scrap consumed
- Secondary lead smelters	0.05 to 8.31	0.05 to 8.31	ng TEQ/kg lead produced
Drum and barrel reclamation	16.5	16.5	ng TEQ/drum
Chemical Manuf./Processing Sources			
Ethylene dichloride/vinyl chloride	0.95[a]		ng TEQ/kg EDC produced

a Different emission factors were derived for various subcategories within this industry; the value listed is a weighted average.
b Included within total for Wood Combustion - Industrial.
c Emission factor of 0.56 ng I-TEQ$_{DF}$/kg used for non-salt-laden wood; emission factor of 13.2 ng I-TEQ$_{DF}$/kg used for salt-laden wood.
d Facility-specific emission factors were used ranging from 3.6 to 16,600 ng I-TEQ$_{DF}$/kg scrap consumed.
e Emission factor of 1.04 ng I-TEQ$_{DF}$/kg used for kilns with APCD inlet temperatures less than 450°F; emission factor of 28.58 ng I-TEQ$_{DF}$/kg used for kilns with APCD inlet temperatures greater than 450°F.
TEQ = Toxic equivalency factor.
ng = nanogram.
kg = kilogram.
pg = picogram.

Table 1-10. TEQ_{DF}-WHO_{98} Emission Factors Used to Develop National Emission Inventory Estimates of Releases to Air

Emission Source	TEQ_{DF}-WHO_{98} Emission Factor		Emission Factor Units
	1995	1987	
Waste Incineration			
Municipal waste incineration	43.4[a]	644[a]	ng TEQ/kg waste combusted
Hazardous waste incineration	3.88	3.88	ng TEQ/kg waste combusted
Boilers/industrial furnaces	0.65	0.65	ng TEQ/kg waste combusted
Medical waste/pathological incineration	633[a]	1,811[a]	ng TEQ/kg waste combusted
Crematoria	17[f]	17[f]	μg TEQ/body
Sewage sludge incineration	7.04	7.04	ng TEQ/kg dry sludge combusted
Tire combustion	0.281	0.281	ng TEQ/kg tires combusted
Pulp and paper mill sludge incinerators	b	b	
Power/Energy Generation			
Vehicle fuel combustion - leaded[b]	53	53	pg TEQ/km driven
- unleaded	1.6	1.6	pg TEQ/km driven
- diesel	182	182	pg TEQ/km driven
Wood combustion - residential	2[f]	2[f]	ng TEQ/kg wood combusted
- industrial	0.60 to 13.2	0.60 to 13.2	ng TEQ/kg wood combusted
Coal combustion - utility	0.078	0.078	ng TEQ/kg coal combusted
Oil combustion - industrial/utility	0.23	0.23	ng TEQ/L oil combusted
Other High Temperature Sources			
Cement kilns burning hazardous waste	1.11 to 30.70[e]	1.11 to 30.70[e]	ng TEQ/kg clinker produced
Cement kilns not burning hazardous waste	0.29	0.29	ng TEQ/kg clinker produced
Petroleum refining catalyst regeneration	1.59	1.59	ng TEQ/barrel reformer feed
Cigarette combustion	0.00044 to 0.0030	0.00044 to 0.0030	ng TEQ/cigarette
Carbon reactivation furnaces	1.2[f]	1.2[f]	ng TEQ/kg of reactivated carbon
Kraft recovery boilers	0.028	0.028	ng TEQ/kg solids combusted
Minimally Controlled or Uncontrolled Combustion			
Backyard barrel burning	76.8[f]	76.8[f]	ng TEQ/kg waste combusted
Metallurgical Processes			
Ferrous metal smelting/refining			
- Sintering plants	0.62 to 4.61	0.62 to 4.61	ng TEQ/kg sinter
Nonferrous metal smelting/refining			
- Primary copper	<0.31[f]	<0.31[f]	ng TEQ/kg copper produced
- Secondary aluminum smelting	22.4	22.4	ng TEQ/kg scrap feed
- Secondary copper smelting	d	d	ng TEQ/kg scrap consumed
- Secondary lead smelters	0.05 to 8.81	0.05 to 8.81	ng TEQ/kg lead produced
Drum and barrel reclamation	17.5	17.5	ng TEQ/drum
Chemical Manuf./Processing Sources			
Ethylene dichloride/vinyl chloride	0.95[a,f]		ng TEQ/kg EDC produced

a Different emission factors were derived for various subcategories within this industry; the value listed is a weighted average.
b Included within total for Wood Combustion - Industrial.
c Emission factor of 0.60 ng TEQ_{DF}-WHO_{98}/kg used for non-salt-laden wood; emission factor of 13.2 ng I-TEQ_{DF}/kg used for salt-laden wood.
d Facility-specific emission factors were used ranging from 3.6 to 16,900 ng TEQ_{DF}-WHO_{98}/kg scrap consumed.
e Emission factor of 1.11 ng TEQ_{DF}-WHO_{98}/kg used for kilns with APCD inlet temperatures less than 450°F; emission factor of 30.70 ng TEQ_{DF}-WHO_{98}/kg used for kilns with APCD inlet temperatures greater than 450°F.
f Congener-specific data were not available; the I-TEQ_{DF} emission factor was used as a surrogate for the TEQ_{DF}-WHO_{98} emission factor.
TEQ = Toxic equivalency factor.
ng = nanogram.
kg = kilogram.
pg = picogram.

Table 1-11. Identification of Products Containing CDD/CDF in 1995 and 1987
(g I-TEQ_{DF}/yr)

Product	1995	1987
Bleached chemical wood pulp	40	505
Ethylene dichloride/vinyl chloride	0.02	NA
Dioxazine dyes and pigments	0.36	64.0
Pentachlorophenol	8,400	36,000
Total Amounts in Products	8,440	36,569

NA = information not available

Table 1-12. Identification of Products Containing CDD/CDF in 1995 and 1987
(g TEQ_{DF}-WHO_{98} /yr)

Product	1995	1987
Bleached chemical wood pulp	40	505
Ethylene dichloride/vinyl chloride	0.02	NA
Dioxazine dyes and pigments	0.36	64.0
Pentachlorophenol	4,800	20,000
Total Amounts in Products	4,840	20,569

NA = information not available

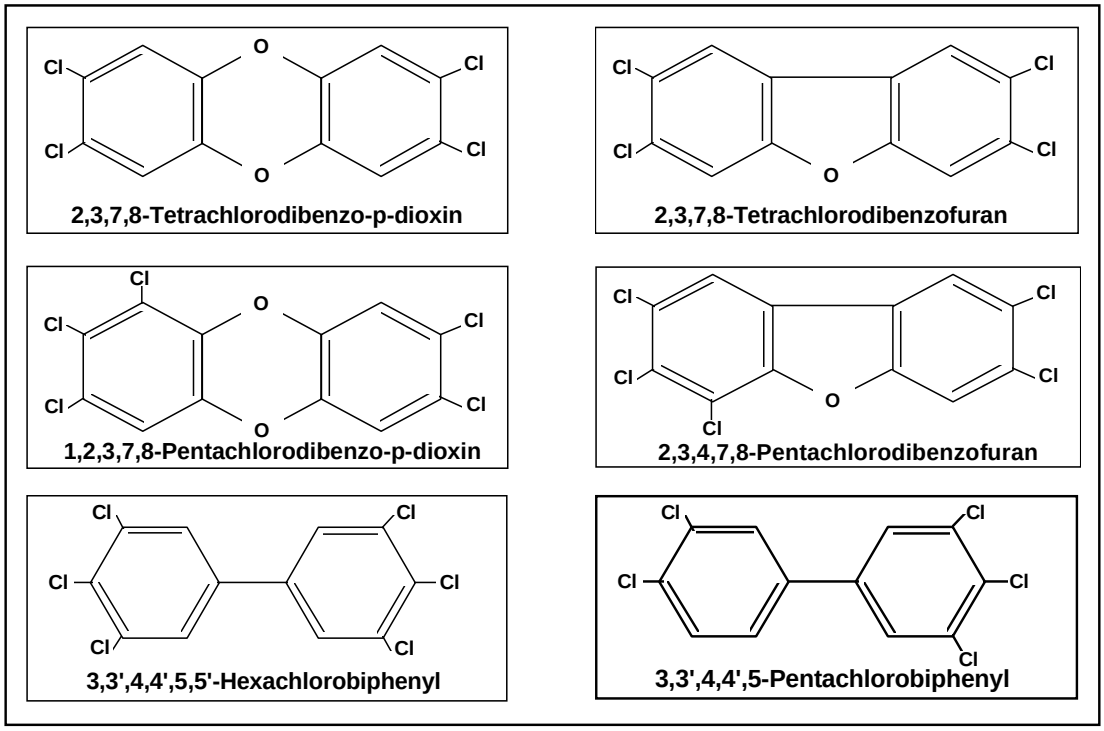
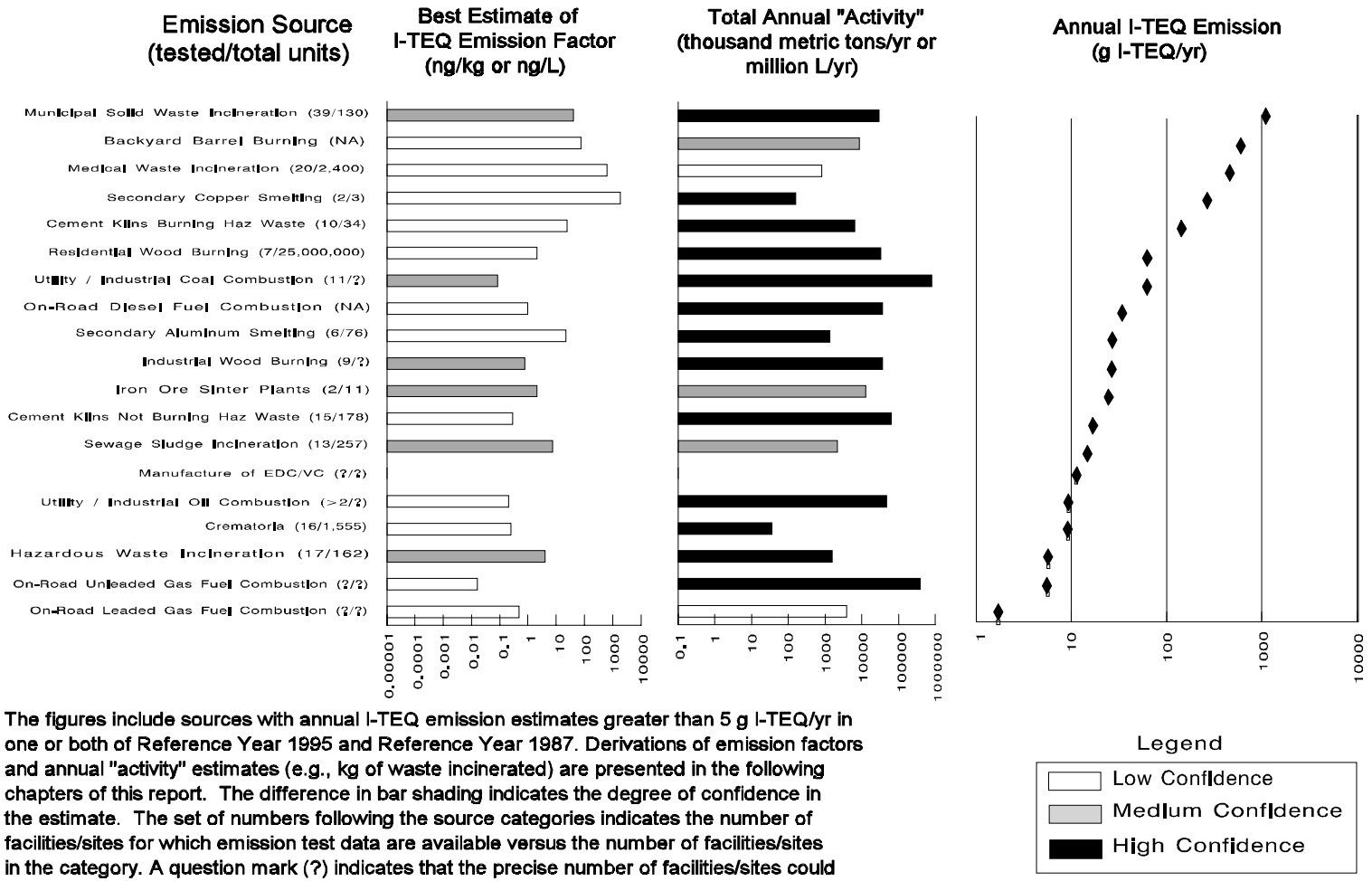
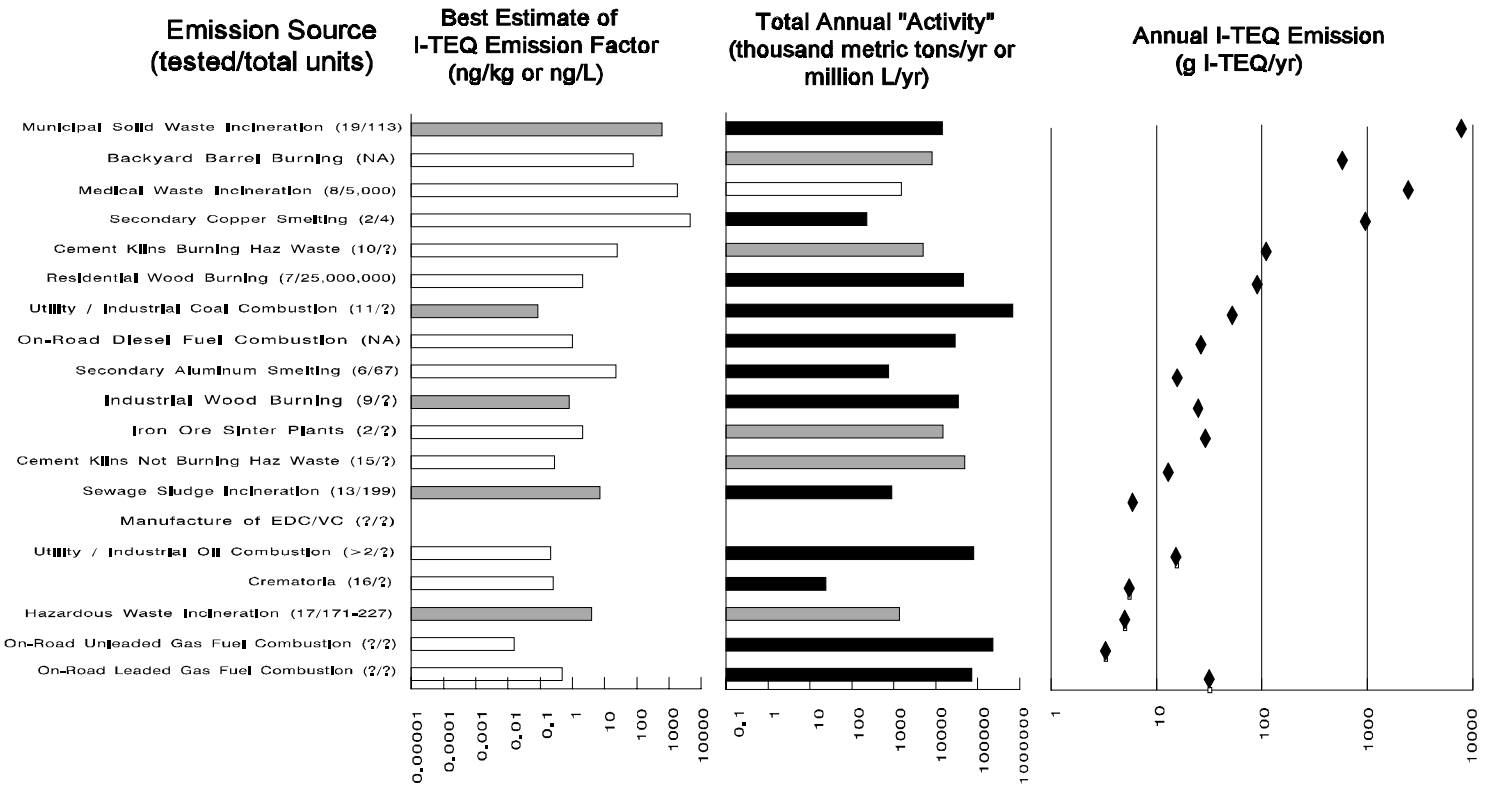


Figure 1-1. Chemical Structure of 2,3,7,8-TCDD and Related Compounds



The figures include sources with annual I-TEQ emission estimates greater than 5 g I-TEQ/yr in one or both of Reference Year 1995 and Reference Year 1987. Derivations of emission factors and annual "activity" estimates (e.g., kg of waste incinerated) are presented in the following chapters of this report. The difference in bar shading indicates the degree of confidence in the estimate. The set of numbers following the source categories indicates the number of facilities/sites for which emission test data are available versus the number of facilities/sites in the category. A question mark (?) indicates that the precise number of facilities/sites could not be estimated.

Figure 1-2. Estimated CDD/CDF I-TEQ Emissions to Air from Combustion Sources in the United States (Reference Time Period: 1995)



The figures include sources with annual I-TEQ emission estimates greater than 5 g I-TEQ/yr in one or both of Reference Year 1995 and Reference Year 1987. Derivations of emission factors and annual "activity" estimates (e.g., kg of waste incinerated) are presented in the following chapters of this report. The difference in bar shading indicates the degree of confidence in the estimate. The set of numbers following the source categories indicates the number of facilities/sites for which emission test data are available versus the number of facilities/sites in the category. A question mark (?) indicates that the precise number of facilities/sites could not be estimated.

Figure 1-3. Estimated CDD/CDF I-TEQ Emissions to Air from Combustion Sources in the United States (Reference Time Period: 1987)

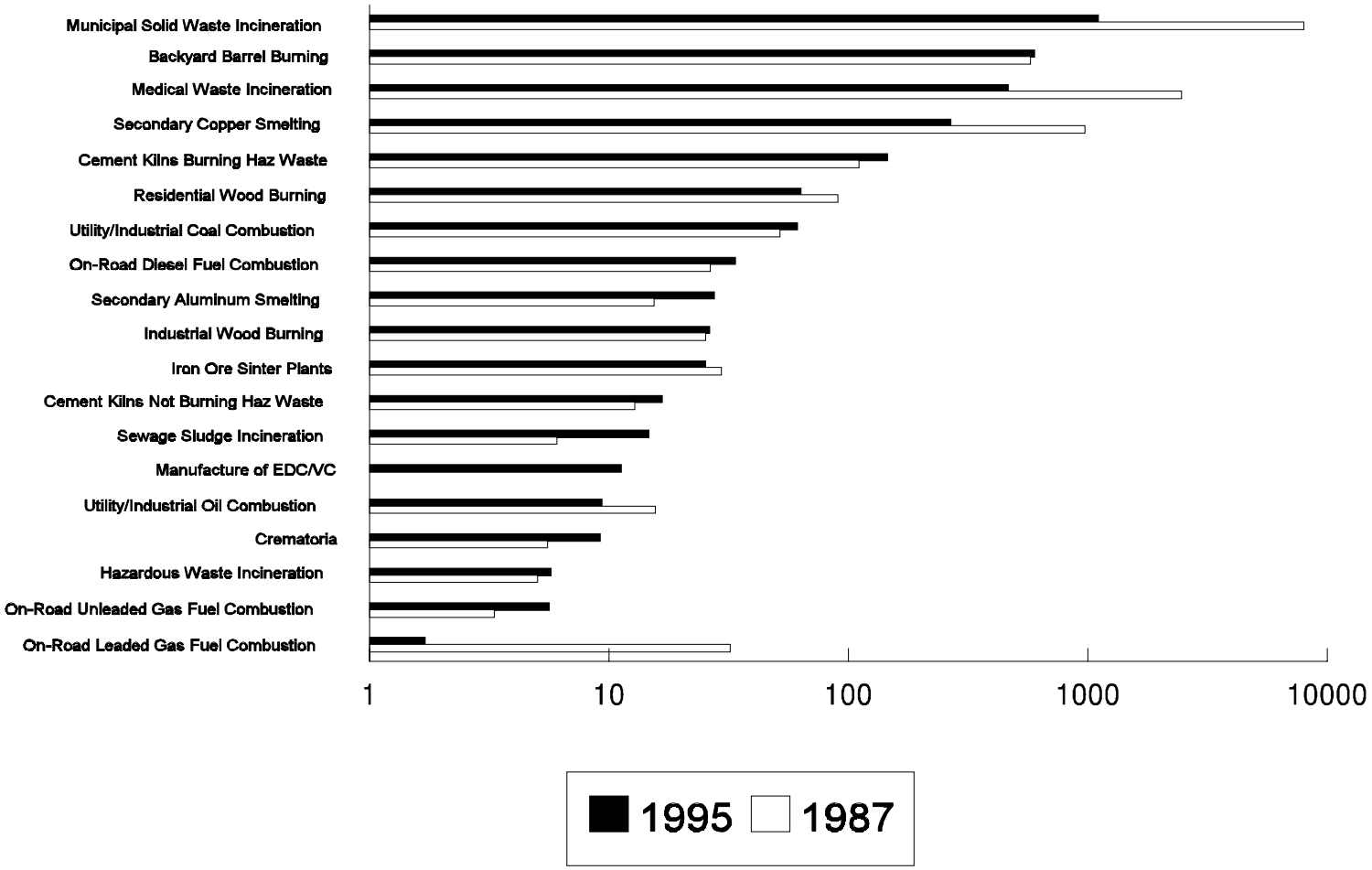
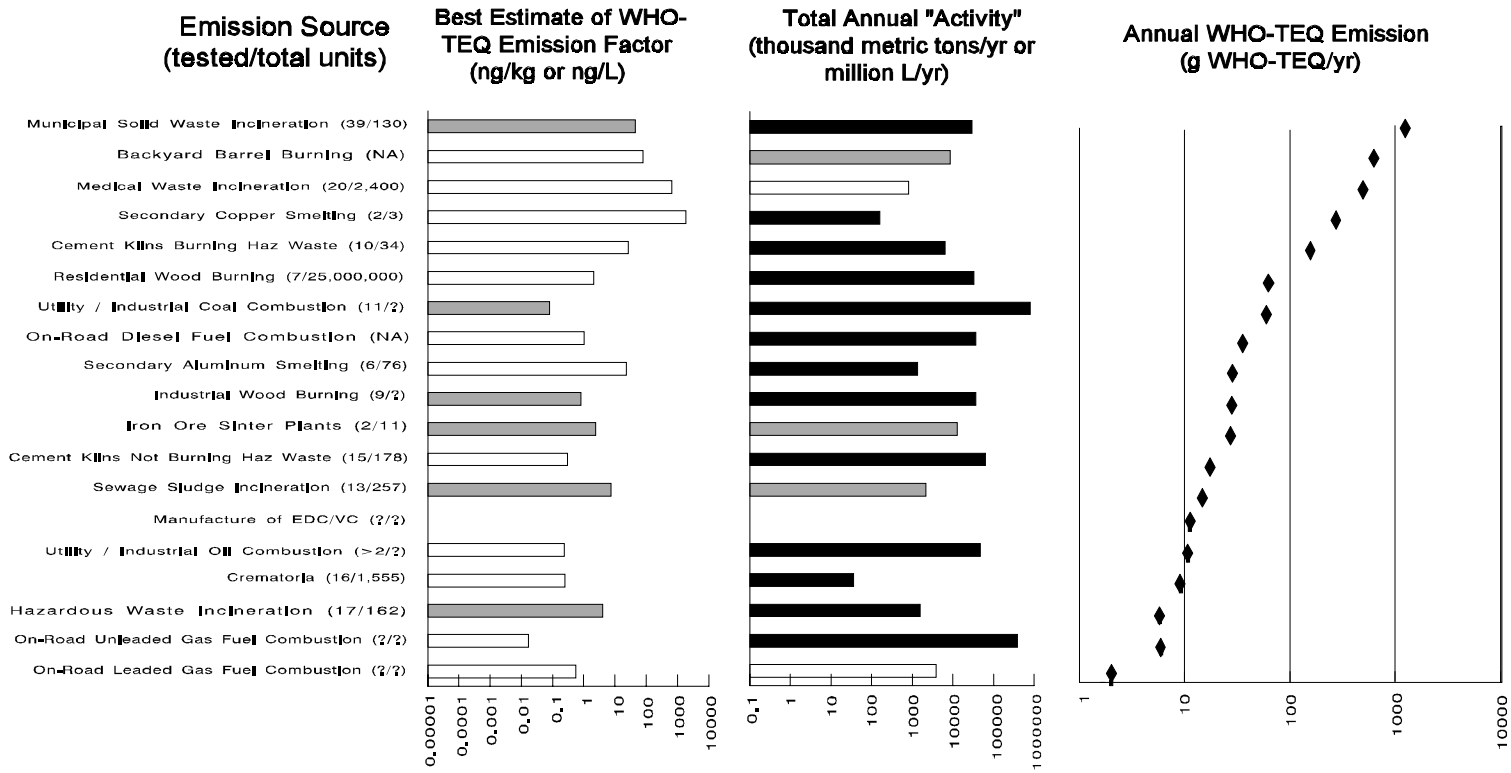
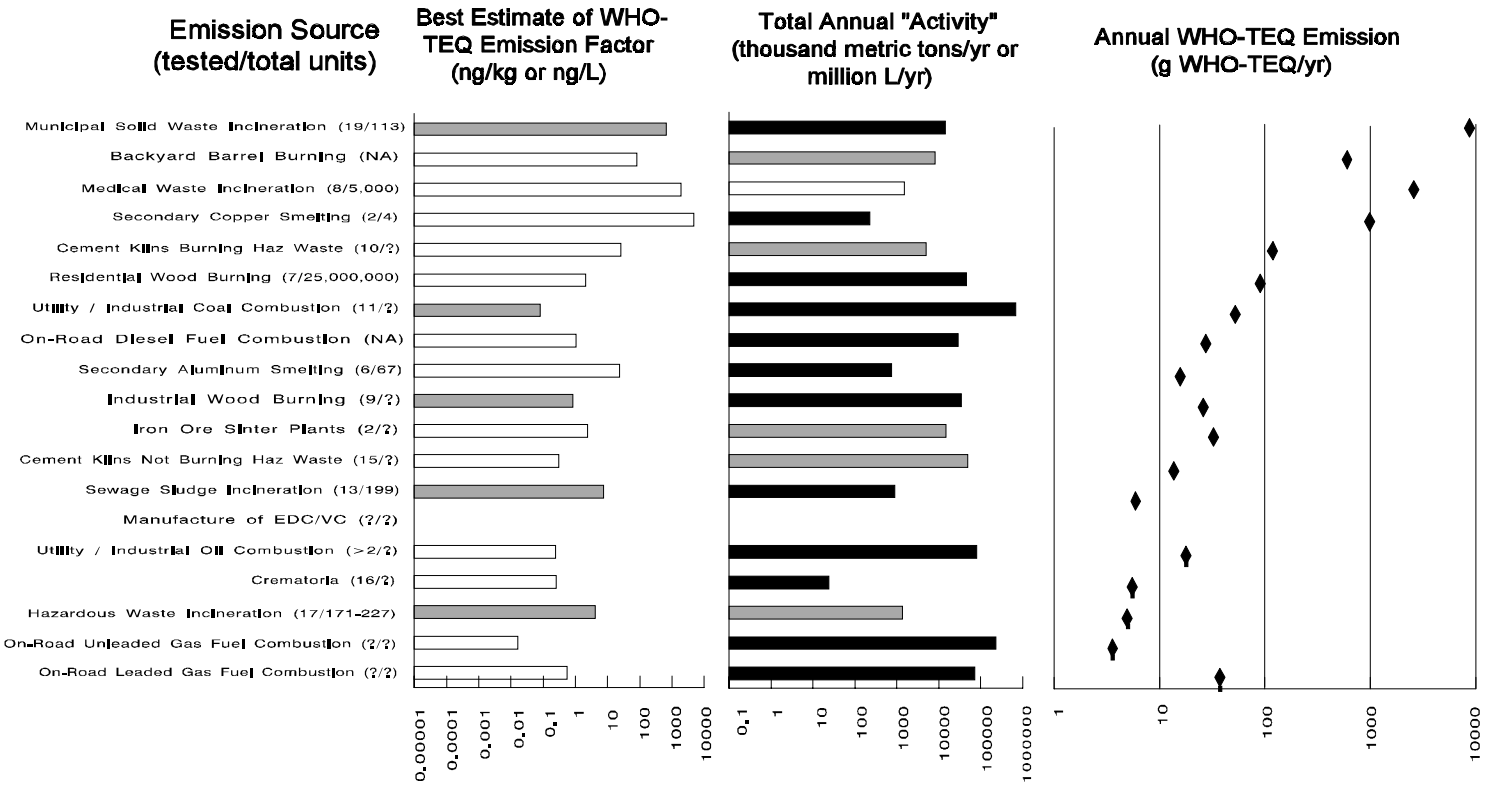


Figure 1-4. Comparison of Estimates of Annual I-TEQ Emissions to Air (grams I-TEQ/year) for Reference Years 1987 and 1995



The figures include sources with annual I-TEQ emission estimates greater than 5 g I-TEQ/yr in one or both of Reference Year 1995 and Reference Year 1987. Derivations of emission factors and annual "activity" estimates (e.g., kg of waste incinerated) are presented in the following chapters of this report. The difference in bar shading indicates the degree of confidence in the estimate. The set of numbers following the source categories indicates the number of facilities/sites for which emission test data are available versus the number of facilities/sites in the category. A question mark (?) indicates that the precise number of facilities/sites could not be estimated.

Figure 1-5. Estimated CDD/CDF WHO-TEQ Emissions to Air from Combustion Sources in the United States (Reference Time Period: 1995)



The figures include sources with annual I-TEQ emission estimates greater than 5 g I-TEQ/yr in one or both of Reference Year 1995 and Reference Year 1987. Derivations of emission factors and annual "activity" estimates (e.g., kg of waste incinerated) are presented in the following chapters of this report. The difference in bar shading indicates the degree of confidence in the estimate. The set of numbers following the source categories indicates the number of facilities/sites for which emission test data are available versus the number of facilities/sites in the category. A question mark (?) indicates that the precise number of facilities/sites could not be estimated.

Figure 1-6. Estimated CDD/CDF WHO-TEQ Emissions to Air From Combustion Sources in the United States (Reference Time Period: 1987)

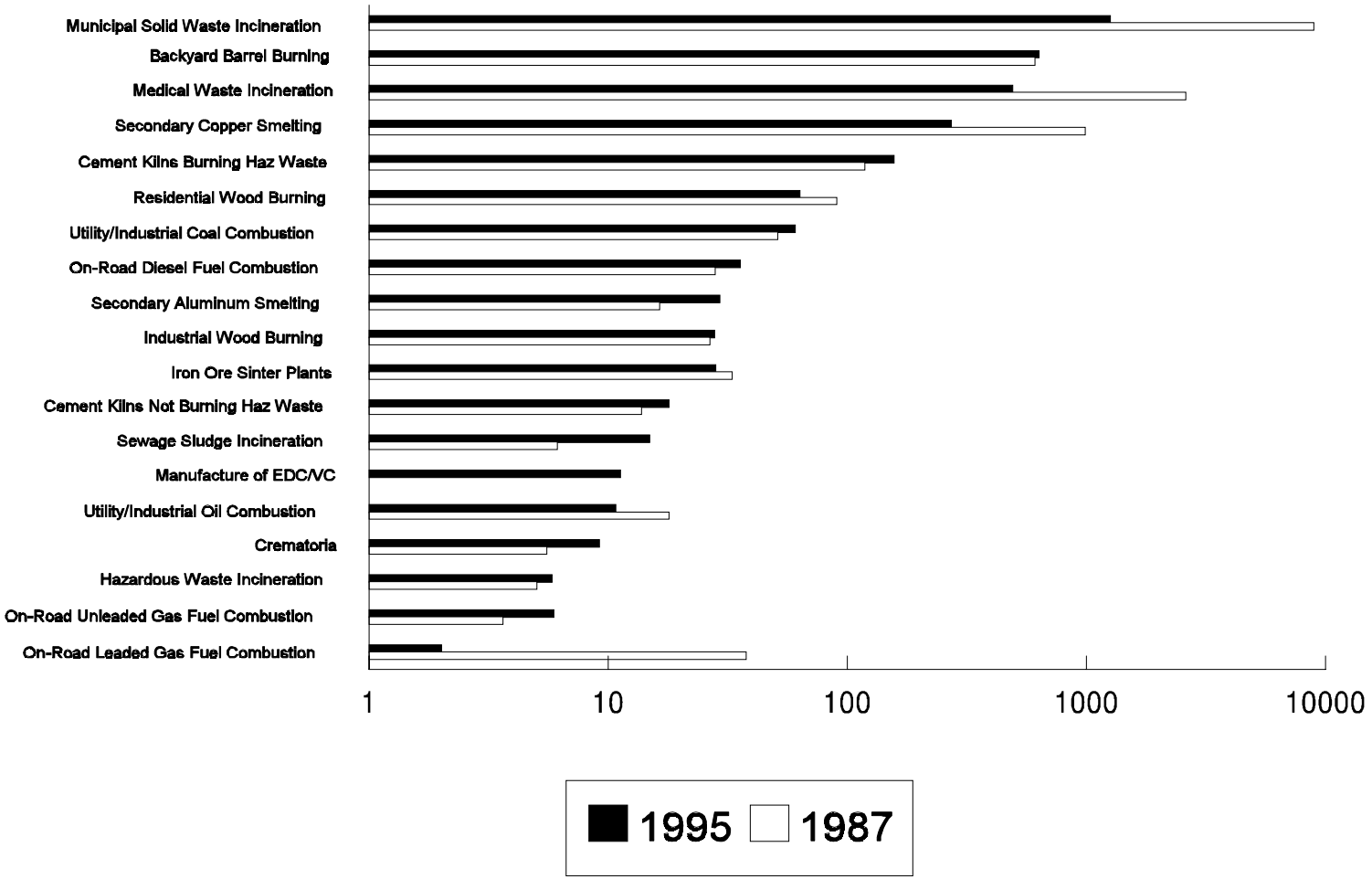
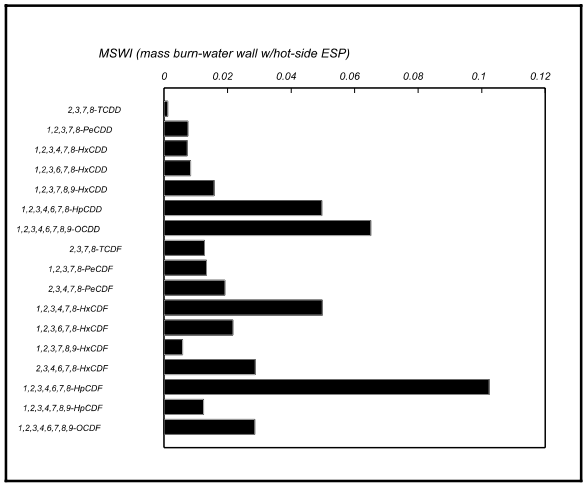
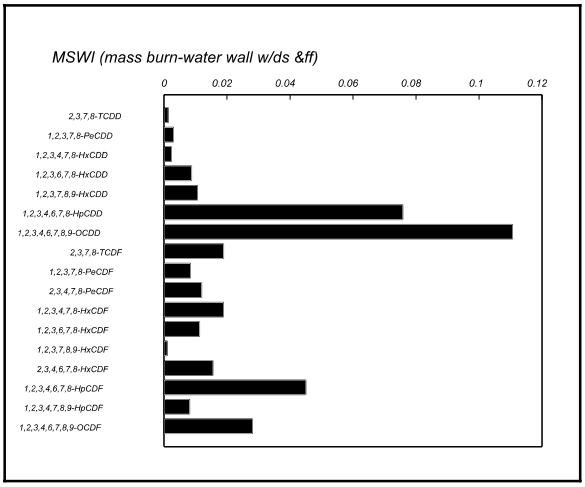
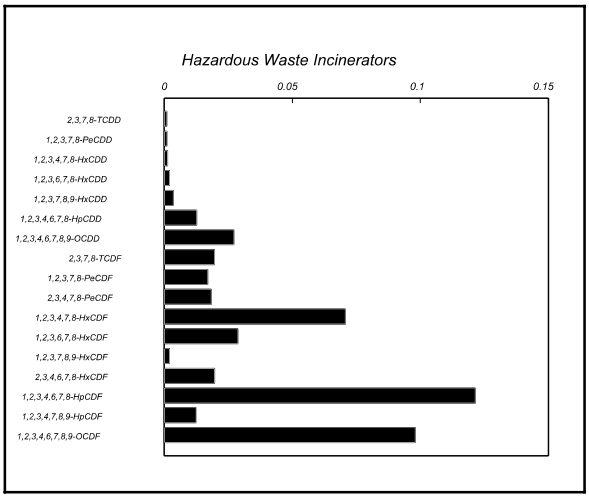


Figure 1-7. Comparison of Estimates of Annual WHO-TEQ Emissions to Air (grams WHO-TEQ/year) for Reference Years 1987 and 1995







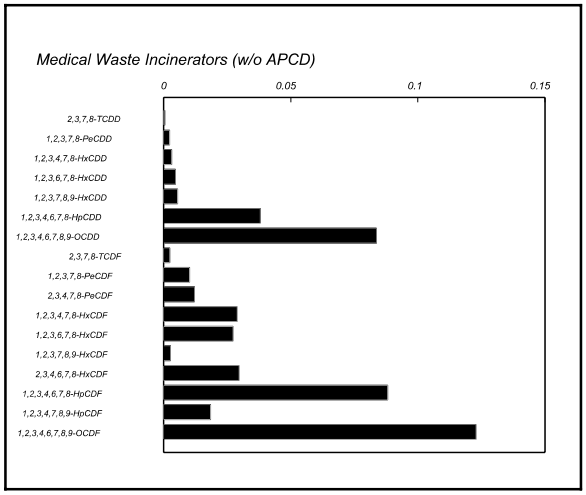
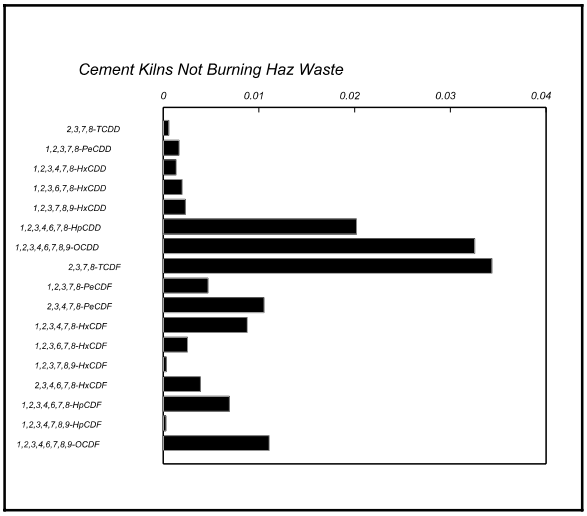
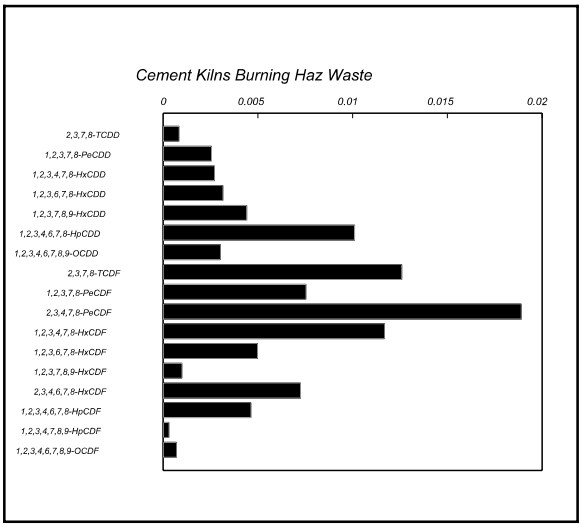
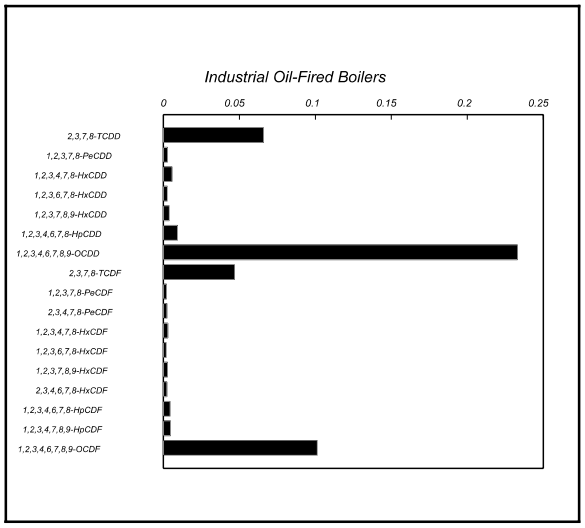


Figure 1-8. The Congener Profiles (as fractional distributions to total CDD/CDF) of Anthropogenic Sources of Chlorinated Dibenzo-p-Dioxins and Chlorinated Dibenzofurans in the United States







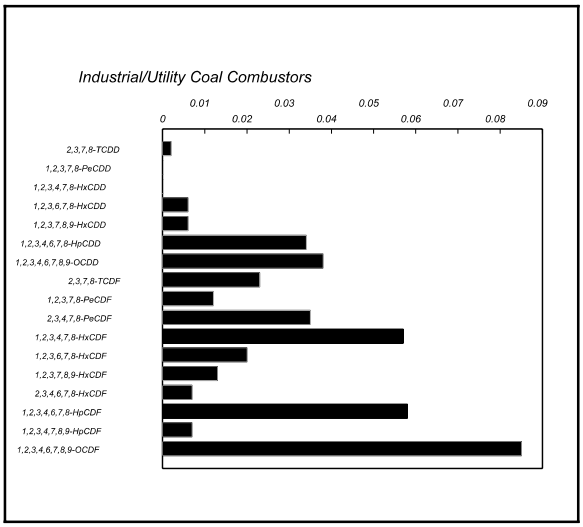


Figure 1-8. The Congener Profiles (as fractional distributions to total CDD/CDF) of Anthropogenic Sources of Chlorinated Dibenzo-p-Dioxins and Chlorinated Dibenzofurans in the United States (continued)

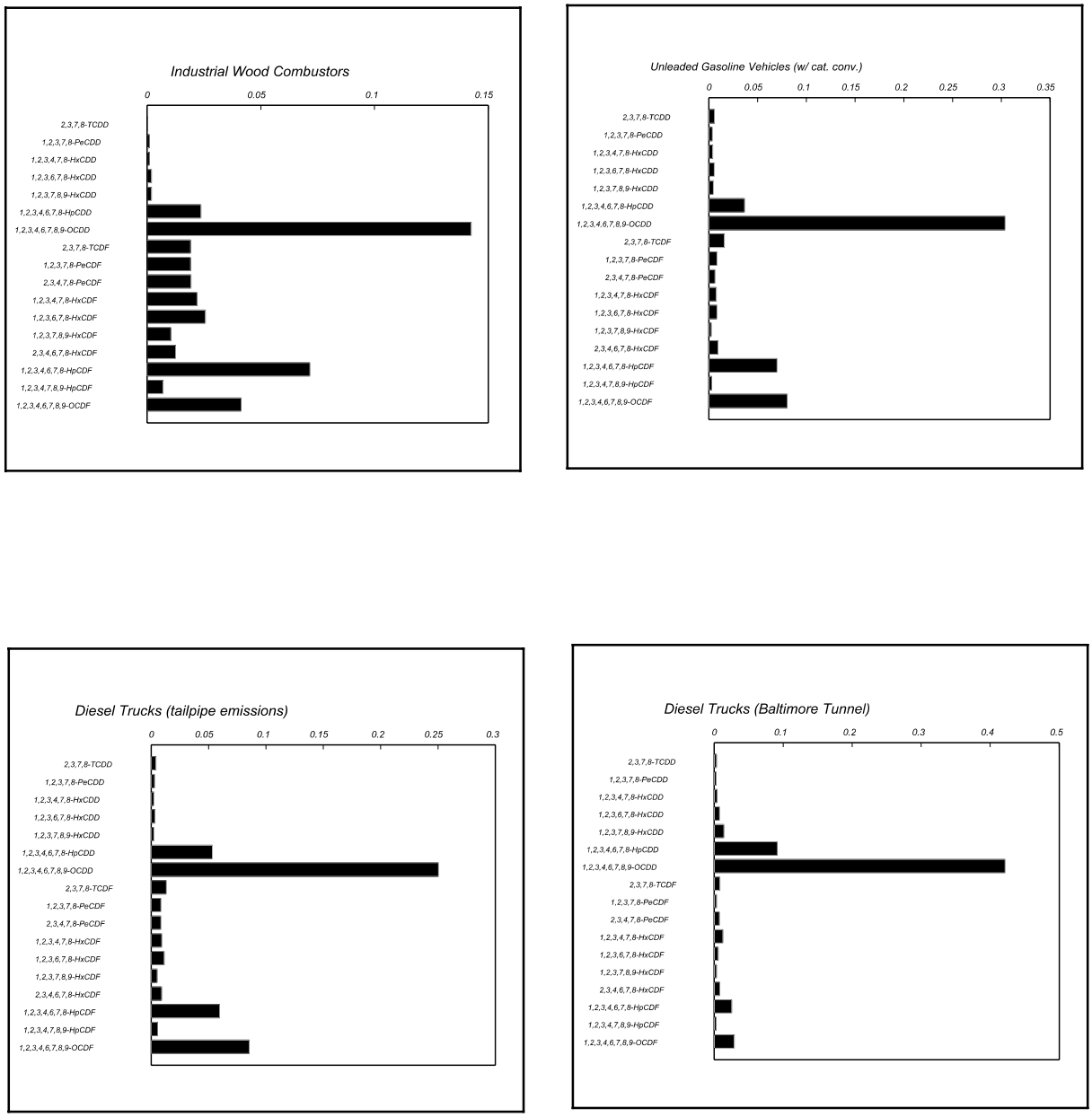


Figure 1-8. The Congener Profiles (as fractional distributions to total CDD/CDF) of Anthropogenic Sources of Chlorinated Dibenzo-p-Dioxins and Chlorinated Dibenzofurans in the United States (continued)

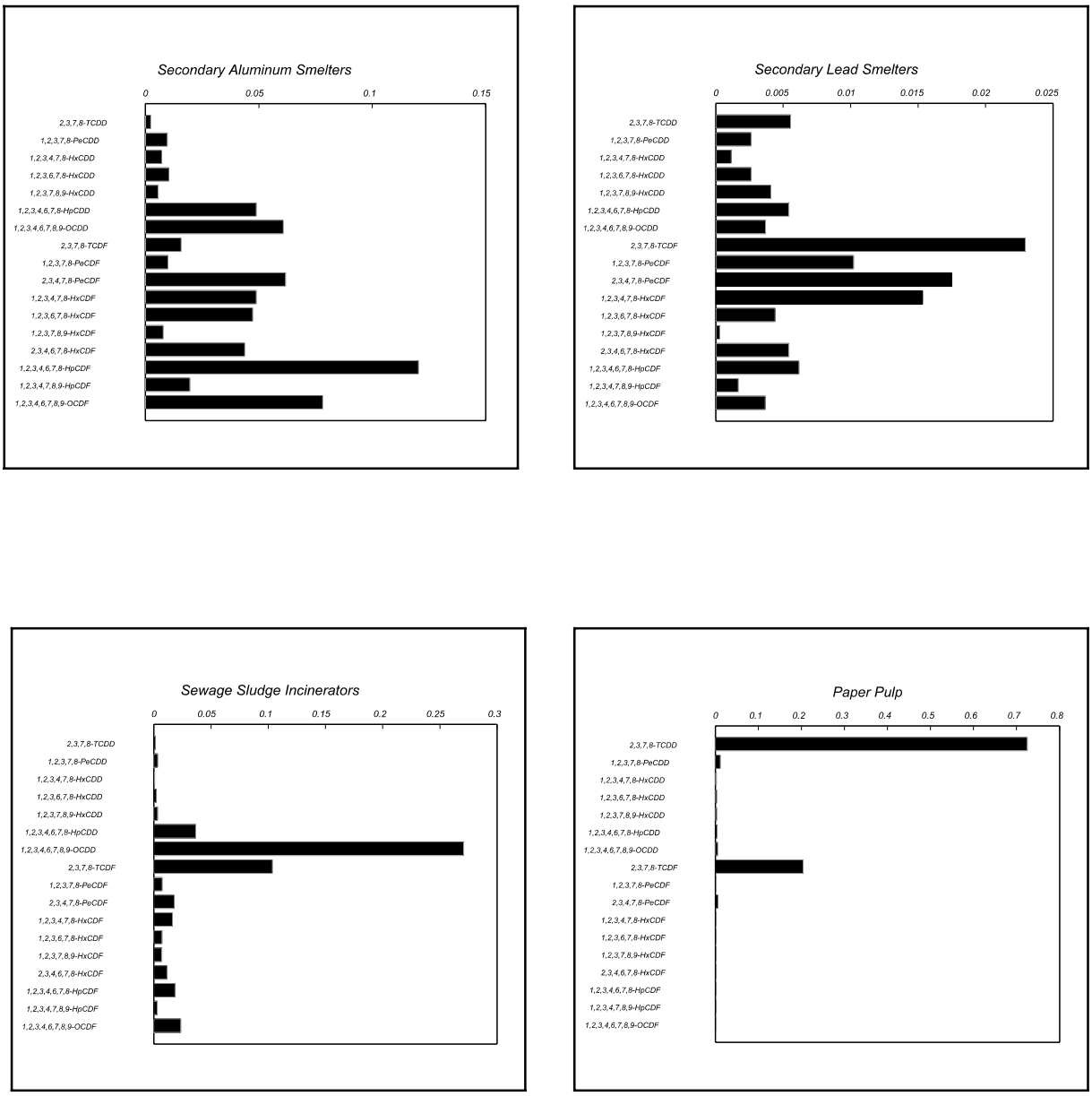
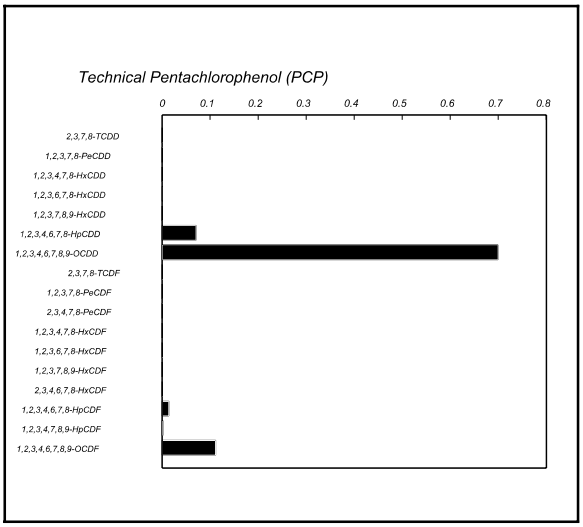


Figure 1-8. The Congener Profiles (as fractional distributions to total CDD/CDF) of Anthropogenic Sources of Chlorinated Dibenzo-p-Dioxins and Chlorinated Dibenzofurans in the United States (continued)



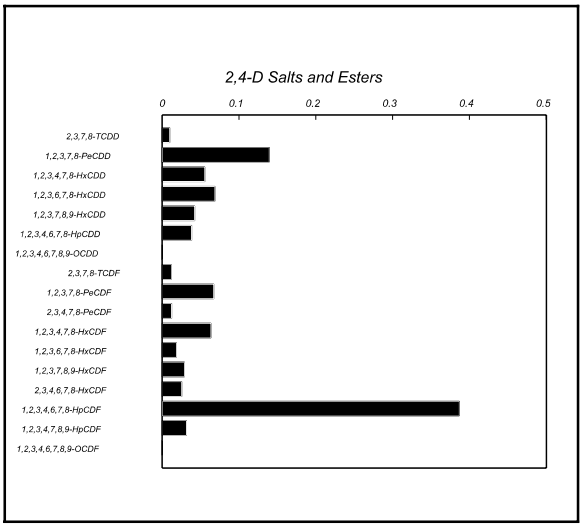


Figure 1-8. The Congener Profiles (as fractional distributions to total CDD/CDF) of Anthropogenic Sources of Chlorinated Dibenzo-p-Dioxins and Chlorinated Dibenzofurans in the United States (continued)

2.0. MECHANISMS OF FORMATION OF DIOXIN-LIKE COMPOUNDS DURING COMBUSTION OF ORGANIC MATERIALS

More than a decade of combustion research has contributed to a general understanding of the central molecular mechanisms that form CDDs and CDFs emitted from combustion sources. Current understanding of the conditions necessary to form CDDs and CDFs were primarily derived from studying full-scale municipal solid waste incinerators (MSWIs), augmented with observations involving the experimental combustion of synthetic fuels and feeds within the laboratory. However, the formation mechanisms elucidated from these studies are generally relevant to most combustion systems in which organic material is burned with chlorine. Intensive studies have examined MSWIs from the perspective of identifying the specific formation mechanism(s) that occur within the system. This knowledge may lead to methods that prevent the formation of CDDs and CDFs and their release into the environment. Although much has been learned from such studies, how to completely prevent CDDs/CDFs from forming during the combustion of certain organic materials in the presence of a source of chlorine and oxygen is still unknown. The wide variability of organic materials incinerated and thermally processed by a wide range of combustion technologies that have variable temperatures, residence times, and oxygen requirements adds to this complex problem. However, central chemical events that participate in forming CDDs and CDFs can be identified by evaluating emission test results from MSWIs in combination with laboratory experiments.

CDD/CDF emissions from combustion sources can potentially be explained by three principal mechanisms, which should not be regarded as being mutually exclusive. The first is that CDDs and CDFs are present as contaminants in the combusted organic material, and pass through the furnace and are emitted unaltered. This mechanism is discussed in Section 2.1. The second is that CDD/CDFs ultimately form from the thermal breakdown and molecular rearrangement of precursor ring compounds, which are defined as chlorinated aromatic hydrocarbons with a structural resemblance to the CDD and CDF molecules. Ringed precursors emanated from the combustion zone are a result of the incomplete oxidation of the constituents of the feed (i.e., products of incomplete combustion). The precursor mechanism is discussed in Section 2.2. The third mechanism, similar to the second and described in Section 2.3, is that CDD/CDFs are synthesized *de novo*. *De novo* synthesis describes a pathway of forming CDD/CDFs from

heterogeneous reactions on fly ash involving carbon, oxygen, hydrogen, chorine, and a transition metal catalyst. With these reactions, intermediate compounds having an aromatic ring structure are formed. Studies in this area suggest that aliphatic compounds, which arise as products of incomplete combustion, may play a critical role in initially forming simple ring molecules, which later evolve into complex aromatic precursors. CDD/CDFs are then formed from the intermediate compounds. In both mechanisms (2) and (3), formation occurs outside the furnace, in the so-called post-combustion zone. Particulate bound carbon is suggested as the primary reagent in the *de novo* syntheses pathway.

Section 2.4 gives an overview of studies that investigate the role that chlorine plays in forming CDDs and CDFs. Although chlorine is an essential component for the formation of CDD/CDFs in combustion systems, the empirical evidence indicates that for commercial scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of CDD/CDF stack emissions. There are complexities related to the combustion process itself, and types of air pollution control equipment that tend to mask any direct association. Therefore, the chlorine content of fuel and feeds to a combustion source is not a good indicator of levels of CDDs and CDFs emitted from the stack of the same source.

Section 2.5 discusses the generation and formation of coplanar PCBs. The presence of coplanar PCBs in stack emissions to combustors is an area in need of further research. Evidence to date suggests that PCB emissions are mostly attributed to PCB contamination in waste feeds, and that emissions are related to mechanism (1). However, newly published research has also indicated that it is possible to form PCBs in much the same way as described in mechanisms (2) and (3) identified in the formation of CDD/CDFs within the post-combustion zone.

Section 2.7 provides a closing summary of the three principal formation mechanisms and the role of chlorine. From the discussion in this chapter, it should be evident that no clear distinction exists between the precursor and de novo synthesis mechanisms for forming CDDs and CDFs. Both formation pathways depend on the evolution of precursors within combustion gases, the interaction of reactive fly ashes, a generally oxidative environment, the presence of a transition metal catalyst, the presence of gaseous chlorine, and a favorable range of temperature. Temperature of the

combustion gases (i.e., flue gases) is perhaps the single most important factor in forming dioxin-like compounds. Temperatures between 200° and 450° Celsius (C) are most conducive to forming CDD/CDFs, with maximum formation occurring at around 350°C. If temperature falls outside this range in temperature, the amount of CDD/CDFs formed is minimized.

2.1. MECHANISM 1: CDD/CDF CONTAMINATION IN FUEL AS A SOURCE OF COMBUSTION STACK EMISSIONS

The first mechanism involved in the stack emission of CDDs and CDFs is the incomplete destruction of CDD/CDF contaminants present in the fuel or feeds delivered to the combustion chamber. Not all of these molecules are destroyed by the combustion system, thus allowing trace amounts to be emitted from the stack. Most work in this area has involved the study of municipal solid waste incineration (MSWI), where CDDs and CDFs were analytically measured in the raw refuse fed into the incinerator.

As discussed in Volume 2 to this report, CDD/CDFs are ubiquitous in the environment (air, water, soil) and in foods and paper. Therefore, CDD/CDFs are clearly present in municipal waste. Tosine et al. (1983) first reported detecting trace amounts of HpCDD and OCDD in the MSW fed into an MSWI in Canada. HpCDD ranged in concentration from 100 ppt to 1 ppb, and OCDD ranged from 400 to 600 ppt. Wilken et al. (1992) separated the various solid waste fractions of MSW collected from municipalities in Germany and analyzed them for the presence of CDD/CDFs and other organochlorine compounds. Total CDD/CDFs were detected in all MSW fractions in the following range of concentrations: paper and cardboard = 3.1 to 45.5 ppb; plastics, wood, leather, and textiles combined = 9.5 to 109.2 ppb; vegetable matter = 0.9 to 16.9 ppb; and "fine debris" (defined as particles < 8 mm) = 0.8 to 83.8 ppb. Ozvacic (1985) measured CDD/CDFs in the raw MSW fed into two MSWIs operating in Canada. In one MSWI, CDDs were detected in the refuse; concentration ranged from 10 to 30 ppb, but no CDFs were detected (detection limit: 1 pg/g). In the MSW fed to the second MSWI, CDDs were detected in a range of 75 to 439 ppb, and CDFs were detected only in one of three samples at a total concentration of 11 ppb. EPA has reported detecting CDD/CDFs in refuse derived fuel (RDF) burned in a large urban MSWI (Federal Register, 1991a). CDDs were detected in 13 MSW samples taken prior to incineration at

concentrations ranging from 1 to 13 ppb; CDFs ranged from not detected to 0.6 ppb. In these samples, OCDD predominated; the lower chlorinated congeners were not detected. Clement et al. (1988) performed a mass balance involving an input versus output of CDD/CDFs at two operational MSWIs in Canada. The mass balance showed that the mass of CDDs and CDFs emitted at the stack point was much greater than the mass of CDD/CDFs in the raw MSW fed into the incinerator, and that the profiles of the distributions of CDD/CDF congeners were strikingly different. Primarily, higher chlorinated congeners were detected as contaminants in the waste; whereas, the total array of tetra - octa CDD/CDFs could be detected in the stack gases.

CDDs/CDFs present in the waste feeds may account for some fraction of the CDD/CDFs released from the stack. However, mass balance studies have clearly shown that more CDD/CDF can be detected downstream of the furnace than what is detected in the feed, indicating that CDD/CDFs are being synthesized after the feed has been combusted (Commoner et al., 1984, 1985, 1987; Clement et al., 1988; Hay et al., 1986; Environment Canada, 1985). Moreover, it is expected that the conditions of thermal stress imposed by high temperatures reached in typical combustion would destroy and reduce the CDDs and CDFs present as contaminants in the waste feed to levels that are 0.0001 to 10 percent of the initial concentration, depending on the performance of the combustion source and the level of combustion efficiency. Stehl et al. (1973) demonstrated that the moderate temperature of 800°C enhances the decomposition of CDDs at a rate of about 99.95 percent, but that lower temperatures result in a higher survival rate. Theoretical modeling has shown that unimolecular destruction of CDDs/CDFs at 99.99 percent can occur at the following temperatures and retention times within the combustion zone: 977°C with a retention time of 1 second; 1,000°C at a retention time of ½ second; 1,227°C at a retention time of 4 milliseconds; and 1,727°C at a retention time of 5 microseconds (Schaub and Tsang, 1983). Thus, CDDs and CDFs would have to be in parts per million concentration in the feed to the combustor to be found in the part per billion or part per trillion level in the stack gas emission (Shaub and Tsang, 1983). However, it cannot be ruled out is that CDDs/CDFs in the waste or fuel may contribute (up to some percentage) to the overall concentration leaving the stack. This leaves the only other possible explanation for CDD/CDF emissions from high temperature combustion of organic material, formation outside and downstream of the

furnace. These studies point to formation mechanisms other than simple pass through of non-combusted feed contamination. These formation mechanisms are discussed and reviewed in the sections which follow.

2.2. MECHANISM 2: FORMATION OF CDD/CDFs FROM PRECURSOR COMPOUNDS

The second mechanism involves the formation of CDDs and CDFs from aromatic precursor compounds in the presence of a chlorine donor. This mechanism has been elucidated from laboratory experiments involving the combustion of known precursors in quartz ampules under starved-air conditions, and in experiments that investigate the role of combustion fly ash in promoting the formation of CDD/CDFs from precursor compounds. The general reaction in this formation pathway is an interaction between an aromatic precursor compound and chlorine promoted by a transition metal catalyst on a reactive fly ash surface (Dickson and Karasek, 1987; Liberti and Brocco, 1982). Examples of well studied precursor compounds include chorobenzenes, chlorophenols, phenol, and benzene (Esposito et al., 1980). Examples of diverse chlorine donor compounds are polyvinyl chloride (PVC), and gaseous hydrogen chloride (HCl). CDD and CDF formation results from heterogeneous gas-phase reactions involving chlorinated precursor compounds and a source of chlorine. Chlorophenol and chlorobenzene compounds are measured in flue gases from MSWIs (Dickson and Karasek, 1987). Precursors are carried from the furnace to the flue duct as products of incomplete combustion. These compounds can adsorb on the surface of combustion fly ash, or entrain in the gas phase within the flue gases. In the post-combustion region outside the furnace, heterogeneous reactions ensue to form CDD/CDFs. Laboratory experiments involving the controlled combustion of precursor compounds have caused the breakdown of the precursor reagent and the subsequent appearance of CDD/CDFs as products of the reaction. For example, Jansson et al. (1977) produced CDDs through the pyrolysis of wood chips treated with tri-, tetra-, and pentachlorophenol in a bench-scale furnace operated at 500-600°C. Stehl and Lamparski (1977) combusted grass and paper treated with the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) in a bench-scale furnace at 600-800°C and generated ppm_v levels of TCDD. Ahling and Lindskog (1982) reported CDD formation during the combustion of tri- and tetrachlorophenol formulations at temperatures of 500-600°C. Decreases in oxygen during combustion generally increased the CDD yield.

Ahling and Lindskog (1982) noted that adding copper salts to the tetrachlorophenol formulation significantly enhanced the yield of CDDs. This may have been an early indication of copper's role in catalyzing the condensation of chlorophenol to dioxin. Combustion of pentachlorophenol (PCP) resulted in low yields of CDDs. However, when PCP was burned with an insufficient supply of oxygen, investigators noted the formation of tetra- through octa-chlorinated congeners. Buser (1979) generated CDD/CDFs on the order of 0.001-0.08 percent (by weight) by heating tri-, tetra-, and pentachlorobenzenes at 620°C in quartz ampules in the presence of oxygen. It was noted that chlorophenols formed as combustion byproducts; Buser (1979) speculated that these were acting as reaction intermediates in the formation of CDD/CDFs.

Temperature of the combustion gases is, perhaps, the most dominant factor in the formation of CDDs and CDFs from aromatic precursor compounds (Fangmark et al., 1994; Vogg et al., 1987, 1992; Oberg et al.,1989; Weber and Hagenmaier, 1999). Vogg et al. (1987) found that formation probably occurs outside and downstream from the combustion zone of a furnace to a combustion source in regions where the temperature of the combustion offgases has cooled within a range of 200° to 450°C.

After carefully removing organic contaminants from MSWI fly ash, Vogg et al. (1987) added known concentrations of isotopically labeled CDD/CDFs to the matrix. The MSWI fly ash was then heated for 2 hours in a laboratory furnace at varying temperatures. The treated fly ash was exposed to increasing temperatures in 50°C increments in a temperature range of 150^0 to 500°C. Table 2-1 summarizes these data. Because the relative concentration of CDD/CDFs increased while exposed to varying temperature, it was concluded that the temperature of the combustion gas is crucial to promoting the formation of CDD/CDFs on the surface of fly ash. Within a temperature range of 200° to 450°C, the concentration of CDD/CDFs increases to some maxima; outside this range, the concentration diminishes.

The region of cooler gas temperature is often referred to as the "post-combustion zone." The heat loss may be inherent to the conduction and transfer through the combustion gas metal ducting system, or related to adsorbing/exchanging heat to water in boiler tubes. This region extends from near the exit of the furnace to the point of release of the combustion gases at stack tip.

Fangmark et al. (1994) found that CDD/CDFs exhibit a similar dependence on temperature and residence times between 260° and 430°C, with maximum formation occurring around 340°C. Using a pilot-scale combustor, Behrooz and Altwicker (1996) found the formation of CDD/CDFs from the precursor 1,2-dichlorobenzene rapidly occurred within the post-combustion region in a temperature range of 390° to 400°C, with residence times of only 4-5 seconds. On the other hand, CDD/CDF formation from 1,2-dichlorophenol seemed to require higher temperatures; still outside the furnace, but likely in the exit to the furnace where gas temperatures are >400°C.

Oberg et al. (1989) investigated the role that temperature plays in the formation kinetics using a full-scale hazardous waste incinerator operating in Sweden. Oberg et al. (1989) observed that maximum CDD/CDF formation transpired in the boiler used to extract heat for co-generation of energy. In this investigation, significant increases in total concentration of I-TEQ_{DF} occurred between temperatures of 280° to 400°C, and concentrations declined at temperatures above 400°C. Weber and Hagenmaier (1999) showed that in gas phase reactions chlorophenols react in the presence of oxygen at above 340°C to form CDDs and CDFs. Phenoxyradicals were formed which, in turn, caused the formation of CDDs. Polychlorinated dihydroxybiphenyls were identified as reaction intermediates in the gas phase dimerization of chlorophenols, and these intermediates could form PCDFs.

Other conditions postulated to regulate the synthesis of CDDs and CDFs from the aromatic precursor compound are adsorption and interaction with the reactive surface of combustion generated fly ash (particulate matter) entrained in the combustion plasma, and the presence of a transition metal catalyst (Vogg et al., 1987; Bruce et al., 1991; Cleverly et al., 1991; Gullet et al., 1990a; Commoner et al., 1987; Dickson and Karasek, 1987; Dickson et al., 1992). The molecular precursor leaves the gas-phase and condenses to the fly ash particle. This places greater emphasis on heterogeneous surface reactions and less emphasis on homogeneous gas-phase reactions. This condition was first postulated by Shaub and Tsang (1983) using thermal-kinetic models based on heats of formation, adsorption, and desorption. Shaub and Tsang (1983) modeled CDD production from chlorophenols and concluded that gas-phase formation within an incineration system is likely to be of low probability and importance given the short (i.e., seconds) residence time of the combustion gases. Konduri and Altwicker (1994) proposed that rate limiting

factors were the nature and the concentrations of the precursors, the reactivity and availability of the fly ash surface, and the residence time in the post-combustion zone. Dickson and Karasek (1987) investigated fly ash reactivity with $^{13}C_6$-chlorophenol compounds. Several fly ashes from a variety of combustion fuels were heated at 300°C in quartz tubes under conditions known to catalyze the conversion of chlorophenols to CDD/CDFs (i.e., MSWI, and copper smelter fly ashes). The MSW ashes included a sample from a poorly-operated mass burn refractory incinerator and a sample from a well-operated fluidized bed combustor. The MSWI fly ashes proved to be the most active catalytic medium, despite similarities with respect to specific surface area and average pore diameters. The ash from the refractory MSWI generated about seven times more mass of dioxin-like compounds than the fluidized-bed MSW incinerator. In the MSW ashes, all CDD/CDF congener groups were formed from labeled chlorophenols; however, only trace amounts of heptachloro- and octachlorodioxin were formed with the copper smelter/refiner. X-ray photoelectron spectroscopy revealed the presence of chlorine adsorbed to the surface of the MSWI fly ashes, but an absence of chlorine sorbed to the copper smelter fly ash.

CDD congener groups were postulated to form from the labeled pentachlorophenol precursors by: (1) first forming octachlorodioxin by the condensation of two pentachlorophenol molecules, and (2) forming other lower chlorinated dioxins through dechlorination of the more highly chlorinated isomers. These steps seemed to proceed by an increased reactivity of the chemisorbed precursor molecule caused by the removal of one or more hydrogen or chlorine atoms along the ring structure (Dickson and Karasek, 1987), an observation consistent with the kinetic model of Shaub and Tsang (1983). In related experiments, Dickson and Karasek (1987) more specifically reported on forming CDD/CDFs from condensation reactions of chlorophenols on the surface of MSWI fly ash heated in a bench-scale furnace. Their experiment was designed to mimic conditions of MSW incineration, to identify the step-wise chemical reactions involved in converting a precursor compound into dioxin, and to determine if MSWI fly ash could promote these reactions. MSWI fly ash was obtained from facilities in Canada and Japan. The MSWI fly ash was rinsed with solvent to remove any organic constituents prior to initiating the experiment. Twenty grams of fly ash were introduced into a bench-scale oven (consisting of a simple flow-tube combustion apparatus) and heated at 340°C overnight to desorb

any remaining organic compounds from the matrix. $^{13}C_{12}$ -labeled pentachlorophenol (PCP) and two trichlorophenol isotopes ($^{13}C_{12}$- 2,3,5-Trichlorophenol and 3,4,5-Trichlorophenol) were added to the surface of the clean fly ash matrix and placed into the oven for 1 hour at 300°C. Pure inert nitrogen gas (flow rate of 10 mL/min) was passed through the flow tube to maintain constant temperatures. Tetra- through octa- CDDs were formed from the labeled pentachlorophenol experiment; over 100 μg/g of total CDDs were produced. The congener pattern was similar to that found in MSWI emissions. The 2,3,5-Trichlorophenol experiment primarily produced HxCDDs and very small amounts of tetra- and octa-CDD. The 3,4,5-Trichlorophenol experiment mainly produced OCDD and 1,2,3,4,6,7,8-HpCDD. Dickson and Karasek (1987) proposed that CDDs on the fly ash surface may result from chlorophenol undergoing molecular rearrangement or isomerization as a result of dechlorination, dehydrogenation, and trans-chlorination before condensation occurs. These reactions were proposed as controlling the types and amounts of CDDs that are ultimately formed. Born et al. (1993) conducted experiments on the oxidation of chlorophenols with fly ash in a quartz tube reactor heated to about 300°C. The MSWI fly ash mediated the oxidation of chlorophenols to produce carbon dioxide and carbon monoxide as major products, and polychlorinated benzenes, monobenzofurans, and nonhalogenated dibenzo-p-dioxins as trace species. Formation of these trace aromatic species occurred after residence times of only 7 - 8 seconds which was consistent with the later experimental result of Behrooz and Altwicker (1995) which showed the potential for rapid formation from a precursor. Milligan and Altwicker (1996) fitted experimental flow-tube reactor data to classical catalytic reaction models to empirically explain the interaction of 2,3,4,6-tetrachlorophenol (as a model precursor) with reactive MSWI fly ash during MSW incineration. The precursor was found to be highly adsorptive on fly ash, with a first-order dependence on gas-phase precursor concentration to CDD formation. Milligan and Altwicker (1996) concluded that chlorophenol's dependence on gas-phase concentration to form CDD on fly ash reflects the highly heterogeneous nature of the fly ash surface. Moreover the estimated 6 x 10^{18} adsorption sites per gram of fly ash suggest the presence of highly energetic sites, which may be important in the surface-catalyzed reactions forming CDDs. An interesting observation of Milligan and Altwicker (1996) was that precursor molecules appeared to compete with oxygen molecules for the reactive sites; therefore, chlorophenols are expected to adsorb less readily to the fly ash

surface in the presence of oxygen. Experimental evidence suggests that condensation to CDD of chlorophenol compounds via isomerization and the Smiles rearrangement on reactive MSWI fly ash surfaces is a proven pathway for forming dioxins from a precursor compound (Addink and Olie, 1995). However, no detailed mechanisms have been presented for CDD/CDF formation from other precursors, such as chlorobenzenes under conditions simulating incineration.

A condition to the synthesis of CDD/CDFs from aromatic precursor compounds is that the presence of a transition metal catalyst promotes the chemical reaction on the surface of fly ash. Copper chloride is a strong catalyst for promoting surface reactions on particulate matter to convert aromatic precursor compounds to chlorinated dioxins and dibenzofurans (Vogg et al., 1987). Copper chloride promotes ring condensation reactions (e.g., chorophenols) on fly ash to form CDD/CDFs (Addink and Olie, 1995) via the Ullman reaction (Born et al., 1993). In the Ullman reaction, copper catalyzes the formation of diphenyl ethers by the reaction of halogenated benzenes with alkali metal phenolates (Born et al., 1993), with copper participating in a nucleophilic aromatic substitution reaction. Thus, Born et al. (1993) proposes a similar mechanism in catalyzing the formation of dioxin-like compounds. Using the Ullman reaction as a model, Born et al. (1993) proposed that the copper-catalyzed condensation of two ortho-substituted chlorophenol molecules form chlorine-free dibenzo-p-dioxins. Vogg et al. (1987) proposed an oxidation reaction pathway, giving rise to the formation of CDDs and CDFs in the post-furnace regions of the incinerator in the following order: (1) hydrogen chloride gas (HCl) is thermolytically derived as a product of the combustion of heterogeneous fuels containing abundant chlorinated organic chemicals and chlorides; (2) oxidation of HCl, with copper chloride ($CuCl_2$) as a catalyst, yields free gaseous chlorine via the Deacon reaction; (3) phenolic compounds (present from combustion of lignin in the waste or other sources) entrained in the combustion plasma are substituted on the ring structure by contact with the free chlorine; and (4) the chlorinated precursor to dioxin (e.g., chlorophenol) is further oxidized (with copper chloride as a catalyst) to yield CDDs and CDFs and chlorine.

Gullett et al. (1990a; 1990b; 1991a; 1991b; 1992) studied the formation mechanisms through extensive combustion research at EPA, and verified the observations of Vogg et al. (1987). It was proven that CDDs and CDFs could be ultimately produced from low temperature reactions (i.e., 350°C) between Cl_2 and a phenolic precursor,

combining to form a chlorinated precursor, followed by oxidation of the chlorinated precursors (catalyzed by a copper catalyst such as copper chloride) as in examples (1) and (2), below.

(1) The initial step in forming dioxin is the formation of chlorine from HCl in the presence of oxygen (the Deacon process), as follows (Vogg et al., 1987; Bruce et al., 1991):

$$2HCl + \tfrac{1}{2} O_2 \xrightarrow{\Delta} H_2O + Cl_2$$

(2) Phenolic compounds adsorbed on the fly ash surface are chlorinated to form the dioxin precursor, and the dioxin is formed as a product from the breakdown and molecular rearrangement of the precursor. The reaction is promoted by copper chloride acting as a catalyst (Vogg et al., 1987; Dickson and Karasek, 1987; Gullett et al., 1992):

(a) phenol + Cl_2 ———> chlorophenol (dioxin precursor)

(b) 2-chlorophenol + $\tfrac{1}{2} O_2 \xrightarrow{CuCl_2}$ dioxin + Cl_2

On the other hand, Eklund et al. (1986) observed the high temperature formation of a large variety of chlorinated toxic compounds, including CDDs and CDFs, from precursors during a simple experiment in which phenol was oxidized with HCl at 550°C. One milligram of phenol was placed in a quartz tube reactor with an aqueous solution (10μL) of HCl and heated at 550°C for 5 minutes. Trichlorobenzene, dichlorophenol, dichlorobenzofuran, tetrachlorobenzene, trichlorophenol, and tetrachlorophenol were identified as major products formed. Monochlorobenzene, chlorophenol, dichlorobenzene, tetrachloropropene, pentachloropropene, trichlorobenzofuran, tetrachlorodibenzofuran, trichlorodibenzodioxin, tetrachlorodibenzodioxin, hexachlorodibenzodioxin, hexachlorodibenzofuran, pentachlorobenzene, pentachlorobiphenyl, and pentachlorodihydroxycylohexane were seen as minor products. Trace species formed included: monochlorodibenzofuran, pentachlorodibenzofuran, pentachlorodibenzodioxin, octachlorodibenzofuran, and octachlorodibenzodioxin. Eklund et al. (1986) hypothesized

that chlorinated organic compounds can be produced from phenols, acids, and any chlorine source in the hot post-combustion region (e.g., just exit to the furnace). The reaction was seen as very sensitive to HCl concentration. At HCl $< 10^{-3}$ moles, no chlorinated compounds could be detected. Nestrick et al. (1987) reported that the thermolytic reaction between benzene (an unsubstituted precursor) and iron (III) chloride on a silicate surface yielded CDD/CDFs at temperatures $\geq$150°C. The experimental protocol introduced 100 - 700 mg of native and $^{13}C_6$-benzene into a macro-reactor system, consisting of a benzene volatilization chamber connected to a glass tube furnace. The investigators noted the relevance of this experiment to generalizations about combustion processes because benzene is the usual combustion byproduct of organic fuels. Inert nitrogen gas carried the benzene vapor to the furnace area. The exit from the glass tubing to the furnace was plugged with glass wool, and silica gel was introduced from the entrance end to give a bed depth of 7 cm to which the $FeCl_3$ was added to form a $FeCl_3$/silica reagent. The thermolytic reaction took place in a temperature ranging from 150-400°C, at a residence time of 20 minutes. Although di- through octa-CDD/CDF were formed by this reaction at all the temperatures studied, the percent yields were extremely small. Table 2-2 summarizes these data.

2.3. MECHANISM 3: THE *DE NOVO* SYNTHESIS OF CDDS/CDFS DURING COMBUSTION OF ORGANIC MATERIALS

The third and last mechanism, *de novo* synthesis, promotes CDD/CDF formation in combustion processes from the oxidation of carbon particulate catalyzed by a transition metal in the presence of chlorine. As in mechanism 2, synthesis is believed to occur in regions outside of the furnace zone of the combustion process, where the combustion gases have cooled to a range of temperatures considered favorable to formation chemistry. A key component to *de novo* synthesis is the production of intermediate compounds (either halogenated or nonhalogenated) that are precursors to CDD/CDF formation. Research in this area has produced CDD/CDFs directly by heating carbonaceous fly ash in the presence of a transition metal catalyst, without the apparent generation of reactive intermediates. Thus, the specific steps involved in the *de novo* process have not been fully and succinctly delineated. However, laboratory experimentation has proven that MSWI fly ash, itself, is a reactive substrate, and the

matrix can actually catalyze the *de novo* formation chemistry. Typically, fly ash is composed of an alumina-silicate construct, with 5-10 percent concentrations of silicon, chlorine (as inorganic chlorides), sulfur, and potassium (NATO, 1988). Twenty percent of the weight of fly ash particles are carbon, and the particles have specific surface areas in the range of 2-4 m^2 (NATO, 1988). The *de novo* synthesis essentially is the oxidative breakdown of macromolecular carbon structures, and CDD/CDFs are formed partially from the aromatic carbon-oxygen functional groups embedded in the carbon skeleton (Huang et al., 1999). The distinguishing feature of the *de novo* synthesis over the precursor synthesis is the oxidation of carbon in particulate at the start of the process to yield precursor compounds. In mechanism 2, the precursor compound is the starting molecule to the condensation reactions forming CDD/CDFs (Dickson et al., 1992). By this distinction, however, one could argue that mechanism 3 is really an augmentation to mechanism 2, because the production of CDD/CDFs may still require the formation of a CDD/CDF precursor as an intermediate species. Nevertheless, a distinction is presented here to describe additional pathways suggested for the thermal formation of these compounds.

To delineate the *de novo* synthesis of CDD/CDFs, Stieglitz et al. (1989a) conducted experiments that involved heating particulate carbon containing adsorbed mixtures of Mg-Al silicate in the presence of copper chloride (as a catalyst to the reaction). The authors described heating mixtures of Mg-Al silicate with activated charcoal (4 percent by weight), chloride as potassium chloride (7 percent by weight), and 1 percent copper chloride ($CuCl_2$) (in water) in a quartz flow tube reactor at 300°C. The retention time was varied at 15 minutes, 30 minutes, and 1, 2, and 4 hours to obtain differences in the amounts of CDD/CDFs that could be formed. The results are summarized in Table 2-3. In addition to the CDD/CDFs formed as primary products of the *de novo* synthesis, the investigators observed precursors formed at the varying retention times during the experiment. In particular, similar yields of tri- though hexa-chlorobenzenes, tri- through hepta-chloronaphthalenes, and tetra- through hepta-chlorobiphenyls were quantified; this was seen as highly suggestive of the role these compounds may play as intermediates in the continued formation of CDD/CDFs. Stieglitz et al. (1989a) made the following observations:

- The *de novo* synthesis of CDD/CDFs via the oxidation of carbonaceous particulate matter occurred at a temperature of 300°C. Additionally, the experiment yielded

ppb to ppm concentrations of chlorinated benzenes, chlorinated biphenyls, and chlorinated naphthalenes through a similar mechanism. When potassium bromide was substituted for potassium chloride as a source of halogen for the organic compounds in the reaction, polybrominated dibenzo-p-dioxins and dibenzofurans formed as reaction products.

- The transition metal compound copper chloride catalyzed the *de novo* synthesis of CDD/CDFs on the surface of particulate carbon in the presence of oxygen, yielding carbon dioxide and chlorinated/brominated aromatic compounds.

- Particulate carbon, which is characteristic of combustion processes, may act as the source for the direct formation of CDD/CDFs, as well as other chlorinated organics. More recently, Stieglitz et al. (1991) investigated the role that particulate carbon plays in the *de novo* formation of CDD/CDFs from fly ash containing appreciable quantities of organic chlorine. Stieglitz et al. (1991) found that the fly ash contained 900 μg/g of bound organic chlorine. Only 1 percent of the organic chlorine was extractable. Heating the fly ash at 300-400°C for several hours caused the carbon to oxidize, leading to a reduction in the total organic chlorine in the matrix and a corresponding increase in the total extractable organic chlorine (TOX) (e.g., 5 percent extractable TOX at 300°C and 25-30 percent extractable total organic chlorine at 400°C). From this, Stieglitz et al. (1991) concluded that the oxidation and degradation of carbon in the fly ash are the source for the formation of CDD/CDFs; therefore, they are essential in the *de novo* synthesis of these compounds.

Addink et al. (1991) conducted a series of experiments to observe the *de novo* synthesis of CDD/CDFs in a carbon-fly ash system. In this experiment, 4 grams of carbon-free MSWI fly ash were combined with 0.1 gram of activated carbon and placed into a glass tube between two glass wool plugs. The glass tube was then placed into a furnace at a specific temperature, ranging from 200 to 400°C. This was repeated for a series of retention times and temperatures. The investigators observed that CDD/CDF formation was optimized at 300°C and at the furnace retention times of 4-6 hours. Figure 2-1 displays the relationship between retention time, temperature, and CDD/CDF production from the heating of carbon particulate. Addink et al. (1991) also investigated the relationship between furnace temperature and CDD/CDF production from the heating of carbonaceous fly ash. Figure 2-2 displays this relationship. In general, the concentration began to increase at 250°C and crested at 350°C, with a sharp decrease in concentration above 350°C. The authors also noted a relationship between temperature

and the CDD/CDF congener profile; at 300°C to 350°C, the lower chlorinated tetra- and penta-CDD/CDF congeners increased in concentration, while hexa-, hepta-, and octa-CDD/CDF congeners either remained the same or decreased in concentration. The congener profile of the original MSWI fly ash (not subject to *de novo* experimentation) was investigated with respect to changes caused by either temperature or residence time in the furnace. No significant changes occurred, leading the authors to propose an interesting hypothesis for further testing: after formation of CDD/CDFs occurs on the surface of fly ash, the congener profile remains fixed and insensitive to changes in temperature or residence time, indicating some form of equilibrium is reached in the formation kinetics.

Gullett et al. (1994) used a pilot-scale combustor to study the effect of varying the combustion gas composition, temperature, residence time, quench rate, and sorbent ($Ca[OH]_2$) injection on CDD/CDF formation. The fly ash loading was simulated by injecting on fly ash collected from a full-scale MSWI. Sampling and analysis indicated CDD/CDF formed on the injected fly ash at levels representative of those observed at full-scale MSWIs. A statistical analysis of the results showed that, although the effect of combustor operating parameters of CDD/CDF formation is interactive and very complicated, substantial reduction in CDD/CDF formation can be realized with high temperature sorbent injection to reduce HCl or Cl_2 concentrations, control of excess air (also affects ratio of CDDs to CDFs formed), and increased quench rate.

Several steps may be involved in the copper-catalyzed formation of CDDs and CDFs, with residual carbon on fly ash at 300°C (Addink and Olie, 1995). Copper initially reacts with chlorine to form $CuCl_2$, and then the ligand transfers the halide to a carbon atom of an organic macromolecule. The chlorinated macromolecular structure oxidizes into small compounds. Milligan and Altwicker (1995) found that increases in the carbon gasification rate caused increases in the amounts of CDDs and CDFs formed, and gave further evidence linking the oxidation of carbon to the formation of CDD/CDFs. Neither the gas-phase CO_2 nor CO (products of carbon oxidation) act as precursors to chlorobenzenes or CDD/CDF from reactions with carbon particulate (Milligan and Altwicker, 1995). Activated carbon, with a high surface area and excellent adsorptive characteristics, also has the highest gasification rate of all residual carbon (Addink and Olie, 1995). Experimental evidence suggest that the conditions for the *de novo* synthesis of CDDs and CDFs from carbon are: (a) the carbon consists of imperfect and degenerated

layers of graphite; (b) oxygen must be present; (c) chlorine must be present; (d) the reactions are catalyzed by copper chloride or some other transition metal; and (e) temperatures in the range of 200°C to 350°C (Huang and Buekens, 1995). The oxidation of carbon in fly ash is apparently inhibited at temperatures below 200°C, thus indicating the lower temperature limit for the thermal inertization of *de novo* synthesis (Lasagni et al., 2000). Lasagni et al. (2000) determined that at a temperature of 250^0 C, the primary product of the gasification of carbon in fly ash is CO_2 , but in a temperature range of 250-325°C, organic compounds are formed as products of the oxidation of the carbon. Addink and Olie (1995) raised the possibility that the molecular backbone of CDDs and CDFs may be present in carbon. If this is the case, the generation of dioxins and furans from the oxidation of carbon would not require the formation of intermediate aromatic ring structures. More work is needed to identify these possibilities.

The *de novo* synthesis of CDD/CDFs also involves the possibility that aromatic precursors could be formed within the post-combustion zone as in the following manner: (1) fuel molecules are broken into smaller molecular species (e.g., C_1, C_2 molecules) during primary combustion; and (2) these simple molecules recombine in the post-combustion zone to form larger molecular aromatic species (i.e., chlorobenzenes and chlorophenols) (Altwicker et al., 1993). Thus, small molecular products that evolve in the hot-zone of the furnace as a consequence of the incomplete fuel or feed material combustion may be important foundation molecules to the subsequent formation of precursor compounds in the cooler, post-combustion region. Eklund et al. (1988) reported formation of a wide range of chlorinated organic compounds, including CDDs, CDFs, and PCBs, from the oxidation of methane with HCl at temperatures of 400° to 950°C in a quartz flow tube reactor. No active catalysts nor reactive fly ashes were added to the combustion system. From these experimental results, Eklund et al. (1988) hypothesized that chlorocarbons, including CDDs and CDFs, are formed at high temperatures via a series of reversible reactions starting with chloromethyl radicals. The chloromethyl radicals can be formed from the reaction of methyl radicals and hydrogen chloride in a sooting flame. Methane is chlorinated by HCl in the presence of oxygen at high temperatures, forming chlorinated methanes, which react with methyl radicals at higher temperature (e.g., 800°C) to form aromatic compounds. In an oxidative atmosphere, chlorinated phenols are formed, but

alkanes and alkenes are the primary products. The chlorinated phenols then act as precursors for the subsequent formation of CDD/CDFs.

Aliphatic compounds are common products of incomplete combustion, and may be critical to the formation of simple ring structures in the post-combustion zone (Weber et al., 1999; Sidhu, 1999; Froese and Hutzinger, 1996a; Froese and Hutzinger, 1996b; Jarmohamed and Mulder, 1994). The aromatic precursor compounds may be formed in a potentially rich reaction environment of aliphatic compounds, reactive fly ash particles, HCl, and oxygen. Sidhu (1999) noted that combustion of acetylene on carbon (a common combustion effluent) in the presence of gaseous HCl and copper chloride (as a catalyst) at 300°C formed intermediate precursors, and subsequently, CDDs and CDFs. Propene oxidized at 350° to 550°C in contact with reactive MSWI fly ash in a flow tube reactor forms a wide range of chlorinated aromatic compounds, when the resulting combustion gases are mixed with hydrogen chloride gas (Jarmohamed and Mulder, 1994). Although the conversion was low (i.e., 1-3 percent), the oxidation of propene on fly ash in the presence of HCl can yield chlorinated benzenes and monobenzofurans. Incorporating an oxygen atom into the monobenzofuran structure leads then to the formation of monodibenzofuran. The HCl contributes chlorine to the aromatic ring through the Deacon reaction, and cyclization on the fly ash surface can yield cyclohexadienyl-substituted benzenes, which, in turn, can be further oxidized into CDFs (Jarmohamed and Mulder, 1994). Froese and Hutzinger (1996a) investigated the heterogeneous combustion reactions of the nonchlorinated C_2 aliphatics. Acetylene, as a model aliphatic compound, was allowed to react with pre-cleaned MSWI fly ash in a tube flow reactor at ca. 600°C. Metal oxides (e.g., SiO_2, Fe_2O_3, and CuO) were added separately as catalysts, instead of the metal chlorides used in other precursor experiments. The reactants were put into contact with HCl vapor, introduced at a constant flow rate. The acetylene flow was set at 1.1 mL/min and constantly fell to near 0.9 mL/min over 30 minutes. Regulated air flow maintained homeostatic oxidation conditions. Chorobenzenes and chlorophenols were formed, with isomer patterns generally resembling isomer patterns of chlorobenzene and chlorophenol emissions from MSWIs. CuO was seen as catalyzing condensation and chlorination reactions under heterogeneous conditions to form the chlorinated CDD/CDF precursor compounds. Additional more volatile compounds formed were short-chain aliphatic products, such as chloromethane, dichloromethane, and chloro-and

dichloroacetylene. Chlorobenzene congeners were not the major products formed; perchlorinated aliphatic compounds dominated as gas-phase reaction products. Froese and Hutzinger (1997) noted that perchlorinated aliphatic compounds (e.g., hexachloropropene, hexachloro-1,3-butadiene, and hexachlorocyclopentadiene) are important intermediates in aromatic ring formation; they concluded that the catalytic reaction of C_2 aliphatic compounds at 600°C dramatically contributes to formation of chlorinated and nonchlorinated aromatic compounds during combustion. Thus, aliphatic compounds can form CDD/CDF precursor compounds. Variable temperature effects were observed in the formation of CDD/CDF in the same reactions. Maximal OCDD formation occurred at 400°C, and the tetra-hepta homologue groups were maximally formed at 600°C. For CDFs, production of higher chlorinated homologues occurred at 400°C, and 500°C favored the formation of tetrachlorodibenzofurans. Froese and Hutzinger (1996a) noted a 100-fold increase in TCDF formation at 500°C, when compared to formation at 400°C. An explanation for this is that the higher temperature of 500°C maximized the formation CDD/CDF precursor (chlorophenol) from the aliphatic starting compound; whereas, at the lower temperature of 300°C, practically no ring structures were observed. Froese and Hutzinger (1996b) have produced polychlorinated benzene and phenol compounds from the high temperature (i.e., 300° to 600°C) heterogeneous combustion reactions of ethylene and ethane over fly ash in the presence of HCl, oxygen, and a metal catalyst in a combustion flow tube. No chlorobenzene congener precursors were formed from ethylene and ethane at 300°C; however, the formation rate increased with temperature, until a maximum production was achieved at 600°C. No definitive temperature dependence was observed for the formation of chlorophenols from the aliphatic starting compounds. However, at 500°C, 2,4,6-trichlorophenol dominated the reaction products; at 300°C, pentachlorophenol was initially produced. Froese and Hutzinger (1996b) also investigated the effects of elemental catalysts on potentiating the heterogeneous combustion reactions by measuring the amount of chlorobenzene and chlorophenol product formed from the reactions of ethylene/HCl over each catalyst at 600°C. The reaction with SiO_2 did not have a catalytic effect. Al_2O_3 catalytic action showed high intensity for the dichlorobenzene isomers, and decreasing intensity for the higher chlorinated isomers. Comparison of the amount of dichlorobenzene product formed indicated that an equal quantity was produced with either Al_2O_3 or fly ash; however, Al_2O_3

formed four to five times more product than the CuO catalyst. For tri- to hexa-chlorobenzene congeners, MSWI fly ash reactions produced 5 to 10 times more product that the metal catalysts. However, the presence of the CuO catalyst in these reactions produced a chlorobenzene congener pattern comparable to the fly ash reactions. With regard to chlorophenol production, Al_2O_3 also produced a unique dichlorophenol pattern, suggesting that Al_2O_3 has a unique catalytic effect in the high-temperature reactions of C_2 aliphatic compounds. Reactions over CuO produced additional products, including chlorinated methyl compounds, chlorinated C_2 aliphatics, and perchlorinated C_3 - C_5 alkyl compounds. Froese and Hutzinger (1996b) noted that these perchlorinated alkyl groups, formed by reacting ethylene and ethane over fly ash in the presence of the CuO catalyst, are key intermediate compounds to the formation of first aromatic rings in typical combustion systems. This emphasizes the importance of copper's catalytic effects in a combustion fly ash system. Al_2O_3 catalyzed reactions produced nonchlorinated naphthalene and akyalbiphenyl compounds. Furthermore, the organic chlorine in aliphatic compounds may also act as a direct source of chlorine for the formation of CDDs, CDFs in a carbon fly ash system (Weber et al., 1999).

In an earlier experiment using a similar flow-tube apparatus, Froese and Hutzinger (1994) formed chlorinated benzenes and phenols in fly ash catalyzed reactions with trichloroethylene at temperatures of 400° to 500°C. In this case, metal oxides (CuO, FeO_3, Al_2O_3) were used as catalysts, but no HCl was added for oxychlorination of product compounds. Under combustion conditions, a temperature dependent formation of chlorinated aromatics occurred from the trichloroethylene starting compound. Reaction with fly ash at 600°C formed hexachlorobenzene in concentrations that were about 1,000 times greater than at 400° and 500°C, with similar results for chlorophenols. Froese and Hutzinger (1994) hypothesized that key aromatic precursors for CDD/CDFs are formed in the higher temperature region of a post-combustion zone (ca. 600°C), which are then carried to the cooler post-combustion region (ca. 300°C), where the precursors form CDDs and CDFs.

2.4. THE ROLE OF CHLORINE IN THE FORMATION OF CDDS AND CDFS IN COMBUSTION SYSTEMS

The formation of CDDs and CDFs in the post-combustion region of combustion systems via either the precursor or *de novo* synthesis pathways requires the availability of gaseous chlorine (Luijk et al., 1994; Addink et al., 1995). Chlorine concentration in this region is related somehow to the chlorine content of combustion fuels and feed materials in incineration/combustion systems, because there can be no other source. The central question of the role of chlorine in forming CDDs and CDFs is whether or not their exists a positive and direct correlation between the amount of chlorine in feeds and the amount of CDDs and CDFs formed and emitted from the stack. If a direct relationship appears, then reductions in the chlorine content of fuels/feeds prior to combustion should result in a corresponding reduction in the concentrations of CDDs and CDFs formed after combustion. If the oxychlorination reactions require a number of steps, then the relationship between chlorine in uncombusted fuels and CDD/CDFs formed after combustion may not be linear, although still dependent in some nonlinear association. The central question can best be addressed by examining both formation mechanisms revealed in laboratory scale combustion experiments and correlations between Cl inputs with CDD/CDF outputs in commercial scale combustors.

2.4.1. Review of Laboratory-Scale Studies

A wide body of experimental evidence has elucidated the direct and indirect associations between chlorine in feeds and fuels and the potential formation of CDDs and CDFs during combustion. The *de novo* synthesis of CDDs and CDFs requires two basic reactions: the transfer of chlorine to residual carbon particulate with subsequent formation of carbon-chlorine bonds, and the oxidation of this macromolecular complex to yield carbon dioxide and volatile and semivolatile organic compounds as side products (Weber et al., 1999). Transition metal compounds, such as copper chloride, catalyze these reactions. Hydrogen chloride gas is the major direct source of chlorine available for participating in the formation of CDD/CDFs, which is initially formed as a combustion by-product from the inorganic and organic chlorine contained in the fuel (Vogg et al., 1987; Bruce et al., 1991; Gullet et al., 1990; Commoner et al., 1987; Addink et al., 1995; Luijk et al., 1994; Dickson et al., 1992; Wagner and Green, 1993; Halonen et al., 1994; Rigo

et al., 1995; Rigo, 1998; Altwicker et al.,1993). MSW contains approximately 0.45-0.90 percent (by weight) chlorine (Domalski et al., 1986). If left uncontrolled, MSW incinerators are a major stationary combustion source of HCl air emissions, which average between 400 to 600 ppm in the combustion gas (U.S. EPA, 1987a). In the presence of oxygen, HCl may oxidize to yield free chlorine gas by the Deacon process, and the free chlorine directly chlorinates a CDD/CDF precursor along the aromatic ring structure. Further oxidation of the chlorinated precursor in the presence of a transition metal catalyst (of which copper chloride was found to be the most active) yields CDDs and CDFs (Altwicker et al.,1993). Increasing the yield of chlorine in vapor phase from HCl oxidation generally increases the rate of CDD/CDF formation. Formation kinetics are most favored at temperatures between 200°C to 450°C. Chlorine production can be reduced either by limiting initial HCl concentration or by shortening the residence time in the Deacon process temperature (Bruce et al., 1991; Gullett et al., 1990b; Commoner et al., 1987). Bruce et al. (1991) observed a general increase in CDD and CDF formation, with increases in the vapor phase concentration of chlorine. Figure 2-3 shows the apparent dependence of the extent of formation of CDDs and CDFs upon chlorine concentration in the vapor phase. Bruce et al. (1991) verified a dependence on the concentration and availability of gaseous chlorine in the formation of CDD/CDFs in the post-combustion zone. This is in agreement with a simple experiment of Eklund et al. (1986) in which unsubstituted phenol was mixed with HCl at 550°C in a quartz tube reactor and formed a wide range of toxic chlorinated hydrocarbons, including CDDs and CDFs as reaction products. Eklund et al. (1988) also found a dependence of the amounts of chlorinated phenol product formed from the nonchlorinated starting material with the increased amount of HCl introduced into the reaction. Under the conditions of this experiment, no chlorinated compounds were formed at an HCl concentration of less than 10^{-3} moles, and maximum chlorophenol concentration occurred at ca. 10^{+8} M. Born et al. (1993) also observed that increasing levels of HCl give rise to increasing rates of oxychlorination of precursors, with increasing chances for the post-combustion formation of CDDs and CDFs. However, recently Addink et al. (1995) observed that an HCl atmosphere and/or chlorine produced approximately equal quantities of CDD/CDFs during the *de novo* synthesis from oxidation of particulate carbon. These experimental results suggest that chlorine production via the Deacon process reaction in the *de novo* synthesis may not be the only chlorination pathway, and may

indicate that the HCl molecule can be a direct chlorinating agent. In addition, some chlorine is expected to be formed from the oxidation of metal chlorides (e.g., $CuCl_2$), but Cl_2 formation from the Deacon process is greater because of the continuous supply of HCl delivered from the combustion chamber (Bruce et al., 1991). In this case, a first order dependence of HCl to Cl_2 is observed.

Wagner and Green (1993) investigated the correlation of chlorine content in feed to stack emissions of chlorinated organic compounds in a pilot-scale incinerator, using HCl flue gas measurements as a surrogate for fuel-bound organic chlorine. In addition to MSW as a fuel, variable amounts of PVC resin were added during 6 of 18 stack test runs. The resulting data were regressed to determine the coefficient of correlation between HCl measurements and total chlorobenzene compound emission measurements. In nearly all of the different regression analyses performed, the relationship between HCl emission and emissions of chlorinated organic compounds was positive and well-defined. In addition, Wagner and Green (1993) found a direct dependence of HCl emission levels to the level of PVC in the waste, with generally increasing amounts of HCl formed as increasing amounts of PVC were added. From these experiments, Wagner and Green (1993) concluded that decreases in the levels of organically bound chlorine in the input to an incinerator led to decreases in chlorinated organic compound stack emissions. Kanters and Louw (1994) investigated a possible relationship of chlorine content in waste feed to chlorophenol emissions in a bench-scale thermal reactor. MSWI, with a higher content of chlorine, caused a higher emission of chlorophenols via the *de novo* synthesis pathway. Kanters and Louw (1994) lowered the chlorine content of the prototype MSWI by replacing Cl-containing fractions with cellulose. They observed appreciable decreases in the amounts of chlorophenol formed from combustion. Kanters and Louw (1994) concluded that reductions in the chlorine content of waste feeds or elimination of PVC prior to MSWI combustion should result in a corresponding reduction in chlorophenol and CDD/CDF emissions.

In a similar experiment, Wikstrom et al. (1996) investigated the influence of chlorine in feed materials to the formation of CDDs, CDFs, and benzenes in a laboratory-scale fluidized bed reactor. An artificial fuel (composed of 34 percent paper, 30 percent wheat flour, 14 percent saw dust, 7 percent polyethylene, and 2 percent metals) to which varying amounts of organic chlorine (PVC) and inorganic chlorine ($CaCl_2 \cdot 6H_2O$) were

added, was combusted. Seven fuels were studied, and the chlorine content was varied from 0.12 to 2 percent. Flue gases were sampled for CDDs, CDFs, and chlorobenzenes. All combustion was performed with a high degree of combustion efficiency (e.g., 99.999 percent) to avoid forming polyvinylidene chloride and naphthalenes as products of incomplete combustion of pure PVC. With the combustion conditions held constant, only the chlorine content of the fuel was varied. From these experiments, about 1,000-fold higher concentrations of PCB isomers were produced, as compared to CDD/CDF (expressed as concentration of I-TEQ_{DF}). Moreover, a correlation was found between I-TEQ_{DF} and PCB levels in the flue gases and the chlorine content of the fuel. A 5-fold increase in both I-TEQ_{DF} and PCB concentration was observed in the flue gases from combustion of fuels containing 0.5 and 1.7 percent total chlorine. Moreover, no differences were observed in the amount of chlorinated product produced or whether the source of chlorine in the fuel was organic or inorganic. No correlation was observed between total CDD/CDF and PCB formation and total chlorine in the feed when chlorine levels in feed were 0.5 percent or lower. Highest amounts of CDD/CDFs and PCBs were formed from the fuel having the highest total chlorine content (1.7 percent). Under the conditions of this experiment, Wikstrom et al. (1996) observed that a chlorine fuel content of 1.0 percent was a threshold for forming excess CDDs, CDFs, and PCBs during combustion. The authors noted that Swedish MSW contains about 0.7 percent chlorine, of which approximately 40 percent are organic chlorine. They concluded that Swedish MSW is below the observed threshold value of 1.0 percent chlorine associated with a general increase in CDD, CDF, and PCB formation in the post-combustion region. Wikstrom et al. (1996) stated that their study does not support the thesis that elimination of only PVC from the waste prior to combustion will cause a significant reduction of CDD/CDF emissions if the combustion process is well controlled (high combustion efficiency).

A primary byproduct of combusting PVC is the generation of HCl. Paciorek et al. (1974) thermally degraded pure PVC resin at 400°C and produced 550 mg/g HCl vapor as a primary thermolysis product, which was observed as being 94 percent of the theoretical amount based on the percent weight chlorine on the molecule. Ahling et al. (1978) concluded that HCl can act as a chlorine donor to ultimately yield chlorinated aromatic hydrocarbons from the thermolytic degradation of pure PVC, and that these yields are a

function of transit time, percent oxygen, and temperature. They observed data from 11 separate experiments, conducted with a range of temperatures from 570 to 1,130°C. These data indicated that significant quantities of various isomers of dichloro-, trichloro-, tetrachloro-, and hexachlorobenzenes could be produced. Choudhry and Hutzinger (1983) proposed that the radical species $Cl\cdot$ and $H\cdot$ generated in the incineration process may attack the chlorinated benzenes thus formed, and abstract hydrogen atoms to produce ortho-chlorine substituted chlorophenol radicals. These intermediate radical species then react with molecular oxygen to yield ortho-substituted chlorophenols. As a final step, the ortho-substituted chlorophenols act as ideal precursors to yield CDD/CDFs with heat and oxygen. The chlorine in aliphatic compounds has been observed as both yielding high amounts of HCL during combustion, and also acting as a direct chlorine source for the *de novo* synthesis of CDDs/CDFs (Weber et al., 1999).

Recently Addink and Altwicker (1999) have reported on the role of the inorganic chloride ion in the formation of CDD/CDFs using the labeled compound, $Na^{37}Cl$. The inorganic chloride ion forms carbon-chlorine bonds on soot particles during combustion. The chlorine in the soot can both be directly inserted into a CDD/CDF molecule during formation, or can exchange with the chloride ions in the transitional metal catalyst which promotes CDD/CDF formation. Thus, the inorganic chlorine ion participates as a chlorine donor to CDD/CDF formation.

De Fre and Rymen (1989) reported on forming CDDs and CDFs from hydrocarbon combustion in a domestic gas/oil heating burner in the presence of 15 and 300 ppm concentrations of HCl. Over 100 chlorinated organic compounds were detected in the flue gases whenever HCl was injected into the system. De Fre and Rymen (1989) observed formation of CDDs and CDFs in all experiments where HCl was injected in a hydrocarbon flame. In this case, CDFs were always more abundant that CDDs. De Fre and Rymen (1989) concluded that the relationship between the HCl concentration and the emitted concentration of CDD/CDF under fixed combustion conditions appeared to be exponential for a wide range in temperature (e.g., 240° to 900°C).

2.4.2. Review of Full Scale Combustion Systems

The review of experimental data clearly indicates an association between chlorine content of feed/fuels and the potential synthesis of CDDs and CDFs. Paradoxically, the

review of full-scale operating incineration processes does not yield such unequivocal results indicating that complex kinetic events make strong associations difficult in full-scale systems. The following is a review of studies of the association between chlorine in feeds and stack releases of CDD/CDFs in full-scale incineration systems. In the stack testing of a variety of industrial stationary combustion sources during the National Dioxin Study in 1987, EPA made a series of qualitative observations on the relationship between total chlorine present in the fuel/waste and the magnitude of emissions of CDDs and CDFs from the stack of the tested facilities (U.S. EPA, 1987a). In general, combustion units with the highest CDD emission concentrations had greater quantities of chlorine in the fuel; conversely, sites with the lowest CDD emission concentrations contained only trace quantities of chlorine in the feed. The typical chlorine content of various combustion fuels was reported by Lustenhouwer et al. (1980) as: coal: 1,300 μg/g; MSW: 2,500 μg/g; leaded gasoline: 300-1,600 μg/g; and unleaded gasoline: 1-6 μg/g.

Thomas and Spiro (1995) also analyzed the relationship of CDD/CDF emissions from combustion to the chlorine content of feed materials. Thomas and Spiro (1996) plotted average CDD/CDF emission factors for a variety of combustion processes (black liquor boilers, unleaded gasoline combustion, leaded gasoline combustion, wire incineration, cigarette combustion, sewage sludge incineration, MSWI, PCP-treated wood combustion, hazardous waste incineration, and hospital waste incineration) against the average chlorine concentration of the combusted material. The plot showed that average CDD/CDF emissions of combustion source categories tend to increase with the average chlorine content of the combusted fuel. The analysis clearly indicated that combustion sources with relatively high combustion efficiency and adequate air pollution controls tended to have two order of magnitude lower emissions than poorly operated sources. This suggested a strong dependence on chlorine concentration in fuels and the magnitude of CDD/CDF emissions in the more poorly controlled combustion sources. The slope of the log-log plot was between 1 and 2, indicating that the relationship of chlorine content to CDD/CDF emissions was more than proportional.

Recently Costner (1998) reported finding a positive correlation between chlorine content of feed material and CDD/CDF emissions at a full-scale hazardous waste incinerator. Costner concluded that emissions at this facility were dependent on chlorine

input at a chlorine concentration as low as 0.031 percent, and that there was no evidence of a threshold in the relationship between chlorine in feed and CDD/CDF emissions.

Rigo et al. (1995) summarized the results of a study commissioned by the American Society of Mechanical Engineers (ASME, 1995). The study was a statistical evaluation of the relationship of HCl concentration in flue gases to various combustion systems (i.e., MSWI, hospital waste incineration, hazardous waste incineration, biomass combustors, laboratory and bench-scale combustors) to the stack emission of total CDDs and CDFs. HCl was a surrogate for total chlorine feed content in this study. The data analysis was sufficient for 92 facilities in the data base that showed both HCl and CDD/CDF emissions. From the 92 facilities, 72 did not show statistically significant relationship between chlorine input and CDD/CDF output in emissions streams; 2 facilities showed increasing CDD/CDF concentrations with increasing chlorine; and 8 facilities showed decreasing CDD/CDF concentrations with increasing chlorine. AMSE (1995) concluded that:

> "The failure to find simultaneous increases in most cases and finding inverse relationships in a few indicates that any effect chlorine has on PCDD/F emissions is smaller than the variability of other causative factors. Whatever effect chlorine has on PCDD/F emissions in commercial scale systems is masked by the effect of APCS (air pollution control systems) temperature, ash chemistry, combustion conditions, measurement imprecision, and localized flow stratification."

Liberson and Belanger (1995) reported the results of an analysis of the formation and emission of CDDs and CDFs as a function of total chlorine in combustion feed materials at a rotary kiln hazardous waste incinerator (HWI). The data were generated from multiple test series conducted over a 13-month period at the HWI, while operating a carbon injection system specifically designed to control and reduce CDD and CDF stack emissions. The chlorine feed rates ranged from 0 to 3,300 pounds per hour, while the CDD/CDF emission rates ranged between 0.7 and 39 ng/DSCM. The authors noted that multiple series of CDD/CDF control systems were employed on this HWI (e.g., a high temperature secondary combustion chamber, a spray dryer-evaporative quench that

further cools the combustion gases, activated carbon injection to adsorb semi-volatile organics, and a cool-side electrostatic precipitator followed by an acid gas scrubber to collect HCl and Cl_2). From the analyses of data, Liberson and Belanger (1995) concluded no correlation exists between CDD/CDF emissions and chlorine feed in a modern MWI, using carbon injection for CDD/CDF control.

2.5. POTENTIAL PREVENTION OF CDD/CDF FORMATION IN COMBUSTION SYSTEMS

Given what is currently understood about oxychlorination reactions in the synthesis of CDDs and CDFs, researchers have identified certain interventions that could be taken to reduce or impede formation in combustion systems. Recently, Haghunathan and Gullett (1996) demonstrated in a pilot-scale incinerator that sulfur compounds can combine with the metal catalyst necessary to stimulate the Deacon reaction of HCl and O_2 to yield Cl_2, thereby, neutralizing the catalyzing agent and reducing the formation of CDDs and CDFs. The Deacon reaction, which forms free chlorine in the combustion plasma, is seen as only occurring in the presence of a catalyst. Thus, the SO_2 molecule (formed when sulfur in the fuel combines with oxygen) can either inhibit the catalytic activity of the fly ash by combining with a metal-based Deacon catalyst in the fly ash, or by depleting the Cl_2 formed. Haghunathan and Gullett (1996) observed that the principal action of sulfur for inhibiting the formation of CDDs and CDFs in combustion systems is through SO_2 depletion of Cl_2, as follows:

$$Cl_2 + SO_2 + H_2O \leftrightarrow 2HCl + SO_2$$

The relevance of this finding is that the co-combustion of municipal solid waste with coal (that contains sulfur) should lead to dramatic reductions in the amount of CDDs and CDFs formed and emitted, and may explain why, in the United States, coal combustion at power plants results in over a magnitude lower CDD/CDF emission rate than MSWIs.

Naikwadi and Karasek (1989) investigated the addition of calcium oxide (CaO) and triethylamine (TEA) to the flue gases of a combustion system as an inhibitor of the catalytic activity of fly ash. They placed 500 μg C-13-labeled pentachlorophenol (a dioxin precursor) in a combustion flow tube and allowed it to react with organic-extracted MSWI fly ash at 300°C under an air stream. Under these condition, CDD/CDFs were formed at

concentrations ranging from 1,660 ng to 2,200 ng per 100 μg ^{13}C-PCP. The experimental method was then modified by mixing reactive MSWI fly ash with either CaO or TEA. The results showed that the amount of CDD/CDF formed could be reduced by an order of magnitude from the reaction of PCP with fly ash and the addition of TEA as an inhibitor. When CaO was mixed with fly ash, the amount of CDD/CDFs formed decreased by over 20 times.

2.6. THEORY ON THE EMISSION OF POLYCHLORINATED BIPHENYLS

The air emission of PCBs from MSW incineration is less well studied. Probably the formation mechanisms that apply to CDDs/CDFs would also apply to PCBs. Mechanism 1 (pass through) is implicit in the TSCA rule which requires 99.9999 percent destruction in hazardous waste incinerators. When this occurs, 0.0001 percent of the initial amount of PCBs fed into the hazardous waste incinerator may be emitted out the stack. This may indicate that some small fraction of the PCBs present in the fuel fed into an incineration process may result in PCB emissions from the stack of the process.

PCBs have been measured as contaminants in the raw refuse prior to incineration in an MSWI (Choudhry and Hutzinger, 1983; Federal Register, 1991a). Using this information, it is possible to test Theory mechanism 1 involved in CDD/CDF emissions: that the PCB contamination present in the fuel is responsible for emissions from the stack. The mass balance of total PCB, beginning with measurement in the raw refuse and ending with measurement at the stack to an RDF MSW incinerator (Federal Register, 1991a), can be used to calculate the destruction rated efficiency (DRE) of incineration of the PCB contaminated MSW. Using results from test number 11 at the RDF facility (Federal Register, 1991a), a computation of DRE can be made with the following equation (Brunner, 1984):

$$\text{DRE} = \frac{W_I - W_o}{W_I} \times 100\%$$

Where:

W_I = mass rate of contaminant fed into the incinerator system

W_o = mass rate of contaminant exiting the incinerator system

In test 11, 811 nanograms of total PCBs/gram of refuse (ng/g) were measured in the MSW fed into the incineration system, and 9.52 ng/g of total PCB were measured at the inlet to the pollution control device (i.e., outside the furnace region, but preceding emission control). From these measurements, a DRE of 98.8 percent can be calculated. Therefore, it appears that PCB contamination in the raw MSW, which was fed into this particular incinerator, may have accounted for the PCB emissions from the stack of the MSW incinerator.

PCBs can be thermolytically converted into CDFs (Choudhry and Hutzinger, 1983; U.S. EPA, 1984). This process occurs at temperatures somewhat lower than typically measured inside the firebox of an MSWI. Laboratory experiments conducted by EPA (U.S. EPA, 1984) indicate that the optimum conditions for CDF formation from PCBs are near a temperature of 675°C in the presence of 8 percent oxygen and a residence time of 0.8 seconds. This resulted in a 3 to 4 percent efficiency of conversion of PCBs into CDFs. Because 1 to 2 percent of the PCBs present in the raw refuse may survive the thermal stress imposed in the combustion zone to the incinerator (Federal Register, 1991a), then it is reasonable to presume that PCBs in the MSW may contribute to the total mass of CDF emissions released from the stack of the incinerator.

Although it appears that contamination of waste feeds with PCBs may be an important factor to detecting PCBs in stack emissions from combustion processes, recent research has indicated the possibility that these compounds may also be formed in the post-combustion zone either from *de novo* synthesis or from precursor compounds. Zheng et al. (1999) observed the formation of PCBs in the post-combustion zone from the pyrolysis of chlorobenzenes using a laboratory scale furnace. Zheng and coworkers (1999) observed that PCBs were optimally formed from lower chlorinated chlorobenzenes (i.e., 1,3-dichlorobenzene) catalyzed by copper chloride. In this experiment, maximum PCB production occurred at a temperature of 350°C. Wikstrom et al. (1998) reported secondary formation of PCB in the post-combustion zone similar to the *de novo* synthesis of CDDs and CDFs, albeit, PCBs were formed in only small amounts relative to CDD/CDFs. Fangmark and coworkers (1994) have postulated that formation of PCBs, CDDs, and CDFs in the post-combustion zone may occur either from a common precursor, or by side reactions affected in a similar way by temperature and residence time. On the other hand, Blumenstock et al. (1998) produced results in a pilot-scale furnace that were inconsistent

with the *de novo* formation of CDDs and CDFs in the post-combustion zone (i.e., PCBs seemed to be optimally formed at high temperatures in oxygen deficient atmospheres). Shin and Chang (1999) have noted a positive correlation between PCB concentrations on MSW incineration fly ash and fly ash concentrations of CDDs and CDFs, suggesting that high PCBs levels in fly ash may be a contributory cause to the post-combustion formation of CDDs and CDFs (i.e., PCBs are precursors to CDD/CDFs). Nito et al. (1997) noted the formation of CDFs and CDDs from the pyrolysis of PCBs in a fluidized bed system indicating that PCBs in feeds may account for CDFs formed in municipal solid waste incineration. More combustion related research needs to be conducted to firmly establish whether or not PCB contamination in feeds or post-combustion formation (or both) may explain the presence of PCBs in combustion flue gases.

2.7. SUMMARY AND CONCLUSIONS

2.7.1. Mechanisms of Formation of Dioxin-Like Compounds

There are three primary mechanisms for CDD/CDF emissions from combustion sources:

Mechanism 1: This refers to CDD/CDFs contained in the feed which pass through the combustor intact and are subsequently released to the environment. For most systems, this is not thought to be a major contributor to CDD/CDF emissions for two reasons. First, for commercial systems with good combustion controls, the temperatures and residence times should result in the destruction of most CDD/CDFs in the feed. Second, mass balance studies of a number of combustion systems show that more CDD/CDFs can be detected downstream of the furnace than in the feed. Consequently synthesis appears to be a more important mechanism than pass through.

Mechanism 2: This is the formation of CDD/CDFs from the thermal breakdown and molecular rearrangement of aromatic precursors either originating in the feed or forming as a product of incomplete combustion. Actual synthesis of CDD/CDF occurs in the post-combustor environment. The CDD/CDFs form when the precursors sorb onto binding sites on the surface of fly ash particles. This reaction has been observed to be catalyzed by the presence of a transition metal sorbed to the particulate. The most potent catalyst is copper chloride. Heat in a range of 200 to 450°C has been identified as a necessary condition for these reactions to occur, with either lower or higher temperatures inhibiting

the process. Since these reactions involve heterogenous chemistry, the rate of emissions is less dependent on reactant concentration than conditions that promote formation such as temperature, retention time and availability of catalytic surfaces. For this mechanism to be significant, two broad conditions are needed.

Mechanism 3: This is the formation of CDD/CDFs in the post-combustion environment in the absence of aromatic precursors. This *de novo* synthesis involves the oxidative breakdown of macromolecular carbon structures (e.g., graphite) leading to the formation of aromatic CDD/CDF precursors. These precursors then undergo the transformations associated with mechanism 2 to form CDD/CDFs. As with mechanism 2, since this mechanism involves heterogenous chemistry, the rate of emissions is dominated by the same physical conditions as discussed in mechanism 2. Mechanisms 2 and 3 can occur simultaneously, share a number of common reaction pathways, occur in the same physical environment and are controlled by many of the same physical conditions. In well designed and operated combustion systems, the precursor species needed for mechanism 2 are not in abundant supply; consequently *de novo* synthesis can become the dominant pathway for formation. In systems with incomplete combustion, it is difficult to sort out the relative contribution of these two mechanisms to total emissions. Both mechanisms, however, can be curtailed if steps are taken to minimize the physical conditions needed to support formation (i.e., time, temperature and reactive surface).

The combustion formation chemistry of PCBs is less well-studied than for CDD/CDFs, but it is reasonable to assume that these same three mechanisms would apply. For waste incineration, PCBs can exist in significantly higher concentrations in the feed than CDD/CDFs. Consequently, mechanism 1 may play a more prominent role in PCB emissions from some forms of waste combustion.

2.7.2. Role of Chlorine

From the various analyses on the role and relationship of chlorine in feeds to CDD/CDF formation and emissions, the following observations and conclusions are made:

1. Although chlorine is an essential component for the formation of CDD/CDFs in combustion systems, the empirical evidence indicates that, for commercial scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of

CDD/CDF stack emissions. Important factors which can affect the rate of CDD/CDF formation include the overall combustion efficiency, post-combustion flue gas temperatures and residence times, and the availability of surface catalytic sites to support CDD/CDF synthesis. Data from bench, pilot and commercial scale combustors indicate that CDD/CDF formation can occur by a number of mechanisms. Some of these data, primarily from laboratory and pilot scale combustors, have shown direct correlation between chlorine content in fuels and rates of CDD/CDF formation. Other data, primarily from commercial scale combustors, show little relation with availability of chlorine and rates of CDD/CDF formation. The conclusion that chlorine in feed is not a strong determinant of CDD/CDF emissions applies to the overall population of commercial scale combustors. For any individual commercial scale combustor, circumstances may exist in which changes in chlorine content of feed could affect CDD/CDF emissions. For uncontrolled combustion, such as open burning of household waste, chlorine content of wastes may play a more significant role in affecting levels of CDD/CDF emissions than observed in commercial scale combustors.

2. Both organic and inorganic chlorine in combustion fuels yield HCl in the post-combustion region. HCl vapor is the dominant source of chlorine leading to the formation of CDD/CDFs. The reaction proceeds via the oxidation of HCl in the presence of an inorganic chloride catalyst (the Deacon reaction). Although the preponderance of scientific evidence suggest that this is a dominant pathway for producing chlorinated compounds in emissions, it is still unclear if HCl can also directly chlorinate aromatics, or must first be oxidized to yield free chlorine.

3. Laboratory scale experiments have examined correlations between chlorine content of feeds with total CDD/CDF formation. These experiments have suggested that for feeds containing less than 1% Cl, the rate of CDD/CDF formation is independent of Cl. For feeds with Cl content greater than 1%, a positive correlation is seen. Although this relationship is observed at the laboratory scale, it has been shown not to apply to commercial scale combustors (see 1 above). It has not been determined, however, if these relationships are relevant to other types of combustion such as backyard barrel burning, landfill fires and agricultural burning.

2.7.3. General Conclusion

The trace chemistry of combustion appears to involve a wide variety of formation pathways indicating that the chemistry of CDD/CDF formation is more complicated than the relatively simple constructs described in this review. Despite this complexity, the current weight of evidence would suggest that the role of chlorine and the formation mechanisms outlined above will account for most of the CDD/CDF emissions associated with combustion.

Table 2-1. Concentration of CDD/CDFs on Municipal Incinerator Fly Ash at Varying Temperatures

Congener	CDD/CDF Concentration on Fly Ash (ng/g)				
	Temperature (°C)				
	200°	250°	300°	350°	400°
CDD					
Tetra	15	26	188	220	50
Penta	40	110	517	590	135
Hexa	65	217	1029	550	110
Hepta	100	208	1103	430	60
Octa	90	147	483	200	15
CDF					
Tetra	122	560	1379	1185	530
Penta	129	367	1256	1010	687
Hexa	61	236	944	680	260
Hepta	48	195	689	428	112
Octa	12	74	171	72	12

Source: Adapted from Vogg et al. (1987).

Table 2-2. CDD/CDFs Formed from the Thermolytic Reaction of 690 mg Benzene + $FeCl_3$Silica Complex

Congener	Mass Produced (ng)	Number of Moles Produced	Percent Yield[a]
DiCDD	4.9	0.019	4.3 E-7
TriCDD	54	0.019	4.3 E-6
TCDD	130	0.400	9.0 E-6
PeCDD	220	0.620	1.4 E-5
HxCDD	170	0.440	9.9 E-6
HpCDD	98	0.230	5.2 E-6
OCDD	20	0.040	9.0 E-7
Total CDDs	696.9	1.940	4.4 E-5
DiCDF	990	4.200	9.5 E-5
TriCDF	7,800	29.00	6.6 E-4
TCDF	12,000	39.00	8.8 E-4
PeCDF	20,000	59.00	1.3 E-3
HxCDF	33,000	88.00	2.0 E-3
HpCDF	40,000	98.00	1.1 E-3
OCDF	74,000	167	3.8 E-3
Total CDFs	187,790	484.2	1.1 E-2

[a] Percent yield = (number of moles of CDD or CDF/moles benzene) x 100.

Source: Nestrick et al. (1987)

Table 2-3. *De Novo* Formation of CDDs/CDFs after Heating Mg-Al Silicate, 4% Charcoal, 7% Cl, 1% $CuCl_2.2H_2O$ at 300°C

Congener	Concentrations of CDD/CDF (ng/g)				
	Reaction Time (hrs)				
	0.25	0.5	1	2	4
TCDD	2	4	14	30	100
PeCDD	110	120	250	490	820
HxCDD	730	780	1600	2200	3800
HpCDD	1700	1840	3500	4100	6300
OCDD	800	1000	2000	2250	6000
Total CDD	3342	3744	7364	9070	17020
TCDF	240	280	670	1170	1960
PeCDF	1360	1670	3720	5550	8300
HxCDF	2500	3350	6240	8900	14000
HpCDF	3000	3600	5500	6700	9800
OCDF	1260	1450	1840	1840	4330
Total CDF	8360	10350	17970	24160	38390

Source: Stieglitz et al. (1989a).

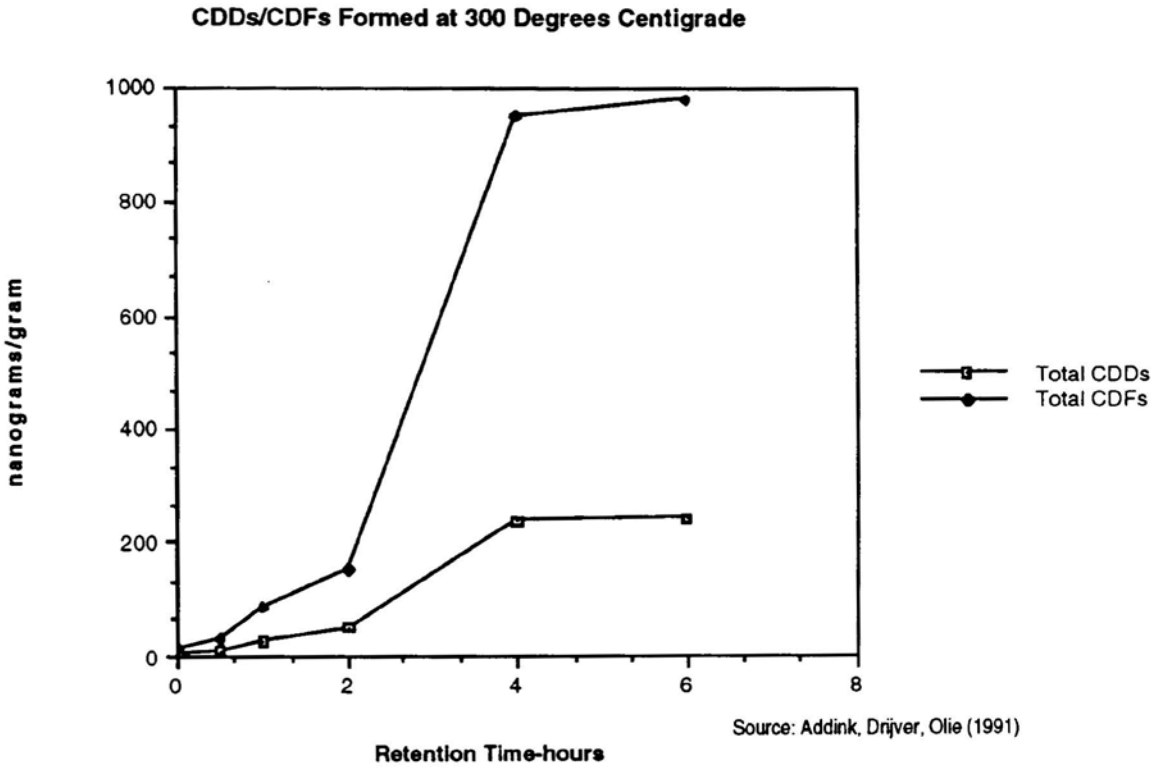


Figure 2-1. The *de novo* Synthesis of CDD/CDFs from Heating Carbon Particulate at 300°C at Varying Retention Times

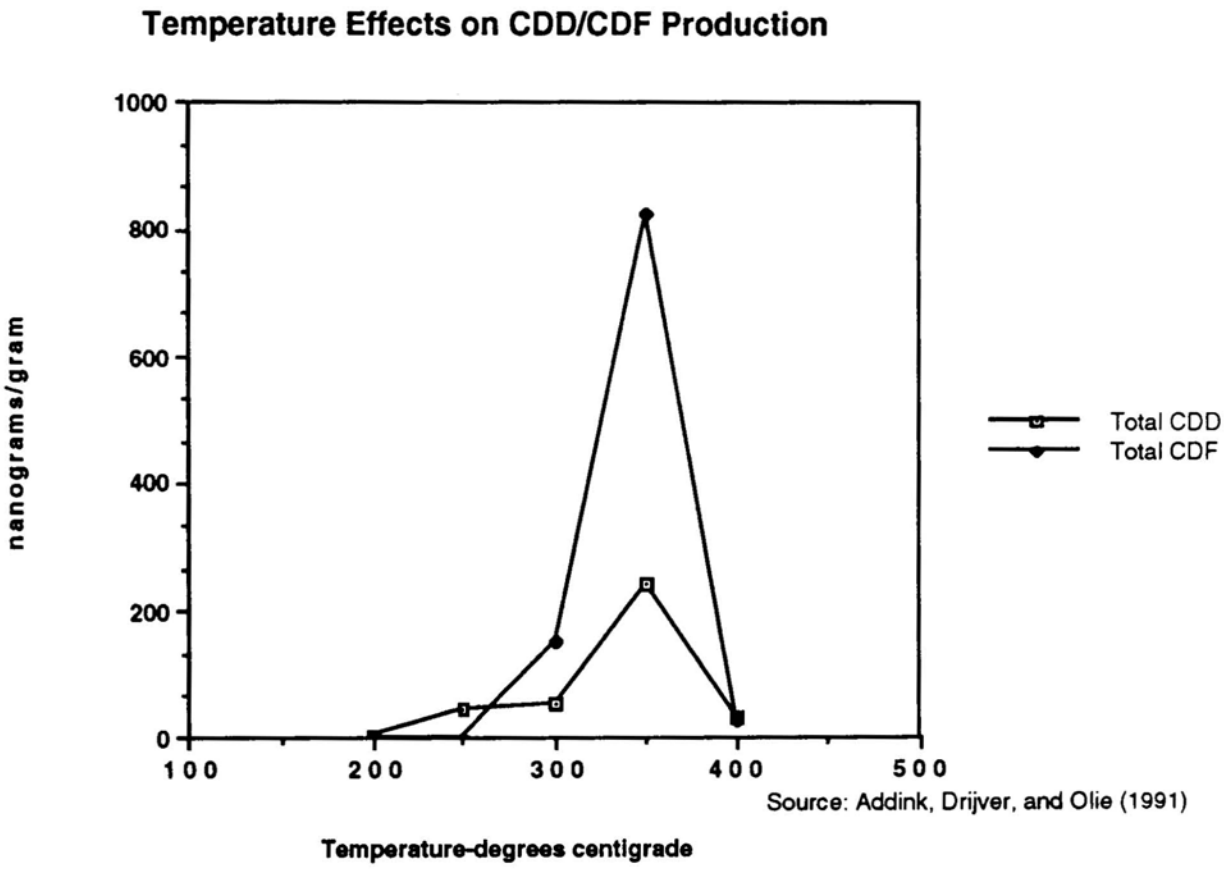


Figure 2-2 Temperature Dependence on CDD/CDF Formation

Figure 2-3. The Association Between Vapor Phase Cl_2 and the Formation of CDDs/CDFs

3. COMBUSTION SOURCES OF CDD/CDF: WASTE INCINERATION

Incineration is the destruction of solid, liquid, or gaseous wastes through the application of heat within a controlled combustion system. The purposes of incineration are to reduce the volume of waste that needs land disposal and to reduce the toxicity of the waste, making it more sterile. In keeping with this definition, incinerator systems can be classified by the types of wastes incinerated: municipal solid waste incineration; medical and pathological waste incineration; hazardous waste incineration; sewage sludge incineration; tire incineration; and biogas flaring. Each of these types of incinerators are discussed in this chapter. The purposes of this chapter are to: characterize and describe waste incineration technologies in the United States and to derive estimates of annual releases of CDDs and CDFs into the atmosphere from these facilities for reference years 1987 and 1995.

Combustion research has developed three theories on the mechanisms involved in the emission of CDDs and CDFs from combustion systems: (1) CDD/CDFs can be introduced into the combustor with the feed and pass through the system unchanged, (2) CDD/CDFs can be formed during combustion, or (3) CDD/CDFs can be formed via chemical reactions in the post-combustion portion of the system. The total CDD/CDF emissions are likely to be the net result of all three mechanisms; however, their relative importance is often uncertain. To the extent practical with the available data, the combustors in each source category were divided into classes judged to have similar emission factors. This classification effort attempted to reflect the emission mechanisms described above. The emission mechanisms suggest that the aspects of combustor design and operation that could affect CDD/CDF emissions are furnace design, composition of the waste feed, temperature in the post-combustion zone of the system, and type of air pollution control device (APCD) used to remove contaminants from the flue gases. Therefore, incineration systems that are similar in terms of these factors should have similar CDD/CDF emissions. Accordingly, this chapter proposes classification schemes that divide combustors into a variety of design classes based on these factors. Design class, as used here, refers to the combination of furnace type and accompanying APCD.

3.1. MUNICIPAL SOLID WASTE INCINERATION

As discussed previously, CDD/CDF emission theory suggests that CDD/CDF emissions can be related to several factors, including furnace design, composition of the waste feed, temperature in the post-combustion zone of the system, and type of APCD used to remove contaminants from the flue gases. Accordingly, this chapter proposes a classification scheme that divides municipal solid waste incinerators (MSWIs) into a variety of design classes based on those factors. Some APCDs are operated at different temperatures; therefore, operating temperature is used to define some design classes. Because the theory also suggests that feed can influence CDD/CDF emissions, the proposed furnace classification system distinguishes refused-derived fuel from normal municipal solid waste (MSW). This section begins with a description of the MSWI technology and then proposes the design classification scheme. Using this scheme, the MSWI industry is characterized for the reference years 1987 and 1995. Finally, the procedures for estimating emissions are explained, and results summarized.

3.1.1. Description of Municipal Solid Waste Incineration Technologies

For purposes of this report, MSWI furnace types are divided into three major categories: mass burn, modular, and refuse-derived fuel. Each of these furnace types is described below, followed with a description of the APCDs used with these systems.

Furnace Types

Mass Burn: Historically, this furnace type derived its name because it burned MSW as received (i.e., no preprocessing of the waste was conducted other than removal of items too large to go through the feed system). Today, a number of other furnace types also burn unprocessed waste (as described below). Mass burn furnaces are distinguished from these others because they burn the waste in a single stationary chamber. In a typical mass burn facility, MSW is placed on a grate that moves through the combustor. The 1995 inventory indicates that the combustion capacity of facilities ranges from 90 to 2,700 metric tons of MSW per day. Three subcategories of mass burn (MB) technologies are described below:

- Mass burn refractory-walled (MB-REF) systems represent an older class of MSWIs (generally built in the late 1970s to early 1980s) that were designed only to reduce

the volume of waste in need of disposal by 70 to 90 percent. These facilities usually lacked boilers to recover the combustion heat for energy purposes. In the MB-REF design, the MSW is delivered to the combustion chamber by a traveling grate and/or a ram feeding system. Combustion air in excess of stoichiometric amounts (i.e., more oxygen is supplied than needed for complete combustion) is supplied both below and above the grate.

- Mass burn waterwall (MB-WW) facilities represent enhanced combustion efficiency, as compared with MB-REF incinerators. Although it achieves similar volume reductions, the MB-WW incinerator design provides a more efficient delivery of combustion air, resulting in sustained higher temperatures. Figure 3-1 is a schematic of a typical MB-WW MSWI. The term 'waterwall ' refers to a series of steel tubes, running vertically along the walls of the furnace. The tubes contain water, which when heated by combustion, transfer energy from the heat of combustion to the water. The water reaches boiling temperature, and steam is produced. The steam is then used to drive an electrical turbine generator or for other industrial needs. This transfer of energy is termed 'energy recovery.'

- Mass burn rotary kiln combustors (MB-RC) use a water-cooled rotary combustor, which consists of a rotating combustion barrel configuration mounted at a 15-20^{o} angle of decline. The refuse is charged at the top of the rotating kiln by a hydraulic ram (Donnelly, 1992). Preheated combustion air is delivered to the kiln through various portals. The slow rotation of the kiln (i.e., 10 to 20 rotations/hour) causes the MSW to tumble, thereby exposing more surface area for complete burnout of the MSW. These systems are also equipped with boilers for energy recovery. Figure 3-2 is a schematic of a typical MB-RC MSWI.

Modular Incinerator: This is the second general type of MSWI furnace used in the United States. As with the mass burn type, modular incinerators burn waste without preprocessing. Modular MSWIs consist of two vertically mounted combustion chambers (i.e., a primary and secondary chamber). In the 1995 inventory, modular combustors' combustion capacity ranged from 4 to 270 metric tons/day. The two major types of modular systems, "excess air" and "starved air," are described below.

- The modular excess-air system consists of a primary and secondary combustion chamber, both of which operate with air levels in excess of stoichiometric requirements (i.e., 100 to 250 percent excess air). Figure 3-3 illustrates a typical modular excess air MSWI.

- Starved (or controlled) air is another type of modular system in which air is supplied to the primary chamber at sub-stoichiometric levels. The products of incomplete combustion entrain in the combustion gases that are formed in the primary combustion chamber, then pass into a secondary combustion chamber. Excess air is added to the secondary chamber, and combustion is completed by elevated

temperatures sustained with auxiliary fuel (usually natural gas). The high and uniform temperature of the secondary chamber, combined with the turbulent mixing of the combustion gases, results in low-levels of particulate matter and organic contaminants being formed and emitted. Therefore, many existing modular units lack post-combustion air pollution control devices. Figure 3-4 is a schematic view of a modular starved air MSWI.

Refuse-Derived Fuel (RDF): The third major type of MSWI furnace technology is designed to combust refuse-derived fuel (RDF). RDF is a general term that describes MSW from which relatively noncombustible items are removed, thereby enhancing the combustibility of the MSW. RDF is commonly prepared by shredding, sorting, and separating out metals to create a dense MSW fuel in a pelletized form having a uniform size. Three types of RDF systems are described below.

- The dedicated RDF system burns RDF exclusively. Figure 3-5 shows a typical dedicated RDF using a spreader-stoker boiler. Pelletized RDF is fed into the combustor through a feed chute, using air-swept distributors; this allows a portion of the feed to burn in suspension and the remainder to burn out after falling on a horizontal traveling grate. The traveling grate moves from the rear to the front of the furnace, and distributor settings are adjusted so that most of the waste lands on the rear two-thirds of the grate. This allows more time to complete combustion on the grate. Underfire and overfire air are introduced to enhance combustion, and these incinerators typically operate at 80 to 100 percent excess air. Waterwall tubes, a superheater, and an economizer are used to recover heat for production of steam and/or electricity. The 1995 inventory indicates that dedicated RDF facilities range in total combustion capacity from 227 to 2,720 metric tons/day.

- Cofired RDFs burn both RDF and normal MSW.

- The fluidized-bed RDF (FB-RDF) burns the waste in a turbulent and semi-suspended bed of sand. The MSW may be fed into the incinerator either as unprocessed waste or as a form of RDF. The RDF may be injected into or above the bed through ports in the combustor wall. The sand bed is suspended during combustion by introducing underfire air at a high velocity, hence the term "fluidized." Overfire air at 100 percent stoichiometric requirements is injected above the sand suspension. Waste-fired FB-RDFs typically operate at 30 to 100 percent excess air levels and at bed temperatures around 815°C (1,500°F). A typical FB-RDF is presented as Figure 3-6. Technology has two basic design concepts: (1) a bubbling-bed incineration unit and (2) a circulating-bed incineration unit. The 1995 inventory indicates that fluidized-bed MSWIs have capacities ranging from 184 to 920 metric tons/day. These systems are usually equipped with boilers to produce steam.

Air Pollution Control Devices (APCDs)

MSWIs are commonly equipped with one or more post-combustion APCDs to remove various pollutants prior to release from the stack (e.g., particulate matter, heavy metals, acid gases, and/or organic contaminants) (U.S. EPA, 1992d). These APCDs include:

- Electrostatic precipitator (ESP),
- Fabric filter (FF),
- Dry scrubber (DS),
- Dry sorbent injection (DSI), and
- Wet scrubber (WS)

Electrostatic Precipitator: The ESP is generally used to collect and control particulate matter that evolves during MSW combustion, by introducing a strong electrical field in the flue gas stream; this, in turn, charges the particles entrained in the combustion gases (Donnelly, 1992). Large collection plates receive an opposite charge to attract and collect the particles. CDD/CDF formation can occur within the ESP at temperatures in the range of 150 to about 350°C. As temperatures at the inlet to the ESP increase from 150 to 300°C, CDD/CDF concentrations have been observed to increase by approximately a factor of two for each 30°C increase in temperature (U.S. EPA, 1994f). As temperature increases beyond 300°C, formation rates decline. Although ESPs in this temperature range efficiently remove most particulates and the associated CDD/CDFs, the formation that occurs can result in a net increase in CDD/CDF emissions. This temperature related formation of CDD/CDF within the ESP can be applied to distinguish hot-side ESPs from cold-side ESPs. For purposes of this report, ESPs are classified as follows:

- A cold-side ESP operates at or below 230°C.
- A hot-side ESP operates at an inlet temperature greater than 230°C.

Fabric Filters (FF): FFs are also particulate matter control devices, which remove dioxins associated with particles and any vapors that adsorb to the particles. Six- to 8-inch diameter bags, made from woven fiberglass material, are usually arranged in series. An induction fan forces the combustion gases through the tightly woven fabric. The porosity of the fabric allows the bags to act as filter media and retain a broad range of particles sizes (i.e., down to less than 1 micrometer in diameter). The FF is sensitive to

acid gas; therefore, it is usually operated in combination with spray dryer adsorption of acid gases.

Dry Scrubbers (DS): DSs, also called spray dryer adsorption, involve both the removal of acid gas and particulate matter from the post-combustion gases. By themselves, these units probably have little effect on dioxin emissions. In a typical DS system, hot combustion gases enter a scrubber reactor vessel. An atomized hydrated lime slurry (water plus lime) is injected into the reactor at a controlled velocity (Donnelly, 1992). The hydrated lime slurry rapidly mixes with the combustion gases within the reactor. The water in the hydrated lime slurry quickly evaporates, and the heat of evaporation causes the combustion gas temperature to rapidly decrease. The neutralizing capacity of hydrated lime reduces the combustion gas content of acid gas constituents (e.g., hydrogen chloride gas, and sulfur dioxide gas) by greater than 70 percent. A dry product, consisting of particulate matter and hydrated lime, settles to the bottom of the reactor vessel. DS technology is used in combination with ESPs. The DS reduces ESP inlet temperatures to make a cold-side ESP. DS/FFs have achieved greater than 95 percent reduction and control of CDD/CDFs in MSWI emissions (U.S. EPA, 1992d).

Dry Sorbent Injection (DSI): DSI is used to reduce acid gas emissions. By themselves, these units probably have little effect on dioxin emissions. DSI involves the injection of dry hydrated lime or soda ash either directly into the combustion chamber or into the flue duct of the hot post-combustion gases. In either case, the reagent reacts with and neutralizes the acid gas constituents (Donnelly, 1992).

Wet Scrubber (WS): WS devices are designed for acid gas removal, and are more common to MSWIs in Europe than in the United States. They should help reduce emissions of dioxin in both vapor and particle forms. WS devices consist of two-stage scrubbers. The first stage removes hydrogen chloride (HCl), and the second stage removes sulfur dioxide (SO_2) (Donnelly, 1992). Water is used to remove the HCl, and caustic or hydrated lime is added to remove SO_2 from the combustion gases.

In addition to the APCDs described above, some less common types are also used in some MSWIs. An example is the Electro Granular Bed (EGB), which consists of a packed bed of activated carbon. An electric field is passed through the packed bed; particles entrained in the flue gases are given a negative charge, and the packed bed is given a positive charge. EGB systems function much like an ESP. Particulate matter is

collected within the bed; therefore, they will remove dioxins associated with collected particles and any vapors that adsorb to the particles. Only one facility in the United States currently employs the EGB system, a fluidized bed-RDF MSWI.

Classification Scheme

Based on the array of MSWI technologies described above, a classification system for deriving CDD/CDF emission estimates was developed. As discussed earlier, it is assumed that facilities with common design and operating characteristics have a similar potential for CDD/CDF emissions. The MSWIs operating in 1987 and 1995 were divided according to the eight furnace types and seven APCDs described above. This resulted in 17 design classes in 1987 and 40 design classes in 1995. Because fewer types of APCDs were used in 1987 than in 1995, fewer design classes are needed for estimating emissions. This taxonomy is summarized in Figures 3-7 and 3-8.

3.1.2. Characterization of MSWI Facilities in Reference Years 1995 and 1987

Table 3-1 lists by design/APCD type, the number of facilities and activity level (kg MSW incinerated per year) for MSWIs in the reference year 1995. A similar inventory is provided for reference year 1987 in Table 3-2. This information was derived from four reports: U.S. EPA (1987b), Systems Applications International (1995), Taylor and Zannes (1996), and Solid Waste Technologies (1994). In general, these studies collected the information via telephone interviews with the plant operators.

Using Tables 3-1 and 3-2, a number of comparisons can be made between the two reference years:

- The number of facilities stayed about the same (113 in 1987 and 130 in 1995), but the amount of MSW incinerated more than doubled (13.8 billion kg in 1987 and 28.8 billion kg in 1995).
- The dominant furnace technology shifted from modular in 1987 (57 units and 1.4 billion kg) to mass burn waterwall facilities in 1995 (57 units and 17 billion kg).
- The dominant APCD technology shifted from hot-sided ESPs in 1987 (54 units and 11 billion kg) to fabric filters in 1995 (55 units and 16 billion kg).
- The use of hot-sided ESPs dropped from 54 facilities in 1987 (11 billion kg) to 16 facilities in 1995 (2.2 billion kg).
- The number of uncontrolled facilities dropped from 38 in 1987 (0.6-billion kg) to 10 facilities in 1995 (0.2 billion kg).

3.1.3. Estimation of CDD/CDF Emissions from MSWIs

Compared to other CDD/CDF source categories, MSWIs have been more extensively evaluated for CDD/CDF emissions. Within the context of this report, adequate emission testing for CDD/CDFs were available for 11 of the 113 facilities in the 1987 inventory and 27 of the 130 facilities in the 1995 inventory. Nationwide CDD/CDF air emissions from MSWIs were estimated using a three-step process as described below.

Step 1. Estimation of emissions from all stack tested facilities. The EPA stack testing method (EPA Method 23) produces a measurement of CDD/CDF in units of mass concentration of CDD/CDF (i.e., nanograms per dry standard cubic meter of combustion gas [ng/dscm]) at standard temperature and pressure (20°C and 1 atmosphere), and adjusted to a measurement of 7 percent oxygen in the flue gas (U.S. EPA, 1995b). This concentration is assumed to represent conditions at the point of release from the stack into the air. Equation 3-1 below was used to derive annual emission estimates for each tested facility:

$$E_{TEQ} = \frac{C \times V \times CF \times H}{10^9 \text{ ng/g}} \qquad \text{(Eqn. 3-1)}$$

Where:

E_{TEQ}	=	Annual TEQ emission (g/yr)
C	=	Combustion flue gas TEQ concentration (ng/dscm) (20°C, 1 atm; adjusted to 7% O_2)
V	=	Volumetric flow rate of combustion flue gas (dscm/hour) (20°C, 1 atm; adjusted to 7% O_2)
CF	=	Capacity factor, fraction of time that the MSWI operates (i.e., 0.85)
H	=	Total hours in a year (8,760 hr/yr)

After calculating annual emissions for each tested facility, the emissions were summed across all tested facilities for each reference year. [Note: Many of the emission tests do not correspond exactly to these 2 years. In these cases, the equipment conditions present at the time of the test were compared to those during the reference year to determine their applicability.]

Step 2. Estimation of emissions from all non-tested facilities. This step involves multiplying the emission factor and annual activity level for each MSWI design class and then summing across classes. The activity levels for reference years 1995 and 1987 are summarized in Tables 3-1 and 3-2, respectively. The emission factors were derived by averaging the emission factors across each tested facility in a design class. The emission factor for each facility was calculated using the following equation:

$$EF_{mswi} = \frac{C \times F_v}{I_w} \qquad \text{(Eqn. 3-2)}$$

Where:

EF_{mswi} = Emission factor, average ng TEQ per kg of waste burned
C = TEQ or CDD/CDF concentration in flue gases (ng TEQ/dscm) (20°C, 1 atm; adjusted to 7% O_2)
F_v = Volumetric flue gas flow rate (dscm/hr) (20°C, 1 atm; adjusted to 7% O_2)
I_w = Average waste incineration rate (kg/hr)

Example: A mass burn waterwall MSWI equipped with cold-sided ESP.

Given:

C = 10 ng TEQ/dscm (20°C, 1 atm; adjusted to 7% O_2)
F_v = 40,000 dscm/hr (20°C, 1 atm; adjusted to 7% O_2)
I_w = 10,000 kg MSW/hr

$$EF_{MBWW} = \frac{10 \text{ ng}}{\text{dscm}} \times \frac{40{,}000 \text{ dscm}}{\text{hr}} \times \frac{\text{hr}}{10{,}000 \text{ kg}}$$

$$EF_{MBWW} = \frac{40 \text{ ng TEQ}}{\text{kg MSW burned}}$$

EPA was not able to obtain engineering test reports of CDD/CDF emissions for a number of design classes. In these cases, the above procedure could not be used to derive emission factors. Instead, the emission factors of the tested design class that was judged most similar in terms of dioxin control was assumed to apply to the untested class. The following logic was used to make this decision:

1. The tested APCDs for the furnace type of the untested class were reviewed to see if any operated at a similar temperature.
2. If any operated at similar temperatures, the one with most similar technology was assumed to apply.
3. If none operated at a similar temperature, then the most similar furnace type with same control device was assumed to apply.

Table 3-3 lists all design categories with no tested facilities and shows the class with tested facilities that was judged most similar.

It should be understood that the emission factors for each design class are the same for both reference years. This is because the emission factor is determined only by the design and operating conditions and is independent of the year of the test.

Step 3. Sum emissions from tested and untested facilities. This step simply involves summing emissions from all tested and untested facilities. This process is shown in Tables 3-4 and 3-5 for the reference years 1995 and 1987, respectively. The tables are organized by design class and show separately the emission estimates for the tested and untested facilities. The calculation of emissions from untested facilities is broken out to show the activity level and emission factor for each design class.

3.1.4. Summary of CDD/CDF (TEQ) Emissions from MSWIs for 1995 and 1987

The activity level estimates (i.e., the amount of MSW that is annually combusted by the various MSWI technologies) are given a high confidence rating for both 1987 (i.e., 13.8 billion kg of waste) and 1995 (i.e., 28.8 billion kg of waste). For both years, comprehensive surveys of activity levels were conducted by independent sources on virtually all facilities (U.S. EPA, 1987b; Systems Application International, 1995; Taylor and Zannes, 1996; Solid Waste Technologies, 1994).

The emission factor estimates are given a medium confidence rating for both 1987 and 1995. A moderate fraction of the facilities were tested in both years: 11 of 113 facilities in 1987 (10 percent), and 27 of 130 facilities (21 percent) in 1995. Moreover, the tested facilities represent 21 and 27 percent of the total activity level of operating MSWIs in 1987 and 1995, respectively. These tests represent most of the design

categories identified in this report. The emission factors were developed from emission tests that followed standard EPA protocols, used strict QA/QC procedures, and were well documented in engineering reports. Because all tests were conducted under normal operating conditions, some uncertainty exists about the magnitude of emissions that may occur during other conditions (i.e., upset conditions, start-up and shut-down).

These confidence ratings produce an overall medium confidence rating in the annual emission estimates of 7,915 g I-TEQ_{DF} (8,877 g TEQ_{DF}-WHO_{98}) in 1987 and 1,100 g I-TEQ_{DF} (1,250 g TEQ_{DF}-WHO_{98}) in 1995.

3.1.5 Congener Profiles of MSWI Facilities

The air emissions from MSWIs contain a mixture of CDD and CDF congeners. These mixtures can be translated into what are termed 'congener profiles,' which represent the distribution of total CDDs and CDFs present in the mixture. A congener profile may serve as a signature of the types of CDDs and CDFs associated with particular MSWI technology and APCD. Figure 3-9 is a congener profile of a mass-burn waterwall MSWI equipped with a dry scrubber and fabric filter (i.e., the most common type of MSWI and APCD design in use today). This congener profile indicates that OCDD dominates CDD/CDF emissions and that every toxic CDD/CDF congener is detected in the emissions.

3.1.6 Estimated CDD/CDFs in MSWI Ash

Ash from MSWIs is required to be disposed of in permitted landfills from which releases to the general environment are controlled. For background purposes, however, some information is presented below about the quantities of CDD/CDFs in ash from MSWIs.

An estimated 7 million metric tons of total ash (bottom ash plus fly ash) were generated by MSWIs in 1992 (telephone conversation between J. Loundsberry, U.S. EPA Office of Solid Waste, and L. Brown, Versar, Inc., on February 24, 1993). U.S. EPA (1991b) indicated that 2 to 5 million metric tons of total ash were produced annually in the late 1980s from MSWIs, with fly ash comprising 5 to 15 percent of the total. U.S. EPA (1990c) reported the results of analyses of MSWI ash samples for CDDs and CDFs. Ashes from five state-of-the-art facilities located in different regions of the United States were analyzed for all 2,3,7,8-substituted CDDs and CDFs. The TEQ levels in the ash (fly

ash mixed with bottom ash) ranged from 106 to 466 ng I-TEQ_{DF}/kg, with a mean value of 258 ng I-TEQ_{DF}/kg. CDD/CDF levels in fly ash are generally much higher than in bottom ash. For example, Fiedler and Hutzinger (1992) reported levels of 13,000 ng I-TEQ_{DF}/kg in fly ash.

In another study (Washington, 1998), CDD/CDF congener data were reported for ash and other solid residuals from three municipal incinerators (Fort Lewis, Bellingham [municipal plus medical wastes], and Spokane). The data were compiled and evaluated to determine a total I-TEQ concentration and loading. Non-detect values were included as either zero, ½ DL, or at the DL. The results were as follows, assuming that non-detect values were at zero concentration:

Location	Type of Residual	T-TEQ (μg/kg)	I-TEQ (mg/day)
Ft. Lewis	Bottom Ash Fly Ash	0.00 4.98	0.00 0.76
Bellingham	Mixed Ash (avg. of 3 tests)	0.038	1.14
Spokane	Mixed Ash Fly Ash Bottom Ash	0.163 0.51 0.0001	38.0 24.3 0.02

In Shane (1990), five municipal incinerator ashes were analyzed for a number of constituents including CDDs (not CDFs) and PCBs. For dioxins, three of the incinerators were at non-detectable levels (detection limit of 1 μg/kg). The other two incinerators had detectable levels of five CDD congener groups. (No analyses were reported for individual congeners.) The average for those two units were:

TCDD	26 μg/kg
PeCDDs	59 μg/kg
HxCDDs	53 μg/kg
HpCDDs	25 μg/kg
OCDDs	12 μg/kg

These levels were much higher that those reported in U.S. EPA (1990c).

For PCBs, the five sets of ashes were analyzed for 10 congener groups. All groups were detected for one of the incinerators. However, the other four incinerators contained little or no octa-, nona-, or deca- congeners. The average PCB concentration (all congener groups) for the five incinerators was 216 μg/kg, with a range of 99-322 μg/kg.

No generation rates of the ashes were given in Shane (1990). Therefore, the measured concentrations cannot be readily converted to quantities of CDDs or PCBs. The ashes from each of the five incinerators were disposed of in multiple fashions. For two of the incinerators, the ash was sent to metal recovery and also landfilled. For a third, the fly ash was sold. For a fourth, the ashes were only landfilled. For the fifth, the ashes were used in road building and also landfilled. For those incinerators with more than one ash disposition, no breakdown was given of how much went to each location. There were 15 other incinerators discussed in Shane (1990). Thirteen of them disposed of their ash exclusively in landfills, and the other two partially disposed of their ash in landfills.

Table 7 of Clement (1988) presented 13 data sets for CDD/CDF congener groups for a municipal incinerator ash. The average data for each congener group and the ranges of each group are given in Table 3-6. No data were presented in Clement (1988) for individual congeners, nor were there data for ash quantities.

In Table 3-3 of U.S. EPA (1987a), there were data stating that ashes from three incinerators (one in North America, one in Europe, and one in Japan) had mean CDD concentrations of 363, 588, and 2.6 μg/kg, respectively. The ranges of those data were from <0.5 to 3.537 μg/kg. Similarly, for CDFs, the respective mean concentrations for the first two incinerators were 923 and 288 μg/kg. The third incinerator was not reported. The CDF range for the two incinerator ashes was <0.5 to 1,770 μg/kg. No data were given for individual congeners, nor were there any data for quantities of the ashes.

In Table 1 of Lahl (1991), data were presented for the concentrations of total CDDs and for total CDFs for the ash from an electrostatic precipitator from a municipal incinerator. Data were reported for summer sampling and for winter sampling. The total CDDs in the summer were 140.46 μg/kg, and for the winter were 86.00 μg/kg. The total CDFs in the summer were 54.97 μg/kg, and for the winter were 73.85 μg/kg. No data

were given for individual congeners, nor was there information about the quantity of precipitator ash generated. It was assumed that the data were not for TEQs.

In Table 3-11 of U.S. EPA (1987a), a wire reclamation incinerator was reported to have 0.41 μg/kg of CDDs and 11.6 μg/kg of CDFs in fly ash from its "stack" emissions. For the same incinerator, the "furnace" ash concentrations were reported as 0.58 μg/kg CDDs and 0.73 μg/kg CDFs. Again, no data were given for individual congeners, nor were there any data for quantities of the ashes.

Data from the aforementioned sources have been compiled in Table 3-7 for comparison purposes. Annual TEQ amounts were estimated by multiplying the mean TEQ total ash concentration by the estimated amount of MSWI ash generated annually (approximately 7 million metric tons in 1995 and 5 million metric tons in 1987). Where possible, ash quantities were broken down into fly ash and/or bottom ash categories. Fly ash is assumed to be 10% of the total ash and bottom ash is assumed to be 90% of the total ash.

Each of the five facilities sampled in U.S. EPA (1990c) had companion ash disposal facilities equipped with leachate collection systems or some means of collecting leachate samples. Leachate samples were collected and analyzed for each of these systems. Detectable levels were only found in the leachate at one facility (3 ng I-TEQ_{DF}/L); the only detectable congeners were HpCDDs, OCDD, and HpCDFs.

3.1.7 Recent EPA Regulatory Activities

On December 19, 1995, EPA promulgated CDD/CDF emission standards for all existing and new MSWI units at facilities with aggregate combustion capacities greater than 35 metric tons per day (Federal Register, 1995e). In response to a court remand, the regulations were subsequently amended to remove small MWC units (i.e., units with capacities ranging from 35 to 225 kkg/day) (Federal Register, 1997c). The specific emission standards (expressed as ng/dscm of total CDD/CDF - based on standard dry gas corrected to 7 percent oxygen) are a function of the size, APCD configuration, and age of the facility as listed below:

1995 Emission standard (ng total CDD/CDF/dscm)	Facility age, size, and APCD
60	• Existing; >225 metric tons/day; ESP-based APCD
30	• Existing; >225 metric tons/day; non-ESP-based APCD
13	• New; >225 metric tons/day

EPA reproposed emission standards for small MWCs (defined as units with capacities of between 32 and 224 kkg/day) on August 30, 1999 (Federal Register, 1999c). The proposed emission standard is 125 ng total CDD/CDF per dscm at 7 percent oxygen.

States have up to 3 years from promulgation of the Federal standards to submit revised State Implementation Plans to EPA for approval. Once approved, States have the primary responsibility to implement the new standards. EPA's Office of Air Quality Planning and Standards (OAQPS) estimates that the full compliance by all MSWIs with the 1995 standards and 1999 proposed standards will result in an annual emission of about 12 g I-TEQ_{DF}/yr (U.S. EPA, 2000a).

3.2. HAZARDOUS WASTE INCINERATION

Hazardous waste incineration (HWI) is the controlled pyrolysis and/or oxidation of potentially dangerous liquid, gaseous and solid waste. HWI is one technology used to manage hazardous waste under the Resource Conservation and Recovery Act (RCRA) and Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (Superfund) programs. As described below, hazardous wastes are burned in a variety of situations and are covered in a number of different sections in this report.

- Much of the hazardous waste is burned in facilities dedicated to burning hazardous waste. Most of these dedicated facilities are located on-site at chemical manufacturing facilities and only burn waste associated with their on-site industrial operations. Hazardous waste is also burned at dedicated facilities located off-site from manufacturing facilities and accept waste from multiple sources. These fixed location facilities dedicated to burning hazardous waste at both on- and off-site locations are addressed in Sections 3.2.1 to 3.2.4.

- Hazardous waste is also burned in industrial boilers and furnaces that are permitted to burn the waste as supplemental fuel. These facilities have significantly different

furnace designs and operations than dedicated HWIs; therefore, they are discussed in Section 3.2.5.

- A number of cement kilns and lightweight aggregate kilns are also permitted to burn hazardous waste as auxiliary fuel; these are discussed separately in Section 5.1.

- Mobile HWIs are typically used for site cleanup at Superfund sites and operate for a limited duration at any given location. These units are mobile in the sense that they can be transported from one location to another. Due to the transitory nature of these facilities, they are not included in this inventory at this time.

The following subsections review the types of HWI technologies commonly in use in the United States, and present the derivation of emissions estimates of CDD/CDFs from all facilities operating in 1995 and 1987.

3.2.1. Furnace Designs for Hazardous Waste Incinerators

The four principal furnace designs employed for the combustion of hazardous waste in the United States are: rotary kiln, liquid injection, fixed hearth, and fluidized-bed incinerators (Dempsey and Oppelt, 1993). The majority of commercial operations are of the rotary kiln incinerator type. On-site (noncommercial) HWI technologies are an equal mix of rotary kiln and liquid injection facilities, with a few additional fixed hearths and fluidized bed operations (U.S. EPA, 1996h). Each of these HWI technologies is discussed below:

Rotary Kiln HWI: Rotary kiln incinerators consist of a rotary kiln, coupled with a high temperature afterburner. Because these are excess air units designed to combust hazardous waste in any physical form (i.e., liquid, semi-solid, or solid), rotary kilns are the most common type of hazardous waste incinerator used by commercial off-site operators. The rotary kiln is a horizontal cylinder lined with refractory material. Rotation of the cylinder on a slight slope provides for gravitational transport of the hazardous waste through the kiln (Buonicore, 1992a). The tumbling action of the rotating kiln causes mixing and exposure of the waste to the heat of combustion, thereby enhancing burnout. Solid and semi-solid wastes are loaded into the top of the kiln by an auger or rotating screw. Fluid and pumpable sludges and wastes are typically introduced into the kiln through a water-cooled tube. Liquid hazardous waste is fed directly into the kiln through a burner nozzle. Auxiliary fuel (natural gas or oil) is burned in the kiln chamber at start-up

to reach elevated temperatures. The typical heating value of hazardous waste (i.e., 8,000 Btu/kg) is sufficient to sustain combustion without auxiliary fuel (U.S. EPA, 1996h). The combustion gases emanating from the kiln are passed through a high temperature afterburner chamber to more completely destroy organic pollutants entrained in the flue gases. Rotary kilns can be designed to operate at temperatures as high as 2,580°C, but more commonly operate at about 1,100°C.

Liquid Injection HWI: Liquid injection incinerators (LIIs) are designed to burn liquid hazardous waste. These wastes must be sufficiently fluid to pass through an atomizer for injection as droplets into the combustion chamber. The LIIs consist of a refractory-lined steel cylinder mounted either in a horizontal or vertical alignment. The combustion chamber is equipped with one or more waste burners. Because of the rather large surface area of the atomized droplets of liquid hazardous waste, the droplets quickly vaporize. The moisture evaporates, leaving a highly combustible mix of waste fumes and combustion air (U.S. EPA, 1996h). Secondary air is added to the combustion chamber to complete the oxidation of the fume/air mixture.

Fixed Hearth HWI: Fixed hearths are starved air or pyrolytic incinerators. Waste is ram-fed into the primary chamber and incinerated below stoichiometric requirements (i.e., at about 50 to 80 percent of stoichiometric air requirements). The resulting smoke and pyrolytic combustion products are then passed though a secondary combustion chamber where relatively high temperatures are maintained by the combustion of auxiliary fuel. Oxygen is introduced into the secondary chamber to promote complete thermal oxidation of the organic molecules entrained in the gases.

Fluidized-bed HWI: The fourth hazardous waste incineration technology is the fluidized-bed incinerator, which is similar in design to that used in municipal solid waste incineration. (See Section 3.1.) In this configuration, a layer of sand is placed on the bottom of the combustion chamber. The bed is preheated by underfire auxiliary fuel at startup. During combustion of auxiliary fuel at start-up, the hot gases are channeled through the sand at relatively high velocity, and the turbulent mixing of combustion gases and combustion air causes the sand to become suspended (Buonicore, 1992a). This takes on the appearance of a fluid medium, hence the incinerator is termed a 'fluidized bed' combustor The incinerator is operated below the melting point temperature of the bed material. Typical temperatures of the fluid medium are within the range of 650 to 940°C.

A constraint on the types of waste burned is that the solid waste particles must be capable of being suspended within the furnace. When the liquid or solid waste is combusted in the fluid medium, the exothermic reaction causes heat to be released into the upper portion of the combustion chamber. The upper portion is typically much larger in volume than the lower portion, and temperatures can reach 1,000°C (Buonicore, 1992a). This high temperature is sufficient to combust volatilized pollutants emanating from the combustion bed.

3.2.2. APCDs for Hazardous Waste Incinerators

Most HWIs use APCDs to remove undesirable components from the flue gases that evolved during the combustion of the hazardous waste. These unwanted pollutants include suspended ash particles (particulate matter or PM), acid gases, metal, and organic pollutants. The APCD controls or collects these pollutants and reduces their discharge from the incinerator stack to the atmosphere. Levels and kinds of these combustion byproducts are highly site-specific, depending on factors such as waste composition and incinerator system design and operating parameters (e.g., temperature and exhaust gas velocity). The APCD is typically comprised of a series of different devices that work together to clean the exhaust combustion flue gas. Unit operations usually include exhaust gas cooling, followed by particulate matter and acid gas control.

Exhaust gas cooling may be achieved using a waste heat boiler or heat exchanger, mixing with cool ambient air, or injection of a water spray into the exhaust gas. A variety of different types of APCDs are employed for the removal of particulate matter and acid gases. Such devices include: wet scrubbers (such as venturi, packed bed, and ionizing systems), electrostatic precipitators, and fabric filters (sometimes used in combination with dry acid gas scrubbing). In general, the control systems can be grouped into the following three categories: wet, dry, and hybrid wet/dry systems. The controls for acid gases (either dry or wet systems) cause temperatures to be reduced preceding the control device. This impedes the extent of formation of CDDs and CDFs in the post-combustion area of the typical HWI. It is not unusual for stack concentrations of CDD/CDFs at a particular HWI to be in the range of 1 to 100 ng CDD/CDF/dscm (Helble, 1993), which is low in comparison to other waste incineration systems. The range of total CDD/CDF flue gas concentrations measured in the stack emissions of HWIs during trial burns across the

class of HWI facilities, however, has spanned four orders of magnitude (ranging from 0.1 to 1,600 ng/dscm) (Helble, 1993). The APCD systems are described below:

- **Wet Systems:** A wet scrubber is used for both particulate and acid gas control. Typically, a venturi scrubber and packed-bed scrubber are used in a back-to-back arrangement. Ionizing wet scrubbers, wet electrostatic precipitators, and innovative venturi-type scrubbers may be used for more efficient particulate control. Wet scrubbers generate a wet effluent liquid wastestream (scrubber blowdown), are relatively inefficient at fine particulate control compared to dry control techniques, and have equipment corrosion concerns. However, wet scrubbers do provide efficient control of acid gases and have lower operating temperatures (compared with dry systems), which may help control the emissions of volatile metals and organic pollutants.
- **Dry Systems:** In dry systems, a fabric filter or electrostatic precipitator (ESP) is used for particulate control. A fabric filter or ESP is frequently used in combination with dry scrubbing for acid gas control. Dry scrubbing systems, in comparison with wet scrubbing systems, are inefficient in controlling acid gases.
- **Hybrid Systems:** In hybrid systems, a dry technique (ESP or fabric filter) is used for particulate control, followed by a wet technique (wet scrubber) for acid gas control. Hybrid systems have the advantages of both wet and dry systems (lower operating temperature for capture of volatile metals, efficient collection of fine particulate, efficient capture of acid gases), while avoiding many of the individual disadvantages. In some hybrid systems, known as "zero discharge systems," the wet scrubber liquid is used in the dry scrubbing operation, thus minimizing the amount of liquid byproduct waste.
- **Uncontrolled HWIs:** Facilities that do not use any air pollution control devices fall under a separate and unique category. These are primarily liquid waste injection facilities, which burn low ash and chlorine content wastes; therefore, they are low emitters of PM and acid gases.

3.2.3. Estimation of CDD/CDF Emission Factors for Hazardous Waste Incinerators

For purposes of estimating emission factors, this document considers subdividing the combustors in each source category into design classes judged to have similar potential for CDD/CDF emissions. As explained below, it was decided not to subdivide dedicated HWIs.

Combustion research has identified three mechanisms involved in the emission of CDD/CDFs from combustion systems: (1) CDD/CDFs can be introduced into the combustor with the feed and pass through the system not completely burned/destroyed; (2) CDD/CDFs can be formed by chemical reactions inside the combustion chamber; and (3) CDD/CDFs can be formed by chemical reactions outside the combustion chamber. The total CDD/CDF emissions are likely to be the net result of all three mechanisms; however, the relative importance of the mechanisms can vary among source categories. In the case of HWIs, the third mechanism (i.e., post-combustion formation) is likely to dominate, because HWIs are typically operated at high temperatures and long residence times, and most have sophsiticated real-time monitoring and controls to manage the combustion process. Therefore, any CDD/CDFs present in the feed or formed during combustion are likely to be destroyed before exiting the combustion chamber. Consequently, for purposes of generating emission factors, it was decided not to subdivide this class on the basis of furnace type.

Emissions resulting from the post-combustion formation in HWIs can be minimized through a variety of technologies:

- **Rapid Flue Gas Quenching**: The use of wet and dry scrubbing devices to remove acid gases usually results in the rapid reduction of flue gas temperatures at the inlet to the PM APCD. If temperature is reduced below 200˚C, the low-temperature catalytic formation of CDD/CDFs is substantially retarded.
- **Use of Particulate Matter (PM) Air Pollution Control Devices**: PM control devices can effectively capture condensed and adsorbed CDD/CDFs that are associated with the entrained particulate matter (in particular, that which is adsorbed on unburned carbon containing particulates).

- **Use of Activated Carbon**: Activated carbon injection is used at some HWIs to collect (sorb) CDD/CDFs from the flue gas. This may be achieved using carbon beds or by injecting carbon and collecting it in a downstream PM APCD.

All of these approaches appear very effective in controlling dioxin emissions at dedicated HWIs, and insufficient emissions data are available to generalize about any minor differences. Consequently, for purposes of generating emission factors, it was decided not to subdivide this class on the basis of APCD type.

EPA compiled a data base summarizing the results of stack testing for CDDs and CDFs at 17 HWIs (U.S. EPA, 1996c). Most facilities were tested between 1993 and 1996. For purposes of this report, CDD/CDF emission factors were estimated based on the results of the emission tests contained in this data base. The breakdown of furnace types of tested HWI facilities is as follows: 10 rotary kiln incinerators, 4 liquid injection incinerators, 1 fluidized-bed incinerator, and 2 fixed-bed.

As stated earlier, EPA/ORD decided not to subclassify the dedicated HWI designs for purposes of deriving an emission factor (EF). Instead, the emission factor was derived as an average across all 17 tested facilties. First, an average emission factor was calculated for each of 17 HWIs with Equation 3-3.

$$EF_{hwi} = \frac{C \times F_v}{I_w} \qquad \text{(Eqn. 3-3)}$$

Where:

EF_{hwi} = Emission factor (average ng TEQ per kg of waste burned)
C = TEQ or CDD/CDF concentration in flue gases (ng TEQ/dscm) (20°C, 1 atm; adjusted to 7% O_2)
F_v = Volumetric flue gas flow rate (dscm/hr) (20°C, 1 atm; adjusted to 7% O_2)
I_w = Average waste incineration rate (kg/hr)

After developing average emission factors for each HWI, the overall average congener-specific emission factor was derived for all 17 tested HWIs using Equation 3-4.

$$EF_{avgHWI_{n=1-17}} = (EF_{HWI_1} + EF_{HWI_2} + EF_{HWI_3} + \ldots\ldots\ldots + EF_{HWI_{17}}) / N \qquad \text{(Eqn. 3-4)}$$

Where:

EF_{HWI} = Average emission factor for the 17 tested HWIs, (ng/kg)
N = Number of tested facilities (i.e., 17)

Table 3-8 presents the average emission factors developed for specific congeners, total CDDs/CDFs, and TEQs for the tested HWIs. The average congener emission profile for the 17 tested HWIs are presented in Figure 3-10. The average I-TEQ_{DF} and TEQ_{DF}-WHO_{98} emission factors for the 17 tested HWIs are 3.83 ng I-TEQ_{DF}/kg of waste feed and 3.88 ng TEQ_{DF}-WHO_{98}/kg of waste feed (assuming not detected values are zero). The available data did not support development of different emission factors for the two reference years, 1987 and 1995.

3.2.4. Emission Estimates for Hazardous Waste Incinerators

Although emissions data were available for 10 percent of the HWIs (i.e., 17 of 162 have been tested), the emission factor estimates are assigned a medium confidence rating due to uncertainties resulting from:

- *Variability of the waste feeds*. The physical and chemical composition of the waste can vary from facility to facility and even within a facility. Consequently, CDD/CDF emissions measured for one feed may not be representative of other feeds.

- *Trial burns*. Much of the CDD/CDF emissions data were collected during trial burns, which are required as part of the RCRA permitting process and are used to establish Destruction Rated Efficiency (DRE) of principal hazardous organic constituents in the waste. During trial burns, a prototype waste is burned, which is intended to maximize the difficulty in achieving good combustion. For example, chlorine, metals, and organics may be added to the waste. The HWI may also be operated outside normal operating conditions. The temperature of both the furnace and the APCD may vary by a wide margin (high and low temperatures), and the waste feed system may be increased to maximum design load. Accordingly, it is uncertain how representative the CDD/CDF emissions measured during the trial burn will be of emissions during normal operating conditions.

Dempsey and Oppelt (1993) estimated that up to 1.3 million metric tons of hazardous waste were combusted in HWIs during 1987. EPA estimated that 1.5 million metric tons of hazardous waste were combusted each year in the early 1990s in HWIs (Federal Register, 1996b). This activity level estimate for 1995 is assigned a high confidence rating, because it is based on a review by EPA of the various studies and surveys conducted in the 1990s to assess the quantity and types of hazardous wastes

being managed by various treatment, storage, and disposal facilities. A confidence rating of medium is assigned to the activity level estimate for 1987.

The annual TEQ emissions for the reference years 1995 and 1987 were estimated using Equation 3-5.

$$E_{HWI} = EF_{HWI} \times A_{HWI} \qquad \text{(Eqn. 3-5)}$$

Where:

E_{HWI} = Annual emissions from all HWIs, tested and non-tested (g TEQ/yr)
EF_{HWI} = Mean emission factor for HWIs (ng TEQ/kg of waste burned)
A_{HWI} = Annual activity level of all operating HWIs (million metric tons/yr)

Applying the average TEQ emission factors for dedicated HWIs (3.83 ng I-TEQ_{DF}/kg and 3.88 ng TEQ_{DF}-WHO_{98}/kg waste) to these production estimates yields estimated emissions of 5.7 g I-TEQ_{DF} (or 5.8 g TEQ_{DF}-WHO_{98}) in 1995 and 5.0 g TEQ (I-TEQ_{DF} or TEQ_{DF}-WHO_{98}) in 1987 for HWIs. The medium confidence rating assigned to the emission factor, combined with the medium confidence rating for the 1995 activity level and medium confidence rating for the 1987 activity level, yields an overall medium confidence rating for both years.

3.2.5. Recent EPA Regulatory Activities

EPA/OSW has also developed estimates of the CDD/CDF emissions from HWIs as part of the development of the Hazardous Waste Combustors Rule (Federal Register, 1999b). Like ORD, OSW also decided not to subdivide the HWIs on the basis of design. Instead of an emission factor approach, OSW used an imputation method to estimate emissions at untested facilities. This procedure involved randomly selecting measured CDD/CDF flue gas concentrations (ng/dscm) from the pool of tested HWI facilities and assigning them to the untested facilities. With this procedure, all non-tested HWIs have an equal chance of being assigned any flue gas concentration from the pool of measured values. The flue gas concentrations were combined with flue gas flow rates for each facility to estimate the emission rate. Using this approach, EPA/OSW estimated that I-TEQ_{DF} emissions in 1997 were 24.8 grams and that the emissions would be reduced to

3.5 g after full implementation of the rule. A key difference in these approaches is that ORD uses waste feed rate directly in the calculation of emissions and the OSW approach is independent of waste feed rate. Both procedures are reasonable ways to deal with the broad range of uncertainties and both yield similar emission estimates. ORD has not identified any inherent advantage of one approach over the other and elected to use the emission factor approach primarily because it is consistent with the methods used in this document to characterize CDD/CDF emissions from all other source categories.

3.2.6. Industrial Boilers and Furnaces Burning Hazardous Waste

In 1991, EPA established rules that allow the combustion of some liquid hazardous waste in industrial boilers and furnaces (Federal Register, 1991c). These facilities typically burn oil or coal for the primary purpose of generating electricity. Liquid hazardous waste can only be burned as supplemental (auxiliary) fuel, and usage is limited by the rule to no more than 5 percent of the primary fuels. These facilities typically use an atomizer to inject the waste as droplets into the combustion chamber and are equipped with particulate and acid gas emission controls. In general, they are sophisticated, well controlled facilities, which achieve good combustion.

The national data base contains congener-specific emission concentrations for two tested boilers burning liquid hazardous waste as supplemental fuel. The average congener and congener group emission profiles for the industrial boiler data set are presented in Figure 3-11. The average congener and TEQ emission factors are presented in Table 3-8. The limited set of emissions data prevented subdividing this class for the purpose of deriving an emission factor. The equation used to derive the emission factor is the same as Equation 3-4 above. The average TEQ emission factor for the two industrial boilers is 0.64 ng I-TEQ_{DF}/kg of waste feed (or 0.65 ng TEQ_{DF}-WHO_{98}/kg of waste feed). These emission factors are assigned a low confidence rating, because they reflect testing at only 2 of the 136 hazardous waste boilers/furnaces.

Dempsey and Oppelt (1993) estimated that approximately 1.2 billion kg of hazardous waste were combusted in industrial boilers/furnaces in 1987. EPA estimates that each year in the early 1990s approximately 0.6 billion kg of hazardous waste were combusted in industrial boilers/furnaces (Federal Register, 1996b). It is possible that cement kilns and lightweight aggregate kilns burning hazardous waste were included in

this estimate by Dempsey and Oppelt for 1987; the estimate for 1995 does not appear to include these hazardous waste burning kilns. This activity level estimate for 1995 is assigned a medium confidence rating, because it was based on a review by EPA of the various studies and surveys conducted in the 1990s to assess the quantity and types of hazardous wastes being managed by various treatment, storage, and disposal facilities. A confidence rating of low is assigned to the estimated activity level for 1987. The 1987 estimate was largely based on a review of State permits (Dempsey and Oppelt,1993).

Equation 3-5, used to calculate annual TEQ emissions for dedicated HWIs, was also used to calculate annual TEQ emissions for industrial boilers/furnaces. Multiplying the average TEQ emission factors by the total estimated kg of liquid hazardous waste burned in 1995 and 1987 yields annual emissions in g-TEQ/yr. From this procedure, the emissions from all industrial boilers/furnaces burning hazardous waste as supplemental fuel are estimated as 0.38 g I-TEQ_{DF} (or 0.39 g TEQ_{DF}-WHO_{98}) in 1995 and 0.77 g I-TEQ_{DF} (or 0.78 g TEQ_{DF}-WHO_{98}) in 1987. Because of the low confidence rating for the emission factor, the overall confidence rating is low for both the 1987 and 1995 emission estimates.

3.2.7. Solid Waste from Hazardous Waste Combustion

U.S. EPA (1987a) contains limited data on ash generated from hazardous waste incineration. Table 3-8 of U.S. EPA (1987a) indicates that 538 μg/kg and 2,853 μg/kg were the mean concentrations of CDDs and CDFs, respectively, from a hazardous waste incinerator with an afterburner. Specific data for congeners and for ash quantities were not given.

3.3. MEDICAL WASTE INCINERATION

Medical waste incineration (MWI) is the controlled burning of solid wastes generated primarily by hospitals, veterinary, and medical research facilities. The U.S. EPA defines medical waste as any solid waste generated in the treatment, diagnosis, or immunization of humans or animals, or research pertaining thereto, or in the production or testing of biologicals (Federal Register, 1997b). The primary purposes of MWI are to reduce the volume and mass of waste in need of land disposal, and to sterilize the infectious materials. The following subsections review the basic types of MWI designs

used to incinerate medical waste, review the distribution of APCDs used on MWIs, summarize the derivation of dioxin TEQ emission factors for MWIs, and summarize the national dioxin TEQ emission estimates for reference years 1995 and 1987.

3.3.1. Design Types of MWIs Operating in the United States

For purposes of this document, EPA has classified MWIs into three broad technology categories: modular furnaces using controlled-air, modular furnaces using excess-air, and rotary kilns. Of the MWIs in use today, the vast majority are believed to be modular furnaces using controlled-air. EPA has estimated that 97 percent are modular furnaces using controlled-air, 2 percent are modular furnaces using excess air, and 1 percent are rotary kiln combustors (U.S. EPA, 1997b).

Modular Furnaces Using Controlled-air: Modular furnaces have two separate combustion chambers mounted in series (one on top of the other). The lower chamber is where the primary combustion of the medical waste occurs. Medical waste is ram-fed into the primary chamber, and underfire air is delivered beneath the incinerator hearth to sustain good burning of the waste. The primary combustion chamber is operated at below stoichiometric levels, hence the terms "controlled" or "starved-air." With sub-stoichiometric conditions, combustion occurs at relatively low temperatures (i.e., 760 to 985°C). Under the conditions of low oxygen and low temperatures, partial pyrolysis of the waste occurs, and volatile compounds are released. The combustion gases pass into a second chamber. Auxiliary fuel (such as natural gas) is burned to sustain elevated temperatures (i.e., 985 to 1,095°C) in this secondary chamber. The net effect of exposing the combustion gases to an elevated temperature is more complete destruction the organic contaminants entrained in the combustion gases emanating from the primary combustion chamber. Combustion air at 100 to 300 percent in excess of stoichiometric requirement is usually added to the secondary chamber. Gases exiting the secondary chamber are directed to an incinerator stack (U.S. EPA, 1997b; U.S. EPA, 1991d; Buonicore, 1992b). Figure 3-12 displays a schematic of a typical modular furnace using controlled-air. Because of it's low cost and good combustion performance, this design has been the most popular choice for MWIs and has accounted for more than 95 percent of systems installed over the past two decades (U.S. EPA, 1990d; U.S. EPA, 1991d; Buonicore, 1992b).

Modular Furnaces Using Excess-air: These systems use the same modular furnace configuration as described above for the controlled air systems. The difference is that the primary combustion chamber is operated at air levels of 100 percent to 300 percent in excess of stoichiometric requirements. Hence the name "excess-air." A secondary chamber is located on top of the primary unit. Auxiliary fuel is added to sustain high temperatures in an excess-air environment. Excess-air MWIs are typically smaller in capacity than controlled-air units and are usually batch-fed operations. This means that the medical waste is ram-fed into the unit and allowed to burn completely before another batch of medical waste is added to the primary combustion chamber.

Rotary Kiln MWI: This technology is similar in terms of design and operational features to the rotary kiln technology employed in both municipal and hazardous waste incineration. (See description in Section 3.1.) Because of their relatively high capital and operating costs, few rotary kiln incinerators are in operation for medical waste treatment (U.S. EPA, 1990d; U.S. EPA, 1991d; Buonicore, 1992b).

MWIs can be operated in three modes: batch, intermittent, and continuous. Batch incinerators burn a single load of waste, typically only once per day. Waste is loaded, and ashes are removed manually. Intermittent incinerators, loaded continuously and frequently with small waste batches, operate less than 24 hours per day, usually on a shift-type basis. Either manual or automated charging systems can be used, but the incinerator must be shut down for ash removal. Continuous incinerators are operated 24 hours per day and use automatic charging systems to charge waste into the unit in small, frequent batches. All continuous incinerators operate using a mechanism to automatically remove the ash from the incinerator (U.S. EPA, 1990d; U.S. EPA, 1991d).

3.3.2. Characterization of MWIs for Reference Years 1995 and 1987

MWI remains a poorly characterized industry in the United States in terms of knowing the exact number of facilities operational over time, the types of APCDs installed on these units, and the aggregate volume and weight of medical waste that is combusted in any given year (U.S. EPA, 1997b). The primary reason for this is that permits were not generally required for the control of pollutant stack emissions from MWIs until the early 1990s when State regulatory agencies began setting limits on emissions of particulate

matter and other contaminants (Federal Register, 1997b). Prior to that timeframe, only opacity was controlled.

The information available to characterize MWIs comes from national telephone surveys, stack emission permits, and data gathered by EPA during public hearings (Federal Register, 1997b). This information suggests the following:

- The number of MWIs in operation was approximately 5,000 in 1987 (U.S. EPA, 1987d) and 2,375 in 1995 (Federal Register, 1997b).
- The amount of medical waste combusted annually in the United States was approximately 1.43 billion kg in 1987 (U.S. EPA, 1987d) and 0.77 billion kg in 1995 (Federal Register, 1997b).

These estimates indicate that, between 1987 and 1995, the total number of operating MWIs and the total amount of waste combusted decreased by more than 50 percent. Certain activities caused this to occur, including more stringent air pollution control requirements by State regulatory agencies and the development of less expensive medical waste treatment technologies, such as autoclaving (Federal Register, 1997b). Because many MWIs have small waste charging capacity (i.e., about 50 metric tons per day), the installation of even elementary APCDs proved not to be cost effective. Thus, a large number of facilities elected to close rather than retrofit.

The actual controls used on MWIs on a facility-by-facility basis in 1987 are unknown, and EPA generally assumes that MWIs were mostly uncontrolled (U.S. EPA,1987d). However, the modular design does cause some destruction of organic pollutants within the secondary combustion chamber. Residence time within the secondary chamber is key to inducing the thermal destruction of the organic compounds. Residence time is the time that the organic compounds entrained within the flue gases are exposed to elevated temperatures in the secondary chamber. EPA has demonstrated with full-scale MWIs that increasing residence time from 1/4 second to 2 seconds in the secondary chamber can reduce organic pollutant emissions, including CDD/CDFs, by up to 90 percent (Federal Register, 1997b). In this regard, residence time can be viewed as a method of air pollution control.

EPA estimates that about two-thirds of medical waste burned in MWIs in 1995 went to facilities equipped with some method of air pollution control (Federal Register, 1997b). The types of APCDs installed and the methods used on MWIs include: dry

sorbent injection, fabric filters, electrostatic precipitators (ESPs), wet scrubbers, and fabric filters combined with packed-bed scrubbers (composed of granular activated carbon). Some organic constituents in the flue gases can be adsorbed by the packed bed. Within the uncontrolled class of MWIs, about 12 percent of the waste were combusted in facilities with design capacities of $<$200 lbs/hr, with the majority of waste burned facilities $>$200 lbs/hr. The estimated breakdown of controlled facilities is: 70 percent of the aggregate activity level are associated with facilities equipped with either wet scrubbers, fabric filters, or ESPs; 29.9 percent are associated with facilities utilizing dry sorbent injection, combined with fabric filters, and less than 1 percent is associated with facilities having the fabric filter/packed-bed APCD (AHA, 1995; Federal Register, 1997b).

3.3.3. Estimation of CDD/CDF Emissions from MWIs

Emission tests reported for 24 MWIs (i.e., about 1 percent of existing facilities) were collected for use in this report. Consequently, most facilities have unmeasured emission levels of dioxin-like compounds. Because so few have been evaluated, the estimation of annual air emissions of CDD/CDFs from MWIs is quite dependent on extrapolations, engineering judgement, and the use of assumptions. In addition, the information about the activity levels of these facilities is also quite limited. With these data limitations, two approaches have been used in the past to estimate CDD/CDF emissions from MWIs, and a third is proposed here. These three approaches are as follows:

1. **EPA/OAQPS Approach**: EPA's Office of Air Quality Planning and Standards (OAQPS) used this approach in support of the promulgation of final air emission standards for hospital/medical/infectious waste incinerators (Federal Register, 1997b).

2. **AHA Approach**: The American Hospital Association proposed an approach in its comments on drafts of this document and on the proposed MWI emissions regulations (AHA, 1995).

3. **EPA/ORD Approach**: In preparation of this document, EPA's Office of Research and Development (ORD) has developed a third approach.

Given the limitations with existing information, both the EPA/OAQPS and AHA approaches are reasonable methods for calculating annual releases of CDD/CDFs from MWIs. Both

methods relied heavily on a series of assumptions to account for missing information. In developing a third approach, EPA/ORD built upon the other two approaches by utilizing the most logical features of each. Because of the uncertainties with existing data, it is currently not known which approach gives the most accurate estimate of CDD/CDF air emissions from all MWIs, nationwide. The three approaches yield different air emission estimates, but the estimates all agree within a factor of four. As discussed below, the EPA/ORD approach used the strengths of the other two approaches, and represents some improvement in estimating CDD/CDF emissions.

3.3.4. EPA/OAQPS Approach for Estimating CDD/CDF Emissions from MWIs

On September 15, 1997, EPA promulgated final standards of performance for new and existing MWIs under the Clean Air Act Amendments (Federal Register, 1997b). CDD/CDF stack emission limits for existing MWIs were established as follows: 125 ng/dscm of total CDD/CDF (at 7 percent O_2, 1 atm), equivalent to 2.3 ng/dscm TEQ. In order to evaluate emissions reductions that will be achieved by the standard, OAQPS estimated, as a baseline for comparison, nationwide annual CDD/CDF emissions from all MWIs operating in 1995.

3.3.4.1. *EPA/OAQPS Approach for Estimating Activity Level*

As a starting point for deriving the national estimates, OAQPS constructed an inventory of the numbers and types of MWIs believed to be operating in 1995. The inventory was based on an inventory of 2,233 MWIs prepared by the American Hospital Association (AHA, 1995), supplemented with additional information compiled by EPA. This created a listing of 2,375 MWIs in the United States. Next a series of assumptions were used to derive activity level estimates, as follows:

1. The analysis divided MWIs into three design types based on the mode of daily operation: batch, intermittent, and continuous. This was done using the information from the inventory on design-rated annual incineration capacity of each facility. The smaller capacity units were assumed to be batch operations, and the others were classified as either intermittent or continuous, assuming a ratio of three to one.

2. The activity level of each facility was estimated by multiplying the design-rated annual incineration capacity of the MWI (kg/hr) by the hours of

operation (hr/yr). The annual hours of operation were determined by assuming a capacity factor (defined as the fraction of time that a unit operates over the year) for each design type of MWI (Randall, 1995). Table 3-9 is a summary of the OAQPS estimated annual operating hours per MWI design type.

3.3.4.2. *EPA/OAQPS Approach for Estimating CDD/CDF Emission Factors*

Based on information obtained from AHA and State regulatory agencies, one-third of the population of MWIs operating in 1995 was etimated to have had no APCDs (i.e., were uncontrolled), and two-thirds had some type of APCD. CDD/CDF TEQ emission factors were then developed for uncontrolled and controlled MWIs. The procedure was as follows:

Estimating TEQ Emission Factors for Uncontrolled Facilities: The uncontrolled category of facilities was subdivided by residence time of the secondary combustion chamber. Based on tests at three MWIs, OAQPS concluded that stack emissions of CDD/CDFs from uncontrolled facilities were dependent on the residence time (i.e., the duration of time the compounds are exposed to elevated temperatures within the secondary combustion chamber) (Strong, 1996). The tests demonstrated that when the residence time in the secondary chamber was short (i.e., <1 sec), the stack emissions of CDDC/CDFs would increase; conversely, the longer the residence time (i.e., >1 sec), the CDD/CDF emissions decrease. The emissions testing at these MWIs provided the basis for the derivation of I-TEQ_{DF} emission factors for residence times of 1/4-sec, 1-sec and 2-sec. Table 3-10 is a summary of the emission factors developed for each MWI type as a function of residence time.

The OAQPS inventory of MWIs in 1995 did not provide residence times for each facility. OAQPS overcame this data gap by assuming that residence time in the secondary combustion chamber approximately corresponds with the particulate matter (PM) stack emission limits established in State air permits. This approach assumed that the more stringent PM emission limits would require longer residence times in the secondary chamber in order to further oxidize carbonaceous soot particles and reduce PM emissions. Table 3-10 lists the assumed residence times in the secondary chamber corresponding to various State PM emission limits. State Implementation Plans (SIPs) were reviewed to determine the PM emission limits for incinerators, and from this review, both a residence

time and an I-TEQ_{DF} emission factor were assigned to each uncontrolled MWI on the inventory.

Estimating TEQ Emission Factors for Controlled MWIs: Two-thirds of the MWI population were assumed to have some form of APCD. As previously discussed, APCDs typically used by MWIs consist of one or more of the following: wet scrubber, dry scrubber, and fabric filter combined with a packed bed. The EPA/OAQPS approach also included the addition of activated carbon to the flue gases as a means of emissions control (i.e., dry scrubbers combined with carbon injection). TEQ emission factors were developed for these control systems based on incinerator emissions testing data gathered in support of the regulations (U.S. EPA, 1997b). Because the inventory did not list the APCDs for all MWIs, State requirements for PM control were used to make assumptions about the type of APCD installed on each facility in the inventory. These assumptions are summarized in Table 3-11.

3.3.4.3. *EPA/OAQPS Approach for Estimating Nationwide CDD/CDF TEQ Air Emissions*

Annual TEQ emissions for each MWI facility were calculated as a function of the design capacity of the incinerator, the annual waste charging hours, the capacity factor, and the TEQ emission factor as shown in Equation 3-6.

$$E_{mwi} = (C \times H \times C_1) \times F_{TEQ} \qquad \text{(Eqn. 3-6)}$$

Where:

E_{mwi}	=	Annual MWI CDD/F TEQ stack emissions (g/yr)
C	=	MWI design capacity (kg/hr)
H	=	Annual medical waste charging hours (hr/yr)
C_1	=	Capacity factor (unitless)
F_{TEQ}	=	CDD/CDF TEQ emission factor (g TEQ/kg)

The annual TEQ air emission of all MWIs operating in 1995 is the sum of the annual emissions of each individual MWI. The following equation is applied to estimate annual TEQ emissions from all MWIs.

$$E_{mwi}(\text{nationwide}) = (Em_{mwi_1} + Em_{mwi_2} + + \ldots\ldots + Em_{mwi_{2375}}) \quad \text{(Eqn. 3-7)}$$

Where:

E_{mwi}(nationwide) = Nationwide MWI TEQ emissions (g/yr)

Table 3-11 is a summary of I-TEQ_{DF} emissions for 1995 estimated using the EPA/OAQPS Approach.

3.3.5. AHA Approach for Estimating CDD/CDF Emissions from MWIs

In 1995, the American Hospital Association (AHA) submitted written comments to EPA in response to EPA's request for public comment of the 1994 draft public release of this document (AHA, 1995). As part of these comments, the AHA attached an analysis of CDD/CDF emissions from MWIs prepared by Doucet (1995) for the AHA. Doucet (1995) estimated the total number of MWIs operating in 1995, the distribution of APCDs, CDD/CDF TEQ emission factors, and the nationwide TEQ emissions. The following is a brief discussion of the AHA inventory and the Doucet (1995) analysis.

From a national telephone survey of member hospitals conducted between September and November 1994, the AHA developed what is generally considered as the first attempt to systematically inventory MWIs in the United States. Approximately 6 percent of the hospitals with MWIs were contacted (AHA,1997). The AHA survey showed that, as of December 1994, 2,233 facilities were in operation. Doucet (1995) subdivided the AHA MWI inventory into two uncontrolled categories based on combustor design-rated capacity and two controlled categories based on APCD equipment. Doucet (1995) then developed CDD/CDF emission factors for each MWI category. Test reports of 19 MWIs were collected and evaluated. Average CDD/CDF TEQ flue gas concentrations (i.e., ng/dscm @7 percent O_2) were derived by combining tests from several MWIs in each capacity range category and APCD. The average TEQ flue gas concentrations were then converted to average TEQ emission factors, which were in units of lb TEQ/10^6 lbs of medical waste incinerated (equation for conversion not given). Table 3-12 lists the I-TEQ_{DF} emission factors calculated by Doucet (1995) for each level of assumed APCDs on MWIs.

Similar to the EPA/OAQPS Approach (Section 3.3.4), the distribution of the APCD categories was derived by assuming that State particulate emission (PM) limits would indicate the APCD on any individual MWI (Doucet, 1995). Table 3-13 displays the AHA assumptions of air pollution control (APC) utilized on MWIs based upon PM emission limits.

With the activity levels, the percent distribution of levels of controls, and the CDD/CDF TEQ emission factors having been calculated with existing data, the final step of the AHA Approach was the estimation of annual I-TEQ_{DF} emissions (g/yr) from MWIs, nationwide. Although no equation is given, it is presumed that the emissions were estimated by multiplying the activity level for each MWI size and APCD category by the associated I-TEQ_{DF} emission factor. The sum of these calculations for each designated class yields the estimated annual I-TEQ_{DF} emissions for all MWIs, nationwide. Doucet (1995) indicates that these computations are appropriate for I-TEQ_{DF} emissions in 1995. Table 3-14 summarizes the nationwide annual I-TEQ_{DF} emissions from MWIs using the AHA Approach.

3.3.6. EPA/ORD Approach for Estimating CDD/CDF Emissions from MWIs

Because of limitations in emissions data and on activity levels, the EPA/ORD approach used many of the logical assumptions developed in the EPA/OAQPS and AHA approaches. The discussion below describes the rationale for how these decisions were made, and presents the resulting emission estimates.

3.3.6.1. *EPA/ORD Approach for Classifying MWIs and Estimating Activity Levels*

As with the EPA/OAQPS and AHA approaches, the EPA/ORD approach divided the MWIs into controlled and uncontrolled classes. The decisions about further dividing these two classes are described below:

Uncontrolled MWIs: For purposes of assigning CDD/CDF emission factors and activity levels to the uncontrolled class of MWIs, the EPA/OAQPS approach divided this class on the basis of residence time within the secondary combustion chamber. This approach has theoretical appeal, because it is logical to expect more complete combustion of CDD/CDFs with longer residence times at high temperatures. Unfortunately, the residence times on a facility-by-facility basis are not known, making it difficult to assign

emission factors and activity levels on this basis. As discussed earlier, the EPA/OAQPS approach assumed that residence time would strongly correlate with State PM stack emission requirements (i.e., the more stringent the PM requirements, the longer the residence time required to meet the standard). This PM method for estimating residence time resulted in the following distribution of residence times: 6 percent of the waste incinerated at MWIs with 1/4-sec residence time; 26 percent of the waste incinerated at MWIs with 1-sec residence time; and 68 percent of the waste incinerated at MWIs with 2-sec residence time. Thus, about two-thirds of the activity level within the uncontrolled class were assumed in the EPA/OAQPS approach to be associated with facilities with the longest residence time and the lowest CDD/CDF emission factor.

The AHA approach subcategorized the uncontrolled class on the basis of design-rated capacity. There is also theoretical support for this approach. Smaller capacity operations (i.e., $<$200 lb/hr) are likely to have higher emissions, because they are more likely to be operating in a batch mode. The batch mode results in infrequent operation with more start-up and shut-down cycles. Thus, the batch-operated MWI usually spends more time outside of the ideal range of operating conditions. In support of this approach, the AHA presented limited empirical evidence indicating that CDD/CDF emission factors calculated from emission test reports for the low capacity units were about a factor of two higher than the emission factors for the high capacity units (Doucet, 1995).

Thus, both the EPA/OAQPS and AHA approaches have a sound theoretical basis but lack strong supporting data. In order to decide which of the two approaches to use, ORD first tested the assumption that there is a strong relationship between State PM requirements and residence time. ORD conducted a limited telephone survey of regulatory agencies in four States where a large number of MWI facilities were in operation: Michigan, Massachusetts, New Jersey, and Virginia (O'Rourke, 1996). The results of the limited survey, summarized in Table 3-15, did not verify the existence of a strong dependent relationship between PM emission limits and residence time in the secondary chamber at MWIs.

Next, the available emission testing data for small and high capacity units (i.e., less than and greater than 200 lb/hr) were evaluated to determine if, as posited in the AHA approach, smaller capacity units have greater emission factors than large capacity units. This evaluation indicated a distinct difference in the emission factors between the two

capacity categories, although the difference in the set of data evaluated was not as great as the difference observed in the data set evaluated in the AHA approach. The EPA/ORD approach, therefore, adopted the subcategorization scheme used in the AHA approach.

Controlled MWIs: Both the EPA/OAQPS approach and the AHA approach subcategorized the controlled MWIs on the basis of APCD equipment. However, the two approaches differed in the subcategories developed. The AHA approach divided the controlled class into two groups: facilities equipped with wet scrubbers (alone, with an ESP, or with a fabric filter), and facilities equipped with dry sorbent injector and a fabric filter (Doucet, 1995). The EPA/OAQPS approach divided the controlled class into three groups: facilities equipped with wet scrubbers, facilities equipped with dry scrubbers (with or without carbon injection), and facilities equipped with fabric filters and packed bed scrubbers. This third category is comprised of a few facilities primarily located in the Northeast United States (O'Rourke, 1996). The EPA/ORD approach adopted the two subcategories of the AHA approach and the third subcategory of the EPA/OAQPS approach. For 1995, EPA/ORD used the activity levels for each facility as reported in the EPA/OAQPS inventory; the activity levels were then summed across facilities for each APCD subclass.

For 1987, the EPA/ORD approach assumed that every MWI was uncontrolled. An EPA study of MWI incineration conducted at that time indicates that MWIs operating in 1987 did not need controls, because they were not subject to State or Federal limits on either PM or organic pollutant emissions (U.S. EPA, 1987d). The activity level estimates were derived from data presented in U.S. EPA (1987d). This approach resulted in the following activity level assumptions for 1987: (a) 15 percent of the activity level (i.e., 0.22 billion kg medical waste) were incinerated/yr by MWIs with capacities less than or equal to 200 lb/hr, and (b) 85 percent of the activity level (i.e., 1.21 billion kg/yr) were incinerated by facilities with capacities greater than 200 lb/hr.

3.3.6.2. *EPA/ORD Approach for Estimating CDD/CDF Emission Factors*

EPA/ORD collected the engineering reports of 24 tested MWIs. After reviewing these test reports, 20 met the criteria for acceptability. (See Section 3.1.3 for further details on the criteria.) In some cases, CDD/CDF congener-specific data were not reported, or values were missing. In other cases, the protocols used in the laboratory

analysis were not described; therefore, no determination of the adequacy of the laboratory methods could be made.

The EPA stack testing method (EPA Method 23) produces a measurement of CDD/CDFs in units of mass concentration (i.e., nanograms per dry standard cubic meter of combustion gas (ng/dscm)) at standard temperature and pressure and one atmosphere and adjusted to a measurement of 7 percent oxygen in the flue gas (U.S. EPA, 1995b). This concentration is assumed to represent conditions at the point of release from the stack into the air, and to be representative of routine emissions. The emission factors were derived by averaging the emission factors across each tested facility in a design class. The emission factor for each tested MWIs was calculated using the following equation:

$$EF_{mwi} = \frac{C \times F_v}{I_w} \qquad \text{(Eqn. 3-8)}$$

Where:

EF_{mwi}	=	Emission Factor per MWI (average ng TEQ per kg of medical waste burned)
C	=	Average TEQ concentration in flue gases of tested MWIs (ng TEQ/dscm) (20°C, 1 atm; adjusted to 7% O_2)
F_v	=	Average volumetric flue gas flow rate (dscm/hr) (20°C, 1 atm; adjusted to 7% O_2)
I_w	=	Average medical waste incineration rate of the tested MWI (kg/hr)

The emission factor estimate for each design class and the number of stack tests used to derive it are shown in Table 3-16. Figures 3-12 and 3-13 present congener and congener group profiles for air emissions from MWIs lacking APCDs and for MWIs equipped with a wet scrubber/baghouse/fabric filter APCD system, respectively.

3.3.7. Summary of CDD/CDF Emissions from MWIs

Because the stack emissions from so few facilities have been tested (i.e., 20 test reports) relative to the number of facilities in this industry (i.e., 2,375 facilities in 1995 and 5,000 facilities in 1987) and because several tested facilities are no longer in operation or have installed new APCD after testing, the EPA/ORD approach did not calculate nationwide CDD/CDF emissions by calculating emissions from the tested

facilities and adding those to calculated emissions for the non-tested facilities. Rather, the EPA/ORD approach (as well as the EPA/OAQPS and AHA approaches) calculated nationwide CDD/CDF emissions by multiplying the emission factor and activity level developed for each design class and then summing the calculated emissions for all classes. Tables 3-16 and 3-17 summarize the resulting national TEQ air emissions for the reference years 1995 and 1987, respectively. Tables 3-16 and 3-17 also indicate the activity level and the TEQ emission factor used in estimating annual TEQ emissions.

In estimating annual TEQ emissions in both reference years, a low confidence rating was assigned to the estimate of the activity level. The primary reason for the low confidence rating is that very limited information is available on a facility level basis for characterizing MWIs in terms of the frequency and duration of operation, the actual waste volume handled, and the level of pollution control. The 1987 inventory of facilities was based on very limited information. Although the 1995 EPA/OAQPS inventory was more comprehensive than the 1987 inventory, it was still based on a fairly limited survey of operating facilities (i.e., approximately 6 percent).

The emission factor estimates were given a low confidence rating, because only the reports of 20 tested MWI facilities could be used to derive emissions factors representing the 2,375 facilities operating in 1995 (i.e., less than 1 percent of estimated number of operating facilities). Even fewer tested facilities could be used to represent the larger number of facilities operating in 1987 (i.e., 8 tested facilities were used to represent 5,000 facilities). The limited emission tests available do cover all design categories used here to develop emission factors. However, because of the large number of facilities in each of these classes, it is very uncertain whether the few tested facilities in each class capture the true variability in emissions. As shown in Table 3-16, the TEQ emissions in 1995 are estimated to have been 461 g I-TEQ_{DF} or 488 g TEQ_{DF}-WHO_{98}. As shown in Table 3-17, the TEQ emissions in 1987 are estimated to have been 2,440 g I-TEQ_{DF} or 2,590 g TEQ_{DF}-WHO_{98}.

As explained above, the EPA/ORD approach to estimating national CDD/CDF TEQ emissions is a 'hybridization' of the EPA/OAQPS and AHA approaches. Table 3-18 compares the main features of each of the three approaches. The 1995 TEQ emissions estimated here (461 g I-TEQ_{DF}/yr) are about 3.5 times higher than those of OAQPS and AHA (141 and 138 g I-TEQ_{DF}/yr, respectively). Most of this difference is due to

differences in the emission estimates for the uncontrolled facilities (ORD - 432 g I-TEQ_{DF}/yr, OAQPS - 136 g I-TEQ_{DF}/yr, AHA - 120 g I-TEQ_{DF}/yr). An analysis of the differences in how these groups estimated emissions from the uncontrolled facilities are presented below:

- **Differences between the EPA/ORD and AHA Approaches:** The ORD approach adopted the classification scheme of the AHA approach for the uncontrolled class and assumed similar activity levels. Thus, the difference in emission estimates is primarily due to differences in the emission factors used. Both groups use similar emission factors for facilities with design capacities less than or equal to 200 lbs/h, but the emission factor for MWIs >200 lbs/hr used in the EPA/ORD approach was higher than that used in the AHA approach by a factor of three. This results from the fact that the two approaches used different sets of emission tests to derive their emission factors.

- **Differences between the EPA/ORD and EPA/OAQPS Approaches**: Because the two approaches subcategorized the uncontrolled facilities into different classes, the activity levels and emission factors cannot be directly compared. Considering the class as a whole, however, both approaches used essentially identical activity levels. The EPA/OAQPS approach assigned 68 percent of the total activity to the class with the lowest emission factor (i.e., those with >2-sec residence time). The emission factor for this class, 74 ng I-TEQ_{DF}/kg, is considerably lower than either emission factor used in the EPA/ORD approach (1,680 and 1,860 ng I-TEQ_{DF}/kg).

Given the uncertain data base available for making these estimates, it is difficult to know which of these three estimation approaches yields the most accurate annual TEQ estimate. However, despite the differences in methodologies and assumptions used, the three approaches yield annual TEQ estimates that are not fundamentally different; the estimates differ from each other by a factor of four or less. Because the EPA/ORD approach was the last of the three to be developed, it has the benefit of being able to utilize the most logical and supportable features of the previously developed EPA/OAQPS and AHA approaches.

3.3.8. Recent EPA Regulatory Activities

Regardless of the approach taken to estimate what the CDD/CDF emissions from 2,375 MWIs were in 1995, the National Emission Standards promulgated by EPA in September 1997 (Federal Register, 1997b) require substantial reductions of CDD/CDF air emissions from MWIs. As a result of these standards, MWI emissions will be thoroughly assessed for purposes of compliance with the CDD/CDF standard. Compliance testing will allow the development of a more comprehensive emissions data base and more accurate characterization of this industry. EPA projects that, following full compliance with these standards, annual emissions will be 5 to 7g I-TEQ_{DF}year.

3.4. CREMATORIA

Bremmer et al. (1994) measured CDD/CDF emissions at two crematoria in The Netherlands. The first, a "cold" type furnace with direct uncooled emissions, was calculated to yield 2.4 μg I-TEQ_{DF} per body. In the cold type furnaces, the coffin is placed inside at a temperature of about 300°C. Using a burner, the temperature of the chamber is increased to 800 to 900°C and kept at that temperature for 2 to 2.5 hours. The second furnace, a "warm" type with cooling of flue gases to 220°C prior to discharge, was calculated to yield 4.9 μg I-TEQ_{DF} per body. In the warm type furnace, the coffin is placed in a chamber preheated to 800°C or higher for 1.2 to 1.5 hours. The chamber exhausts from both furnace types were incinerated in an after burner at a temperature of about 850°C. The higher emission rate for the warm-type furnace was attributed by Bremmer et al. (1994) to the formation of CDD/CDF during the intentional cooling of the flue gases to 220°C.

Jager et al. (1992) (as reported in Bremmer et al., 1994) measured an emission rate of 28 μg I-TEQ_{DF} per body for a crematorium in Berlin, Germany. No operating process information was provided by Bremmer et al. (1994) for the facility.

Mitchell and Loader (1993) reported even higher emission factors for two crematoria in the United Kingdom. The first facility tested was manually-operated, had primary and secondary combustion chambers preheated to 650°C, and had a residence time of 1 second in the secondary combustion chambers. The second tested facility was computer-controlled, had primary and secondary combustion chambers heated to 850°C, and had a residence time of 2 seconds in the secondary combustion chamber. The

measured stack gas concentrations of I-TEQ_{DF} ranged from 42.0 to 71.3 ng I-TEQ_{DF}/m^3 (at 11% O_2) at the first facility and from 25.4 to 45.5 ng I-TEQ_{DF}/m^3 (at 11% O_2) at the second facility. Emission factors based on these test results and gas generation rates reported by Bremmer et al. (1994) were calculated to range from 70 to 80 μg I-TEQ_{DF}/body (HMIP, 1995).

Takeda et al. (1998) measured CDD/CDF emissions at 10 crematoria in Japan. Although there are more than 1,600 crematoria in Japan, the 10 tested facilities handle four percent of the cremations carried out in Japan annually. A wide range in emission factors was observed. When not-detected values are treated as zero, the range was 0.042 to 62 μg I-TEQ_{DF}/body (mean of 9.2 μg I-TEQ_{DF}/body). When not-detected values are treated as one-half the detection limit, the range was 0.45 to 63 μg I-TEQ_{DF}/body (mean of 11 μg I-TEQ_{DF}/body).

In the United States, CDD/CDF emissions have been measured at one crematorium (CARB, 1990c) classified as a warm type facility using the criteria of Bremmer et al. (1994). The combusted material at this facility was comprised of the body, as well as 4 pounds of cardboard, up to 6 pounds of wood, and an unquantified amount of unspecified plastic wrapping. The three emission tests conducted at this facility yielded an average emission factor of 0.50 μg I-TEQ_{DF}/body (or 0.54 μg TEQ_{DF}-WHO_{98}/body). Table 3-19 presents the congener-specific emission factors for this facility. Figure 3-14 presents CDD/CDF congener and congener group emission profiles based on these emission factors.

The emission factor measured at the one tested U.S. facility is at the lower end of the range reported for 10 Japanese facilities by Takeda et al. (1998) and is also lower than the results reported by Bremmer et al. (1994) for two Dutch facilities, by Jager et al. (1992) for one German facility, and by Mitchell and Loader (1993) for two British facilities. The average emission factor for these 16 tested facilities is 17 μg I-TEQ_{DF}/body (assuming not-detected values are zero). Because congener-specific results were not provided in the non-U.S. reports, it was not possible to calculate the average emission factor in units of TEQ_{DF}-WHO_{98}. This average emission factor is assigned a low confidence rating because it is based primarily on tests conducted at non-U.S. facilities.

In 1995, there were 1,155 crematories reported in the United States. However, there are no readily available data on the number of cold versus warm crematoria furnaces. In 1995, 21.1 percent of the deceased bodies were cremated (i.e., 488,224

cremations), and 15.2 percent of the deceased were cremated in 1987 (i.e., 323,371 cremations). Cremations are projected to increase to 25 percent in the year 2000 and 37 percent in the year 2010. A high confidence rating is assigned to these activity level estimates, because they are based on recent data provided by the Crematoria Association of North America (Springer, 1997).

Combining this average emission rate of 17 μg I-TEQ$_{DF}$/body with the number of cremations in 1995 (488,224) yields an estimated annual release of 9.1 g I-TEQ$_{DF}$. Combining the emission rate of 17 μg I-TEQ$_{DF}$/body with the number of cremations in 1987 (323,371) yields an estimated release of 5.5 g.

3.5. SEWAGE SLUDGE INCINERATION

The three principal combustion technologies used to incinerate sewage sludge in the United States are the multiple-hearth incinerator, fluidized-bed incinerator, and the electric furnace (Brunner, 1992; U.S. EPA, 1995b). All of these technologies are "excess-air" processes (i.e., they combust sewage sludge with oxygen in excess of theoretical requirements). Approximately 80 percent of operating sludge incinerators are multiple-hearth design. About 20 percent are fluidized-bed incinerators, and less than 1 percent are electric incinerators. Other types of technologies not widely used in the United States are single-hearth cyclones, rotary kilns, and high-pressure wet-air oxidation (U.S. EPA, 1997b; Maw, 1998).

Multiple-hearth Incinerator: This consists of refractory hearths arranged vertically in series, one on top of the other. Dried sludge cake is fed to the top hearth of the furnace. The sludge is mechanically moved from one hearth to another through the length of the furnace. Moisture is evaporated from the sludge cake in the upper hearths of the furnace. The center hearths are the burning zone, where gas temperatures reach 871°C. The bottom hearths are the burn-out zone, where the sludge solids become ash. A waste-heat boiler is usually included in the burning zone, where steam is produced to provide supplemental energy at the sewage treatment plant. Air pollution control measures typically include a venturi scrubber, an impingement tray scrubber, or a combination of both. Wet cyclones and dry cyclones are also used (U.S. EPA, 1995b).

Fluidized-bed Incinerator: This is a cylindrical refractory-lined shell with a steel plate structure that supports a sand bed near the bottom of the furnace (Brunner, 1992).

Air is introduced through openings in the bed plate supporting the sand. This causes the sand bed to undulate in a turbulent air flow; hence, the sand appears to have a fluid motion when observed through furnace portals. Sludge cake is added to the furnace at a position just above this fluid motion of the sand bed. The fluid motion promotes mixing in the combustion zone. Sludge ash exits the furnace with the combustion gases; therefore, air pollution control systems typically consist of high-energy venturi scrubbers. Air pollution control measures typically include a venturi scrubber or venturi/impingement tray combinations (U.S. EPA, 1995b).

Electric Furnaces: Also called infrared furnaces, these consist of a long rectangular refractory-lined chamber. A belt conveyer system moves the sludge cake through the length of the furnace. To promote combustion of the sludge, supplemental heat is added by electric infrared heating elements within the furnace that are located just above the traveling belt. Electric power is required to initiate and sustain combustion. Emissions are usually controlled with a venturi scrubber or some other wet scrubber (Brunner, 1992; U.S. EPA, 1995b).

3.5.1. Emission Estimates from Sewage Sludge Incinerators

EPA measured CDD/CDF emissions at three multiple-hearth incinerators as part of Tier 4 of the National Dioxin Survey (U.S. EPA, 1987a). During the pre-test surveys, two of the facilities were judged to have "average" potential and one facility was judged to have "high" potential for CDD/CDF emissions with respect to other sewage sludge incinerators. The results of these tests include congener group concentrations in stack gas, but lack measurement results for specific congeners other than 2,3,7,8-TCDD and 2,3,7,8-TCDF. EPA measured CDD/CDF emissions (including all 17 toxic congeners) at a fluidized-bed incinerator and a multiple hearth incinerator in 1990 (U.S. EPA, 1990f). In 1995, the Association of Metropolitan Sewerage Agencies (AMSA) submitted to EPA the results of stack tests conducted at an additional 13 sewage sludge incinerators (Green et al., 1995). Two of these data sets were considered not useable by EPA, because either detection limits or feed rates and stack flow rates were not provided. The average congener and congener group emission factors are presented in Table 3-20 for the three facilities from U.S. EPA (1987a) and the 11 AMSA facilities from Green et al. (1995). A wide variability was observed in the emission factors for the tested facilities. The total

CDD/CDF emission factors for the three U.S. EPA (1987a) facilities ranged from 90 to 3,400 ng/kg. The total CDD/CDF emission factors for the two facilities reported in U.S. EPA (1990f) were 79 to 846 ng/kg. For the 11 facilities reported in Green et al. (1995), a similarly large variability in emission factors was observed. Figure 3-15 presents the average congener and congener group profiles based on these data.

The average TEQ emission factor based on the data for the 11 AMSA facilities and the two facilities reported in U.S. EPA (1990f) is 6.94 ng I-TEQ_{DF}/kg of dry sludge combusted (or 7.04 ng TEQ_{DF}-WHO_{98}/kg of dry sludge), assuming nondetected values are zero. Other countries have reported similar results. Bremmer et al. (1994) reported an emission rate of 5 ng I-TEQ_{DF}/kg for a fluidized-bed sewage sludge incinerator, equipped with a cyclone and wet scrubber, in The Netherlands. Cains and Dyke (1994) measured CDD/CDF emissions at two sewage sludge incinerators in the United Kingdom. The emission rate at an incinerator equipped with an electrostatic precipitator and wet scrubber ranged from 2.75 ng I-TEQ_{DF}/kg to 28.0 ng I-TEQ_{DF}/kg. The emission rate measured at a facility equipped with only an electrostatic precipitator was 43.0 ng I-TEQ_{DF}/kg.

In 1988, approximately 199 sewage sludge incineration facilities combusted about 0.865 million metric tons of dry sewage sludge (Federal Register, 1993b). In 1995, approximately 257 sewage sludge incinerators (some of which were backup or alternate incinerators) combusted about 2.11 million dry metric tons of sewage sludge (Maw, 1998). Given these estimated amounts of sewage sludge incinerated/yr, the estimate of TEQ emissions to air is 6.0 g I-TEQ_{DF} (or 6.1 g TEQ_{DF}-WHO_{98}) in 1987 and 14.6 g I-TEQ_{DF} (or 14.8 g TEQ_{DF}-WHO_{98}) in 1995, using the average TEQ emission factor of 6.94 ng I-TEQ_{DF}/kg (7.04 ng TEQ_{DF}-WHO_{98}/kg).

A medium confidence rating is assigned to the average TEQ emission factor because it was derived from stack testing at 13 U.S. sewage sludge incinerators. The 1988 activity level estimate (used as a surrogate for the 1987 activity level) is assigned a high confidence rating, because it is based on an extensive EPA survey to support rulemaking activities. The 1995 activity level estimate is assigned a medium confidence rating because assumptions concerning hours of operation, operating capacity, and design capacity were made for numerous facilities.

3.5.2. Solid Waste from Sewage Sludge Incinerators

In Table 5-16 of U.S. EPA (1987a), data are presented indicating that 2,3,7,8-TCDD was not detected in the bottom ash or scrubber water filtrate from three sewage sludge incinerators. However, total CDDs for the three incinerators and the filtrate were: non-detect, 20 ng/kg, 10 ng/kg, and 0.3 ng/kg, respectively. For total CDFs, the respective values were: non-detect, 70 ngk/kg, 50 ng/kg, and 4.0 ng/kg. No data were given for any congeners (other than 2,3,7,8-TCDD), nor were there any data on the quantities of ash or filtrate.

3.6. TIRE COMBUSTION

Emissions of CDD/CDFs from the incineration of automobile tires were measured from a dedicated tire incinerator tested by the California Air Resources Board (CARB, 1991a). The facility consists of two excess air furnaces equipped with steam boilers to recovery the energy from the heat of combustion. Discarded whole tires were fed to the incineration units at rates ranging from 2,800 to 5,700 kg/hr during the 3 test days. The facility was equipped with a dry acid gas scrubber and fabric filter for the control of emissions prior to exiting the stack. Table 3-21 presents the congener-specific emission factors for this facility. Figure 3-16 presents CDD/CDF congener and congener group profiles based on these TEQ emission factors. From these data, the average emission factor is estimated to be 0.282 ng I-TEQ_{DF}/kg of tires incinerated (or 0.281 ng TEQ_{DF}-WHO_{98}) when all not detected values are treated as zero.

Cains and Dyke (1994) reported much higher emission rates for two tire incinerators equipped only with simple grit arrestors in the United Kingdom, 188 and 228 ng I-TEQ_{DF}/kg of combusted tire.

EPA estimated that approximately 0.50-million metric tons of tires were incinerated in 1990 in the United States (U.S. EPA, 1992a). This activity level estimate is given a medium confidence rating, because it is based on both published data and professional judgement. The use of scrap tires as a fuel was reported to have increased significantly during the late 1980s; however, no quantitative estimates were provided in U.S. EPA (1992a) for this period. In 1990, 10.7 percent of the 242 million scrap tires generated were burned for fuel. This percentage is expected to continue to increase (U.S. EPA, 1992a). Of the tires burned for energy recovery purposes, approximately 46 percent were

utilized by pulp and paper facilities, 23 percent were utilized by cement kilns, and 19 percent were utilized by one tire-to-energy facility (U.S. EPA, 1995c). Estimates of CDD/CDF emissions from cement kilns (inclusive of emissions from combustion of tires) are addressed in Section 5.1 of this report.

If it is assumed that 385 million kilograms of discarded tires were incinerated in the United States in 1987 and 1995 by facilities other than cement kilns (i.e., 500 million kg less approximately 115 million kg burned by cement kilns), then, using the TEQ emission factor derived from stack data from the one tested facility, an average of 0.11 grams of I-TEQ_{DF} (or 0.11 g TEQ_{DF}-WHO_{98}) per year are estimated to have been emitted to the air in both of these reference years. It must be noted that this may be an underestimate of emissions from this source category, because the one facility tested is a dedicated tire combustion facility and is equipped with a dry scrubber combined with a fabric filter for air pollution control. These devices are capable of greater than 95 percent reduction and control of dioxin-like compounds prior to discharge from the stack. It is not known to what extent other facilities combusting tires are similarly controlled. If such facilities are not so equipped, then the emission of CDD/CDF TEQ could be much greater than the estimates developed above. Therefore, the estimated emission factor for tire incineration is given a low confidence rating.

3.7. COMBUSTION OF WASTEWATER SLUDGE AT BLEACHED CHEMICAL PULP MILLS

Approximately 20.5 percent of the wastewater sludges generated at bleached chemical pulp mills are dewatered and burned in bark boilers at the pulp mills. These sludges can contain CDD/CDFs and elevated levels of chloride. However, the level of heat input from sludge in the mixed feed to bark boilers rarely exceeds 10 percent (NCASI, 1995).

NCASI (1995) provided congener-specific test results for four wood residue/sludge boilers tested between 1987 to 1993. Sludge comprised 6 to 10 percent of the solids in the feed. The average congener-specific emission factors derived from the stack test results obtained from these facilities are presented in Table 3-22. The average TEQ emission factors derived from the test results are 0.061 ng I-TEQ_{DF}/kg of feed (i.e., sludge and wood residue) (or 0.062 ng I-TEQ_{DF}-WHO_{98}), assuming nondetected values are zero. The range in facility-specific emission factors was wide (0.0004 to 0.118 ng I-TEQ_{DF}/kg

assuming nondetected values are zero). NCASI (1995) also presented stack emission test results for five other bark boilers. These boilers combusted only bark during the tests even though the boilers normally fire bark in combination with sludge and coal. These are discussed in Section 4.2.2 for industrial facilities burning wood scrap/residues. The average TEQ emission factor for these facilities was 0.4 ng I-TEQ_{DF}/kg of feed. The emissions test data presented in NCASI (1995), and discussed above, indicate that the CDD/CDF emission factors for bark/sludge combustors are similar to the emission factor developed in Section 4.2.2 for industrial facilities burning only wood residues/scrap. Based on the fact that wood residues comprise a far greater fraction of the feed to these bark/sludge burners than does sludge, the national TEQ emission estimates derived in Section 4.2.2 of this report for industrial wood burning facilities are assumed to include emissions from these bark/sludge combustion units.

3.8. BIOGAS COMBUSTION

Using a specially developed sampling apparatus, Schreiner et al. (1992) measured the CDD/CDF content of a flare combusting exhaust gases from an anaerobic sewage sludge digestor in Germany. The nozzle of the apparatus was moved through three cross-sections of the flame and cooling zone. The CDD/CDF content at the bottom of the flare was 1.4 pg I-TEQ_{DF}/Nm^3, 3.3. pg I-TEQ_{DF}/Nm^3 at the top of the flare, and 13.1 pg I-TEQ_{DF}/Nm^3 in the middle of the flare. Congener-specific results were not reported. Using the theoretical ratio of flare gas volume to digestor gas volume combusted, 78.6:1, and the average CDD/CDF content of the three measurements, 5.9 pg I-TEQ_{DF}/Nm^3, an emission rate of 0.46 ng I-TEQ_{DF}/Nm^3 of digestor gas combusted is yielded.

During 1996, POTWs in the United States treated approximately 122 billion liters of wastewater daily (U.S. EPA, 1997c). Although reliable data are not readily available on the amount of sewage sludge generated by POTWs that is subjected to stabilization by anaerobic digestion, a reasonable approximation is 25 percent of the total sludge generated (i.e., the sludge generated from treatment of about 30 trillion liters per day of wastewater). An estimated 196 kg of sludge solids are generated for every million liters of wastewater subjected to primary and secondary treatment (Water Pollution Control Federation, 1990). Thus, multiplying 30 billion liters per day (i.e., 25 percent of 122

billion liters) by 196 kg/million liters and 365 days/yr yields an annual estimate of 2 million metric tons of sludge solids that may be anaerobically digested in POTWs annually.

The volume of sludge digestor gas combusted in flares annually can be estimated using operation parameters for a "typical" anaerobic digestor system as described in Water Pollution Control Federation (1990). Multiplying the annual amount of sludge solids of 2 million metric tons by the following parameters and appropriate conversion factors yields an annual flared digestor gas volume of 467-million Nm^3:

- Fraction of total solids that are volatile solids = 75 percent;
- Reduction of volatile solids during digestion = 50 percent;
- Specific gas production = 0.94 m^3/kg volatile solids reduced; and
- Fraction of produced gas that is flared = 66 percent.

Because there are no direct measurements of CDD/CDF emissions from U.S. anerobic sludge digestor flares and because of uncertainties about the activity level for biogas combustion, no national emission estimate has been developed for inclusion in the national inventory. However, a preliminary estimate of the potential annual TEQ emissions from this source can be obtained by multiplying the emission factor of 0.46 ng I-TEQ_{DF}/Nm^3 of digestor gas flared by the estimated volume of gas flared annually in the United States, 467 million Nm^3. This calculation yields an annual potential release of 0.22 grams. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions.

Table 3-1. Inventory of MSWIs in 1995 by Technology, APCD, and Annual Activity Level

MSWI		UNC	Hot ESP	Cold ESP	DSI/H-ESP	DS/FF	DS/CI/FF	DS/FF/ C-ESP	WS/FF	WS C-ESP	DS/C-ESP	DS/DSI/ C-ESP	DSI/ CI/ H-ESP	DSI/ C-ESP	DSI/ FF	DSI/ EGB	WS	Total
MB/RC	No. Facilities	0	0	2	0	2	0	0	0	0	0	0	0	6	2	0	0	12
	Activity Level, kg/yr	0	0	2.00E+08	0	1.14E+09	0	0	0	0	0	0	0	5.07E+08	2.59E+08	0	0	2.10E+09
MB/REF	No. Facilities	0	0	1	0	2	0	0	0	0	1	0	0	0	1	0	2	7
	Activity Level, kg/yr	0	0	1.69E+08	0	2.68E+08	0	0	0	0	4.22E+08	0	0	0	1.13E+08	0	2.04E+08	1.18E+09
MB/WW	No. Facilities	0	6	8	1	28	3	0	0	0	8	0	1	0	2	0	0	57
	Activity Level, kg/yr	0	1.04E+09	2.81E+09	4.22E+08	8.57E+09	1.17E+09	0	0	0	2.31E+09	0	2.75E+08	0	1.97E+08	0	0	1.68E+10
FB/RDF	No. Facilities	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	3
	Activity Level, kg/yr	0	0	0	0	1.69E+08	0	0	0	0	0	0	0	0	8.45E+07	1.13E+08	0	3.66E+08
RDF/Ded	No. Facilities	0	1	4	1	7	0	1	0	0	4	0	0	0	1	0	0	19
	Activity Level, kg/yr	0	4.22E+07	1.81E+09	2.00E+08	2.51E+09	0	5.63E+08	0	0	1.75E+09	0	0	0	4.22E+08	0	0	7.30E+09
MOD -SA	No. Facilities	9	4	4	0	0	0	0	1	0	0	1	0	0	1	0	3	23
	Activity Level, kg/yr	1.87E+08	1.82E+08	1.25E+08	0	0	0	0	2.82E+07	0	0	7.60E+07	0	0	3.24E+07	0	4.90E+07	6.80E+08
MOD-EA	No. Facilities	1	1	3	1	1	0	0	0	1	0	0	0	0	1	0	0	9
	Activity Level, kg/yr	1.41E+07	1.97E+07	8.28E+07	1.41E+07	1.18E+08	0	0	0	6.76E+07	0	0	0	0	1.01E+08	0	0	4.18E+08
Total	No. Facilities	10	12	22	3	41	3	1	1	1	13	1	1	6	9	1	5	130
Total	Activity Level, kg/yr	2.01E+08	1.29E+09	5.19E+09	**6.37E+08**	1.28E+10	1.17E+09	5.63E+08	2.82E+07	6.76E+07	4.49E+09	7.60E+07	2.75E+08	5.07E+08	1.21E+09	1.13E+08	2.53E+08	2.88E+10

Table 3-1. Inventory of MSWIs in 1995 by Technology, APCD, and Annual Activity Level (continued)

MB/RC = Mass Burn Rotary Kiln MB/REF = Mass Burn Refractory Walled MB/WW = Mass Burn Waterwalled RDF/Ded = Dedicated Refuse-Derived Fuel FB/RDF = Fluidized Bed Refuse-Derived Fuel MOD/SA = Modular Starved Air MOD/EA = Modular Excess Air	UNC = Uncontrolled Hot ESP = Hot side Electrostatic Precipitator Cold ESP = Cold side Electrostatic Precipitator DS/FF = Dry Scrubber with Fabric Filter FF = Fabric Filter EGB = Electro Gravel Bed WS = Wet Scrubber	DSI/FF = Dry Sorbent Injection with Fabric Filter DS/CI/FF = Spray Dryer - Carbon Injection - Fabric Filter DSI/EGB = Dry Sorbent Injection - Electro Gravel Bed

Table 3-2. Inventory of MSWIs in 1987 by Technology, APCD, and Annual Activity Level

	MSWI Type	UNC	Hot ESP	DS/FF	FF	EGB	WS	Total
MB/RC	No. of Facilities	0	3	0	1	0	0	4
	Activity Level,kg/yr	0	3.94E+08	0	1.58E+07	0	0	4.10E+08
MB/REF	No. of Facilities	0	12	1	0	0	7	20
	Activity Level,kg/yr	0	2.00E+09	1.41E+07	0	0	9.01E+08	3.04E+09
MB/WW	No. of Facilities	0	19	1	0	0	0	20
	Activity Level,kg/yr	0	5.20E+09	1.55E+08	0	0	0	5.35E+09
RDF/Dedicated	No. of Facilities	0	7	0	0	0	2	9
	Activity Level,kg/yr	0	3.01E+09	0	0	0	3.38E+08	3.35E+09
RDF/cofired	No. of Facilities	0	3	0	0	0	0	3
	Activity Level,kg/yr	0	2.53E+08	0	0	0	0	2.53E+08
MOD/SA	No. of Facilities	36	2	0	3	0	4	53
	Activity Level,kg/yr	5.73E+08	1.17E+08	0	1.43E+08	0	5.30E+07	1.15E+09
MOD/EA	No. of Facilities	2	0	0	0	1	1	4
	Activity Level,kg/yr	4.17E+07	0	0	0	6.76E+07	1.27E+08	2.36E+08
	Total No. of Facilities	38	54	2	4	1	14	113
	Total Activity Level,kg/yr	6.15E+08	1.12E+10	2.96E+08	1.59E+08	6.76E+07	1.42E+09	1.38E+10

Table 3-2. Inventory of MSWIs in 1987 by Technology, APCD, and Annual Activity Level (continued)

MB/RC = Mass Burn Rotary Kiln MB/REF = Mass Burn Refractory Walled MB/WW = Mass Burn Waterwalled RDF/Ded = Dedicated Refuse-Derived Fuel RDF/cofired = RDF cofired with coal MOD/SA = Modular Starved Air MOD/EA = Modular Excess Air	UNC = Uncontrolled Hot ESP = Hot side Electrostatic Precipitator DS/FF = Dry Scrubber with Fabric Filter FF = Fabric Filter EGB = Electro Gravel Bed WS = Wet Scrubber kg/y = kilogram per year

Table 3-3. CDD/CDF TEQ Emission Factors (ng TEQ per kg waste) for Municipal Solid Waste Incineration

Municipal Solid Waste Incinerator Design	Air Pollution Control Device	Average I-TEQ_{DF} Emission Factor (ng/kg)	Average TEQ_{DF}-WHO_{98} Emission Factor (ng/kg)	Basis and Rationale
Mass Burn Waterwall	C-ESP	6.10	6.54	Based on MB-WW; DS/C-ESP, same furnace and most similar APCD temperature
	DS/C-ESP	6.10	6.54	Based on direct tests
	DS/CI/FF	1.50	1.61	Based on direct tests
	DS/FF	0.63	0.72	Based on direct tests
	DSI/CI/H-ESP	7.74	8.22	Based on direct tests
	DSI/FF	1.91	2.07	Based on direct tests
	DSI/H-ESP	7.74	8.22	Based on MB-WW; DSI/CI/H-ESP, same furnace and most similar APCD temperature
	H-ESP	473	535	Based on direct tests
Mass Burn Refractory	C-ESP	236	254	Based on direct tests
	DS/C-ESP	51.1	53.2	Based on direct tests
	DS/FF	0.63	0.72	Based on MB-WW; DS/FF, most similar furnace and same APCD
	DSI/FF	1.91	2.07	Based on MB-WW; DSI/FF, most similar furnace and same APCD
	H-ESP	473	535	Based on MB-WW; H-ESP, most similar furnace and same APCD
	WS	236	254	Based on MB-Ref;C-ESP, same furnace and similar APCD temperature
Mass Burn Rotary Kiln	C-ESP	47.0	93.1	Based on MB-RK; DSI/FF, same furnace and similar emission control
	DS/FF	0.646	0.68	Based on direct tests
	DSI/C-ESP	47.0	93.1	Based on MB-RK; DSI/FF, same furnace and similar emission control
	DSI/FF	47.0	93.1	Based on direct tests
	FF	47.0	93.1	Based on MB-RK; DSI/FF, same furnace and similar emission control
	H-ESP	285	316	Based on direct tests
RDF Dedicated	C-ESP	231	253	Based on direct tests
	DS/C-ESP	0.53	0.56	Based on direct tests
	DS/FF	0.24	0.26	Based on direct tests
	DS/FF/C-ESP	0.24	0.26	Based on RDF-Ded; DS/FF, same furnace and similar APCD
	DSI/FF	231	253	Based on RDF-Ded; C-ESP, same furnace and similar emission control
	DSI/H-ESP	231	253	Based on RDF-Ded; C-ESP, same furnace and similar emission control
	H-ESP	1,492	1,679	Based on direct tests
	WS	231	253	Based on RDF-Ded; C-ESP, same furnace and similar APCD temperature

Table 3-3. CDD/CDF TEQ Emission Factors (ng TEQ per kg waste) for Municipal Solid Waste Incineration (continued)

Municipal Solid Waste Incinerator Design	Air Pollution Control Device	Average I-TEQ_{DF} Emission Factor (ng/kg)	Average TEQ_{DF}-WHO_{98} Emission Factor (ng/kg)	Basis and Rationale
Modular Starved-air	C-ESP	16.2	17.0	Based on Mod-EA; C-ESP, similar furnace (modular design) and same APCD
	DS/DSI/C-ESP	16.2	17.0	Based on Mod-EA; C-ESP, similar furnace (modular design) and similar emission control
	DSI/FF	0.025	0.024	Based on direct tests
	FF	16.2	17	Based on Mod-EA; C-ESP, similar furnace (modular design) and similar emission control
	H-ESP	79.0	85.7	Based on direct tests
	UNC	0.025	0.024	Based on Mod-SA; DSI/FF, same furnace and most similar expected emissions
	WS	16.2	17.0	Based on Mod-EA; C-ESP, similar furnace (modular design) and similar APCD temperature
	WS/FF	16.2	17.0	Based on Mod-EA; C-ESP, similar furnace (modular design) and similar APCD temperature
Modular Excess-air	C-ESP	16.2	17.0	Based on direct tests
	DS/FF	16.2	17.0	Based on Mod-EA; C-ESP, same furnace and similar temperature in APCD - may over-estimate emissions
	DSI/FF	0.025	0.024	Based on Mod-SA; DSI/FF, similar (modular design) furnace and same APCD
	DSI/H-ESP	118	119	Based on Mod-EA; H-ESP, same furnace and similar emissions
	EGB	0.025	0.024	Based on Mod-SA; DSI/FF, same furnace and most similar expected emissions
	H-ESP	118	119	Based on direct tests
	UNC	0.025	0.024	Based on Mod-SA; DSI/FF, same furnace and most similar expected emissions
	WS	16.2	17.0	Based on Mod-EA; C-ESP, same furnace and similar APCD temperature
	WS/C-ESP	16.2	17.0	Based on Mod-EA; C-ESP, same furnace and similar APCD
Fluidized-bed RDF	DS/FF	0.63	0.72	Based on MB-WW; DS/FF, similar furnace and same APCD
	DSI/EGB	0.63	0.72	Based on MB-WW; DS/FF, similar furnace - may under-estimate emissions
	DSI/FF	0.63	0.72	Based on MB-WW; DS/FF, similar furnace - may under-estimate emissions

Key:
- ng/kg = Nanograms TEQ per kilograms waste
- DS/FF = Dry scrubber combined with a fabric filter
- DSI/FF = Dry sorbent injection coupled with a fabric filter
- DS/CI/FF = Dry scrubber coupled with carbon injection and a fabric filter
- C-ESP = Cold-sided electrostatic precipitator (temperature at control device is below $\leq$ 230°C
- H-ESP = Hot-sided electrostatic precipitator (temperature at control device is above $\geq$ 230°C
- WS = Wet scrubber
- UNC = Uncontrolled (no APCD)

Table 3-4a. Annual I-TEQ$_{DF}$ Emissions (g/yr) from MSWIs Operating in 1995

Municipal Solid Waste Incinerator Design	Air Pollution Control Device	I-TEQ$_{DF}$ Emissions from Tested Facilities (g TEQ/yr)	Average I-TEQ$_{DF}$ Emission Factor (ng/kg)	Activity Level Non-Tested Facilities (kg/yr)	I-TEQ$_{DF}$ Emissions from Non-Tested Facilities (g TEQ/yr)	Total I-TEQ$_{DF}$ Emissions from All Facilities (g TEQ/yr)
Mass Burn Waterwall	C-ESP	0	6.10	2.81e+09	17.1	17.1
	DS/C-ESP	2.09	6.10	1.88e+09	11.4	13.5
	DS/CI/FF	0.635	1.50	7.44e+08	1.12	1.75
	DS/FF	2.01	0.63	5.98e+09	3.77	5.77
	DSI/CI/H-ESP	2.12	-	0	0	2.12
	DSI/FF	0.279	-	0	0	0.279
	DSI/H-ESP	0	7.74	4.22e+08	3.27	3.27
	H-ESP	163	473	1.79e+08	84.5	247
	Subtotal	170			121	291
Mass Burn Refractory	C-ESP	39.8	-	0	0	39.8
	DS/C-ESP	21.6	-	0	0	21.6
	DS/FF	0	0.63	2.68e+08	0.168	0.168
	DSI/FF	0	1.91	1.13e+08	0.216	0.216
	WS	0	236	2.04e+08	48.1	48.1
	Subtotal	61.4			48.5	110
Mass Burn Rotary Kiln	C-ESP	0	47.0	2.00e+08	9.4	9.4
	DS/FF	0.245	0.646	7.57e+08	0.489	0.734
	DSI/C-ESP	0	47.0	5.07e+08	23.8	23.8
	DSI/FF	5.29	47.0	1.46e+08	6.85	12.1
	Subtotal	5.54			40.6	46.1
RDF Dedicated	C-ESP	32.5	231	1.67e+09	385	418
	DS/C-ESP	0.321	0.53	1.14e+09	0.603	0.924
	DS/FF	0.0975	0.24	1.58e+09	0.379	0.477
	DSI/FF	0	231	4.22e+08	97.6	97.6
	DSI/H-ESP	0	231	2.00e+08	46.2	46.2
	H-ESP	0	1,492	4.22e+07	63	63
	DS/FF/C-ESP	0	0.24	5.63e+08	0.135	0.135
	Subtotal	33			593	626
Modular Starved-air	C-ESP	0	16.2	1.25e+08	2	2
	DSI/FF	0.000801	-	0	0	0.000801
	H-ESP	8.01	79.0	8.03e+07	6.34	14.4
	UNC	0	0.025	1.87e+08	0.00463	0.00463
	WS	0	16.2	4.90e+07	0.785	0.785
	WS/FF	0	16.2	2.82e+07	0.451	0.451
	DS/DSI/C-ESP	0	16.2	7.60e+07	1.22	1.22
	Subtotal	8.01			10.8	18.8
Modular Excess-air	C-ESP	0.0643	16.2	6.25e+07	1	1.07
	DS/FF	0	16.2	1.18e+08	1.9	1.9
	DSI/FF	0	0.025	1.01e+08	0.00251	0.00251
	DSI/H-ESP	0	118	1.41e+07	1.66	1.66
	H-ESP	2.32	-	0	0	2.32
	UNC	0	0.025	1.41e+07	0.000348	0.000348
	WS/C-ESP	0	16.2	6.76e+07	1.08	1.08
	Subtotal	2.39			5.64	8.03
Fluidized-bed RDF	DS/FF	0	0.63	1.69e+08	0.106	0.106
	DSI/EGB	0	0.63	1.13e+08	0.0709	0.0709
	DSI/FF	0	0.63	8.45e+07	0.0532	0.0532
	Subtotal	0			0.231	0.231
Total		280			820	1,100

Key: DS/FF = Dry Scrubber combined with a Fabric Filter
DSI/FF = Dry Sorbent Injection coupled with a Fabric Filter
DS/CI/FF = Dry Scrubber -Carbon Injection-Fabric Filter
C-ESP = Cold-side Electrostatic Precipitator (Temperature at control device is below ≤230°C)
H-ESP = Hot-side Electrostatic Precipitator (Temperature at control device is ≥230°C)
WS = Wet Scrubber
UNC = Uncontrolled (no APCD)
EGB = Electro Granular Activated Carbon Bed
ng/kg = nanogram per kilogram
kg/yr = kilograms per year

Table 3-4b. Annual TEQ_{DF}-WHO_{98} Emissions (g/yr) from MSWIs Operating in 1995

Municipal Solid Waste Incinerator Design	Air Pollution Control Device	TEQ_{DF}-WHO_{98} Emissions from Tested Facilities (g TEQ/yr)	Average TEQ_{DF}-WHO_{98} Emission Factor (ng/kg)	Activity Level Non-Tested Facilities (kg/yr)	TEQ_{DF}-WHO_{98} Emissions from Non-Tested Facilities (g TEQ/yr)	Total TEQ_{DF}-WHO_{98} Emissions from All Facilities (g TEQ/yr)
Mass Burn Waterwall	C-ESP	0	6.54	2.81e+09	18.4	18.4
	DS/C-ESP	2.24	6.54	1.88e+09	12.3	14.54
	DS/CI/FF	0.68	1.61	7.44e+08	1.20	1.88
	DS/FF	2.10	0.72	5.98e+09	4.04	6.14
	DSI/CI/H-ESP	2.26	-	0	0	2.26
	DSI/FF	0.30	-	0	0	0.30
	DSI/H-ESP	0	8.22	4.22e+08	3.47	3.47
	H-ESP	183	535	1.79e+08	94.7	278
	Subtotal	191			134	325
Mass Burn Refractory	C-ESP	43.0	-	0	0	43.0
	DS/C-ESP	22.5	-	0	0	22.5
	DS/FF	0	0.72	2.68e+08	0.181	0.181
	DSI/FF	0	2.07	1.13e+08	0.234	0.234
	WS	0	254	2.04e+08	51.9	51.9
	Subtotal	65.4			52.3	117.8
Mass Burn Rotary Kiln	C-ESP	0	93.1	2.00e+08	18.6	18.6
	DS/FF	0.265	0.68	7.57e+08	0.53	0.80
	DSI/C-ESP	0	93.1	5.07e+08	47.2	47.2
	DSI/FF	10.5	93.1	1.46e+08	13.6	24.1
	Subtotal	10.8			80.0	90.8
RDF Dedicated	C-ESP	35.6	253	1.67e+09	422	458
	DS/C-ESP	0.34	0.56	1.14e+09	0.638	0.98
	DS/FF	0.10	0.26	1.58e+09	0.405	0.50
	DSI/FF	0	253	4.22e+08	107	107
	DSI/H-ESP	0	253	2.00e+08	50.6	50.6
	H-ESP	0	1,679	4.22e+07	70.9	70.9
	DS/FF/C-ESP	0	253	5.63e+08	0.144	0.144
	Subtotal	36.1			651	687
Modular Starved-air	C-ESP	0	17.0	1.25e+08	2.12	2.12
	DSI/FF	0.0008	-	0	0	0.0008
	H-ESP	8.69	85.7	8.03e+07	6.88	15.57
	UNC	0	0.024	1.87e+08	0.005	0.005
	WS	0	17.0	4.90e+07	0.832	0.832
	WS/FF	0	17.0	2.82e+07	0.478	0.478
	DS/DSI/C-ESP	0	17.0	7.60e+07	1.29	1.29
	Subtotal	8.69			11.6	20.3
Modular Excess-air	C-ESP	0.068	17.0	6.25e+07	1.06	1.13
	DS/FF	0	17.0	1.18e+08	2.01	2.01
	DSI/FF	0	0.024	1.01e+08	0.002	0.002
	DSI/H-ESP	0	119	1.41e+07	1.68	1.68
	H-ESP	2.35	-	0	0	2.35
	UNC	0	0.024	1.41e+07	0.003	0.003
	WS/C-ESP	0	17.0	6.76e+07	1.15	1.15
	Subtotal	2.42			5.90	8.32
Fluidized-bed RDF	DS/FF	0	0.72	1.69e+08	0.114	0.114
	DSI/EGB	0	0.72	1.13e+08	0.076	0.076
	DSI/FF	0	0.72	8.45e+07	0.057	0.057
	Subtotal	0			0.247	0.247
Total		315		935		1,250

Key: DS/FF = Dry Scrubber combined with a Fabric Filter
DSI/FF = Dry Sorbent Injection coupled with a Fabric Filter
DS/CI/FF = Dry Scrubber -Carbon Injection-Fabric Filter
C-ESP = Cold-side Electrostatic Precipitator (Temperature at control device is below ≤230°C)
H-ESP = Hot-side Electrostatic Precipitator (Temperature at control device is ≥230°C)
WS = Wet Scrubber
UNC = Uncontrolled (no APCD)
EGB = Electro Granular Activated Carbon Bed
ng/kg = nanogram per kilogram
kg/yr = kilograms per year

Table 3-5a. Annual I-TEQ$_{DF}$ Emissions to the Air From MSWIs Operating in 1987

Municipal Solid Waste Incinerator Design	Air Pollution Control Device	I-TEQ$_{DF}$ Emissions fromTested Facilities (g TEQ/yr)	Average I-TEQ$_{DF}$ Emission Factor (ng/kg)	Activity Level Non-Tested Facilities (kg/yr)	I-TEQ$_{DF}$ Emissions from Non-Tested Facilities (g TEQ/yr)	Total I-TEQ$_{DF}$ Emissions from All Facilities (g TEQ/yr)
Mass Burn Waterwall	DS/FF	0.0373	-	0	0	0.0373
	H-ESP	433	473	3.27e+09	1550	1980
	Subtotal	433			1550	1980
Mass Burn Refractory	DS/FF	0	0.63	1.41e+08	0.0887	0.0887
	H-ESP	0	473	2.00e+09	944	944
	WS	0	236	9.01e+08	212	212
	Subtotal	0			1,160	1,160
Mass Burn Rotary Kiln	FF	0	47.0	1.58e+07	0.741	0.741
	H-ESP	48.2	285	2.25e+08	64.2	112
	Subtotal	48.2			65	113
RDF Dedicated	H-ESP	840	1492	2.45e+09	3660	4500
	WS	0	231	3.38e+08	78.1	78.1
	Subtotal	840			3730	4570
RDF Cofired	H-ESP	0	231	2.53e+08	58.6	58.6
Modular Starved-air	FF	0	16.2	1.43e+08	2.29	2.29
	H-ESP	0.0643	79.0	3.61e+08	28.5	28.5
	UNC	0	0.025	5.73e+08	0.0142	0.0142
	WS	0	16.2	5.30e+07	0.848	0.848
	Subtotal	0.0643			31.6	31.7
Modular Excess-air	EGB	0	0.025	6.76e+07	0.0017	0.0017
	UNC	0	0.025	4.17e+07	0.0010	0.0010
	WS	0	16.2	1.27e+08	2.03	2.03
	Subtotal	0			2.03	2.03
Totals		1,320			6,590	7,915

Key: DS/FF = Dry Scrubber combined with a Fabric Filter
DSI/FF = Dry Sorbent Injection coupled with a Fabric Filter
DS/CI/FF = Dry Scrubber -Carbon Injection-Fabric Filter
C-ESP = Cold-side Electrostatic Precipitator (Temperature at control device is below ≤230°C)
H-ESP = Hot-side Electrostatic Precipitator (Temperature at control device is ≥230°C)
WS = Wet Scrubber
UNC = Uncontrolled (no APCD)
EGB = Electro Granular Activated Carbon Bed
ng/kg = nanogram per kilogram
kg/yr = kilograms per year

Table 3-5b. Annual TEQ_{DF}-WHO_{98} Emissions to the Air From MSWIs Operating in 1987

Municipal Solid Waste Incinerator Design	Air Pollution Control Device	TEQ_{DF}-WHO_{98} Emissions fromTested Facilities (g TEQ/yr)	Average TEQ_{DF}-WHO_{98} Emission Factor (ng/kg)	Activity Level Non-Tested Facilities (kg/yr)	TEQ_{DF}-WHO_{98} Emissions from Non-Tested Facilities (g TEQ/yr)	Total TEQ_{DF}-WHO_{98} Emissions from All Facilities (g TEQ/yr)
Mass Burn Waterwall	DS/FF	0.039	-	0	0	0.039
	H-ESP	485	535	3.27e+09	1,732	2,218
	Subtotal	485			1,732	2,218
Mass Burn Refractory	DS/FF	0	0.72	1.41e+08	0.095	0.095
	H-ESP	0	535	2.00e+09	1,058	1,058
	WS	0	254	9.01e+08	229	229
	Subtotal	0			1,287	1,287
Mass Burn Rotary Kiln	FF	0	93.1	1.58e+07	1.47	1.47
	H-ESP	53.4	316	2.25e+08	71.2	124.6
	Subtotal	53.4			72.7	126.1
RDF Dedicated	H-ESP	946	1,679	2.45e+09	4,114	5,060
	WS	0	253	3.38e+08	85.5	85.5
	Subtotal	946			4,200	5,146
RDF Cofired	H-ESP	0	253	2.53e+08	64.1	64.1
Modular Starved-air	FF	0	17.0	1.43e+08	2.43	2.43
	H-ESP	0.068	85.7	3.61e+08	30.9	31.0
	UNC	0	0.024	5.73e+08	0.014	0.014
	WS	0	17.0	5.30e+07	0.898	0.898
	Subtotal	0.068			34.2	34.3
Modular Excess-air	EGB	0	0.024	6.76e+07	0.0016	0.0016
	UNC	0	0.024	4.17e+07	0.0010	0.0010
	WS	0	17.0	1.27e+08	2.15	2.15
	Subtotal	0			2.15	2.15
Totals		1,485			7,392	8,877

Key: DS/FF = Dry Scrubber combined with a Fabric Filter
DSI/FF = Dry Sorbent Injection coupled with a Fabric Filter
DS/CI/FF = Dry Scrubber -Carbon Injection-Fabric Filter
C-ESP = Cold-side Electrostatic Precipitator (Temperature at control device is below ≤230°C)
H-ESP = Hot-side Electrostatic Precipitator (Temperature at control device is ≥230°C)
WS = Wet Scrubber
UNC = Uncontrolled (no APCD)
EGB = Electro Granular Activated Carbon Bed
ng/kg = nanogram per kilogram
kg/yr = kilograms per year

Table 3-6. Fly Ash from a Municipal Incinerator
(Concentrations in μg/kg)

Congener Group	Average Concentration	Concentration Range
TCDD	3.7	1.6 - 12
PeCDD	6.4	2.0 - 25
HxCDD	9.1	1.5 - 42
HpCDD	2.3	0.5 - 9.2
OCDD	1.5	0.2 - 6.0
TOTAL CDDs	**23**	**6.2 - 94**
TCDF	12	5.1 - 36
PeCDF	17	8.3 - 40
HxCDF	14	3.9 - 40
HpCDF	2.9	0.8 - 9.2
OCDF	1.2	ND - 2.1
TOTAL CDFs	**47**	**22 - 110**

Table 3-7. Comparison of the Amount of TEQs Generated Annually in MSWI Ash

Data Source	Type of Ash	Mean Total CDD/CDF Concentration (ng/kg)	Mean I-TEQ_{DF} (ng/kg)	Annual TEQ Amount 1995 Value[a] (g I-TEQ_{DF}/yr)	Annual TEQ Amount 1987 Value[a] (g I-TEQ_{DF}/yr)
USEPA, 1990c	Mixed	12,383	258	1,806	1,290
Washington, 1998					
Ft. Lewis	Bottom	0	0	0	0
	Fly	71,280	4,980	3,486	2,490
Bellingham	Mixed	1,884	38	266	190
Spokane	Mixed	1,414	163	1,141	815
	Fly	10,320	510	357	255
	Bottom	100	0.1	1	0.05
Shane, 1990	Fly	175,000	-	-	-
Clement, 1988	Fly	70,000	-	-	-
USEPA, 1987a					
North America	Fly	1,286,000	-	-	-
Europe	Fly	876,000	-	-	-
Japan	Fly	2,600	-	-	-
Wire Reclamation	Fly	12,010	-	-	-
	Bottom	1,310	-	-	-
Lahl, 1991	Mixed	177,640	-	-	-

- Indicates that values could not be calculated.

a. In calculating the Annual TEQ Amounts, fly ash and bottom ash were considered to be 10% and 90% of the total ash, respectively.

Table 3-8. CDD/CDF Emission Factors for Hazardous Waste Incinerators and Boilers

Congener/Congener Group	Incinerator Average Mean emission factor (17 facilities) (ng/kg feed)		Hot-Side ESP Boilers Mean emission factor (2 facilities) (ng/kg feed)	
	Nondetects Set to 1/2 Det. Limit	Nondetects Set to Zero	Nondetects Set to 1/2 Det. Limit	Nondetects Set to Zero
2,3,7,8-TCDD	0.44	0.14	0.10	0.00
1,2,3,7,8-PeCDD	0.18	0.14	0.11	0.04
1,2,3,4,7,8-HxCDD	0.22	0.18	0.15	0.08
1,2,3,6,7,8-HxCDD	0.32	0.28	0.20	0.18
1,2,3,7,8,9-HxCDD	0.49	0.48	0.22	0.20
1,2,3,4,6,7,8-HpCDD	1.77	1.74	1.17	1.17
OCDD	4.13	3.74	5.24	5.24
2,3,7,8-TCDF	2.96	2.69	0.81	0.81
1,2,3,7,8-PeCDF	2.36	2.33	0.38	0.38
2,3,4,7,8-PeCDF	2.56	2.51	0.52	0.52
1,2,3,4,7,8-HxCDF	9.71	9.71	0.83	0.83
1,2,3,6,7,8-HxCDF	3.95	3.95	0.37	0.37
1,2,3,7,8,9-HxCDF	0.31	0.29	0.08	0.02
2,3,4,6,7,8-HxCDF	2.70	2.70	0.56	0.56
1,2,3,4,6,7,8-HpCDF	16.87	16.68	1.04	0.93
1,2,3,4,7,8,9-HpCDF	1.74	1.71	0.18	0.16
OCDF	13.79	13.46	0.70	0.70
Total I-TEQ_{DF}	4.22	3.83	0.78	0.64
Total TEQ_{DF}-WHO_{98}	4.29	3.88	0.83	0.65
Total TCDD	NR	NR	0.77	0.77
Total PeCDD	NR	NR	1.15	0.77
Total HxCDD	NR	NR	1.67	1.62
Total HpCDD	NR	NR	2.34	2.34
Total OCDD	4.13	3.74	5.24	5.24
Total TCDF	NR	NR	5.47	5.47
Total PeCDF	NR	NR	5.51	5.51
Total HxCDF	NR	NR	4.04	4.04
Total HpCDF	NR	NR	1.94	1.94
Total OCDF	13.78	13.46	0.70	0.70
Total CDD/CDF	153	153	28.83	28.39

ng/kg = nanograms per kilogram
NR = not reported

Source: U.S. EPA (1996c).

Table 3-9. Summary of Annual Operating Hours for Each MWI Type

MWI Type	Capacity Ranges (lb/hr)	Annual Charging Hours (hr/yr)	Maximum Annual Charging Hours (hr/yr)	Capacity Factor
Continuous commercial	>1,000	7,776	8,760	0.89
Continuous onsite	501 - 1,000 >1,000	1,826 2,174	5,475	0.33 0.40
Intermittent	≤ 500	1,250	4,380	0.29
Batch	Case by case	Case by case		Case by case

lb/hr = pounds per hour
hr/yr = hours per year

Table 3-10. OAQPS Approach: PM Emission Limits for MWIs and Corresponding Residence Times in the Secondary (2°) Combustion Chamber

MWI Type	PM Emission Limit[a] (gr/dscf)	Residence Time in 2° Chamber (seconds)	I-TEQ_{DF} Emission Factor (kg I-TEQ_{DF}/kg waste)
Intermittent and Continuous	≥0.3	0.25	3.96e-9
	0.16 to < 0.30	1.0	9.09e-10
	0.10 to ≤0.16	2.0	7.44e-11
Batch	≥0.079	0.25	3.96e-9
	0.042 to <0.079	1.0	9.09e-10
	0.026 to <0.042	2.0	7.44e-11

[a] gr/dscf = grains per dry standard cubic foot at standard temperature and pressure.

Table 3-11. OAQPS Approach: Estimated Nationwide I-TEQ_{DF} Emissions (g/yr) for 1995

MWI Type	Residence Time or APCD	CDD/CDF Emission Factor (ng/kg)	I-TEQ_{DF} Emission Factor (ng/kg)	Activity Level (kg/yr)	CDD/CDF Emissions (g/yr)	I-TEQ_{DF} Emissions (g/yr)
Batch	0.25 sec	193,997	3,960	5.95e+06	1.15e+03	2.36e+01
	1.00 sec	44,500	909	4.20e+05	1.87e+01	3.82e-01
	2.00 sec	3,650	74	2.14e+05	7.81e-01	1.58e-02
Continuous	0.25 sec	193,997	3,960	1.20e+06	2.33e+02	4.75e+00
	1.00 sec	44,500	909	5.10e+06	2.27e+02	4.64e+00
	2.00 sec	3,650	74	3.01e+07	1.10e+02	2.23e+00
Continuous/ Intermittent	0.25 sec	193,997	3,960	4.54e+06	8.81e+02	1.80e+01
	1.00 sec	44,500	909	5.10e+06	2.27e+02	4.64e+00
	2.00 sec	3,650	74	9.79e+07	3.57e+02	7.24e+00
Intermittent	0.25 sec	193,997	3,960	4.18e+06	8.11e+02	1.66e+01
	1.00 sec	44,500	909	5.57e+07	2.48e+03	5.06e+01
	2.00 sec	3,650	74	4.31e+07	1.57e+02	3.19e+00
Subtotal: Uncontrolled				2.54e+08	6.66e+03	1.36e+02
Batch	Wet Scrubber	426	10	2.42e+04	1.03e-02	2.42e-04
Continuous	Wet Scrubber	426	10	1.88e+08	8.01e+01	1.88e+00
Continuous/ Intermittent	Wet Scrubber	426	10	1.22e+08	5.20e+01	1.22e+00
Intermittent	Wet Scrubber	426	10	6.04e+07	2.57e+01	6.04e-01
Subtotal: Controlled w/Wet Scrubber				3.70e+08	1.58e+02	3.70e+00
Continuous	Dry Scrubber - no carbon	365	7	9.94e+07	3.63e+01	6.96e-01
Continuous/ Intermittent	Dry Scrubber - no carbon	365	7	7.86e+06	2.87e+00	5.50e-02
Intermittent	Dry Scrubber - no carbon	365	7	2.07e+07	7.56e+00	1.45e-01
Continuous	Dry Scrubber - with carbon	70	2	1.43e+07	1.00e+00	2.86e-02
Continuous/ Intermittent	Dry Scrubber - with carbon	70	2	3.70e+06	2.59e-01	7.40e-03
Subtotal: Controlled w/Dry Scrubber				1.46e+08	4.80e+01	9.32e-01
Intermittent	Fabric Filter/ Packed Bed	33,400	681	6.99e+05	2.34e+01	4.76e-01
Total MWI				7.71e+08	6.88e+03	1.41e+02

NA = Not applicable
ng/kg = nanograms per kilogram
kg/yr = kilograms per year
g/yr = grams per year

Table 3-12. AHA Approach: I-TEQ$_{DF}$ Emission Factors Calculated for Air Pollution Control

APC Category	I-TEQ$_{DF}$ Emission Factor (lb/10^6 lbs waste)	Number of MWI Test Reports Used[a]
Uncontrolled		
MWIs up to 200 lb/hr	1.53e-03	4
MWIs > 200 lb/hr	5.51e-04	13
Wet scrubber/BHF/ESP[b]	4.49e-05	11
Dry sorbent injection/Fabric Filter	6.95e-05	8

[a] The same MWI may have been used more than once in deriving emission factors.

[b] Wet scrubbers-bag house filters-electrostatic precipitators. Bag house is also called Fabric Filter.

Source: Doucet (1995).

Table 3-13. AHA Assumptions of the Percent Distribution of Air Pollution Control on MWIs Based on PM Emission Limits

PM Emission Limits[a] (gr/dscf)	Percent MWIs Uncontrolled[b]	Percent MWIs with Scrubbers/ BHFs/ESPs[c]	Percent MWIs DI/FF[d]
≥ 0.10	50%	50%	0%
0.08 to < 0.10	25%	75%	0%
0.03 to < 0.08	0%	98%	2%
< 0.03	0%	30%	70%

[a] Particulate matter (PM) emission limits at the stack, grains per dry standard cubic foot (gr/dscf).

[b] Uncontrolled means there is no air pollution control device installed on the MWI.

[c] Scrubbers/BHFs/ESPs means wet scrubbers/bag house filters/electrostatic precipitators.

[d] DI/FF means dry sorbent injection combined with fabric filters.

Table 3-14. AHA Approach: Estimated Annual Nationwide I-TEQ$_{DF}$ Emissions

APCD[a]	MWI Capacity[b] (lb/hr)	I-TEQ$_{DF}$ Emission Factor[c] (g/kg waste)	MWI Activity Level[d] (kg/yr)	Annual I-TEQ$_{DF}$ Emissions (g/yr)
Uncontrolled	≤ 200 > 200	1.54 e-06 5.51 e-07	2.28 e+07 1.54 e+08	3.51e+01 8.48e+01
Subtotal: Uncontrolled			1.77 e+08	1.20e+02
WS/BHF/ESP	>200	4.49 e-08	3.51 e+08	1.58e+01
DI/FF	>200	6.95 e-08	2.60 e+07	1.81
Subtotal: Controlled			3.77 e+08	1.76e+01
Total			5.54 e+08	1.38e+02

[a] APCD = Air Pollution Control Device assumed by AHA. Uncontrolled means there is no air pollution control device installed on the MWI. WS/BHF/ESP = Wet scrubber-bag house filter-electrostatic precipitator. DI/FF = Dry sorbent injection-fabric filter.

[b] MWI capacity is the design capacity of the primary combustion chamber.

[c] I-TEQ$_{DF}$ Emission Factor derived from tested facilities.

[d] Activity Level is the annual amount of medical waste incinerated by each APCD class.

lb/hr = pounds per hour
g/kg = grams per kilogram
kg/yr = kilograms per year
g/yr = grams per year

Table 3-15. Comparison Between Predicted Residence Times and Residence Times Confirmed by State Agencies in EPA/ORD Telephone Survey

State	Residence Time Categories	Percentage of Uncontrolled MWIs Predicted by PM Method	Percentage of Uncontrolled MWIs Confirmed by State Agency
Michigan	1/4 second 1.0 second 2.0 seconds	2% (6/280 MWIs) 2% (5/280) 96% (269/280)	96% (269/280 MWIs) 3% (9/280) 1% (1/280)
Massachusetts	1/4 second 1.0 second 2.0 seconds	6% (6/94 MWIs) 0% (0/94) 94% (88/94)	Unknown Unknown 4% (2/50)
Virginia	1/4 second 1.0 second 2.0 seconds	11% (6/56) 0 % (0/50) 89% (50/56)	4.5% (1/22) 91% (20/22) 4.5% (1/22)
New Jersey	1/4 second 1.0 second 2.0 seconds	0% (0/53 MWIs) 0% (0/53) 100% (53/53)	Unknown Unknown Unknown

Source: O'Rourke (1996).

Table 3-16. EPA/ORD Approach: TEQ Emissions from Medical Waste Incineration for Reference Year 1995

MWI Class (APCD)	MWI Subclass (Capacity or APCD)	No. of Tested Facilities	Total CDD/CDF Emission Factor (ng/kg)	I-TEQ_{DF} Emission Factor (ng/kg)	TEQ_{DF}-WHO_{98} Emission Factor (ng/kg)	Activity Level (kg/yr)	Annual CDD/CDF Emissions (g/yr)	Annual I-TEQ_{DF} Emissions (g/yr)	Annual TEQ_{DF}-WHO_{98} Emissions (g/yr)
Uncontrolled	≤200 lb/hr	3	9.25e+04	1.86e+03	1.98e+03	3.06e+07	2.83e+03	5.71e+01	6.06e+01
	>200 lb/hr	5	6.05e+04	1.68e+03	1.78e+03	2.23e+08	1.35e+04	3.75e+02	3.98e+02
Controlled	Wet Scrubber/ Fabric Filter/ ESP	9	4.67e+03	7.22e+01	7.43e+01	3.71e+08	1.73e+03	2.68e+01	2.76e+01
	Dry Sorbent Injection/ Fabric Filter	2	2.85e+02	6.78	6.86	1.46e+08	4.16e+01	9.90e-01	1.00e+00
	Fabric Filter/ Packed Bed Scrubber	1	1.11e+05	1.35e+03	1.49e+03	6.99e+05	7.76e+01	9.44e-01	1.04e+00
Total						7.71e+08	1.82e+04	4.61e+02	4.88e+02

APCD = Air Pollution Control Devices
ng/kg = nanograms per kilogram
kg/yr = kilograms per year
g/yr = grams per year
lb/hr = pounds per hour

Table 3-17. Summary of Annual TEQ Emissions from Medical Waste Incineration (MWI) for Reference Year 1987

MWI Class[a]	No. of Tested Facilities	Total CDD/CDF Emission Factor[b] (g/kg)	I-TEQ_{DF} Emission Factor (g/kg)	TEQ_{DF}-WHO_{98} Emission Factor (g/kg)	Activity Level (kg/yr)	Annual CDD/CDF Emissions (g/yr)	Annual I-TEQ_{DF} Emissions (g/yr)	Annual TEQ_{DF}-WHO_{98} Emissions (g/yr)
≤ 200 lb/hr	3	9.25e-05	1.86e-06	1.98e-06	2.19e+08	2.02e+04	4.08e+02	4.34e+02
> 200 lb/hr	5	6.05e-05	1.68e-06	1.78e-06	1.21e+09	7.32e+04	2.03e+03	2.15e+03
Total	8				1.43e+09	9.34e+04	2.44e+03	2.59e+03

[a] This uses the categorization scheme of the AHA Approach (Doucet, 1995).

kg/yr = kilograms per year
g/kg = grams per kilogram
g/yr = grams per year
lb/hr = pounds per hour

Table 3-18. Comparison of Basic Assumptions Used in the EPA/ORD, the EPA/OAQPS, and the AHA Approaches to Estimating Nationwide CDD/CDF TEQ Emissions from MWIs in 1995

Assumptions	EPA/ORD Approach	EPA/OAQPS Approach	AHA Approach
Reference Year	1995	1995	1995
Number of MWIs	2,375	2,375	2,233
Estimated Activity Level	7.71 e+08 kg/yr	7.71 e+08 kg/yr	5.54 e+08 kg/yr
Percent of Activity Level at Uncontrolled MWIs	33%	33%	32%
Percent of Activity Level at Controlled MWIs	67%	67%	68%
Subclassification of Uncontrolled Class	Same as AHA assumption	By residence times (RT) in secondary chamber	By design capacity
Assumed Distribution of Uncontrolled Class	Same as AHA assumption	By RT of 0.25, 1.0 and 2.0 sec by State PM emission limits	By estimated annual hrs of operation of <200 lb/hr and >200 lb/hr design capacity
APCDs Assumed for Controlled Class	WS/FF/ESP DI/FF FF/Packed Bed Scrub	WS DS-no Carbon DS-Carbon FF/Packed Bed Scrub	WS/FF/ESP DI/FF
Assumed Distribution of Controls	Yes/ Analogous to AHA method.	Yes/ Analogous to AHA method	Yes/ Based on survey and State PM emission limits
Emission Factor Approach Used	Yes	Yes	Yes
No. of Tested MWIs Used to Develop Emission Factors	Uncontrolled: 8 Controlled: 11	Uncontrolled: 10 Controlled: 23	Uncontrolled: 13 Controlled: 12
Uncontrolled I-TEQ_{DF} Emission Factors (ng/kg)	1,865 = ≤200 lb/hr 1,680 = >200 lb/hr	a/ 3,960 = 0.25 s RT b/ 909 = 1.0 s RT c/ 74 =2.0 s RT	d/ 1,540 =≤200 lb/hr e/ 551= > 200 lb/hr
Controlled I-TEQ_{DF} Emission Factors (ng/kg)[f]	WS/FF/ESP: 72.2 DSI/FF: 6.8 FF/PBS: 1,350	WS: 10 DS no carbon: 7 DS with carbon: 2 FF/PBS: 681	WS/FF/ESP: 44.9 DSI/FF: 69.5

WS = Wet Scrubber; FF = Fabric Filter; ESP = Electrostatic Precipitator; DSI = Dry Sorbent Injection; DS = Dry Scrubber; no carbon = without the addition of activated carbon; with carbon = with the addition of activated carbon; PBS = Packed Bed Scrubber.

a 0.25 seconds (s) residence time (RT) in the secondary chamber.

b 1.0 seconds (s) residence time (RT) in the secondary chamber.

c 2.0 seconds (s) residence time (RT) in the secondary chamber.

d design capacities less than or equal to 200 lbs/hr.

e design capacities greater than 200 lbs/hr.

f emission factors as reported in Tables 3-9, 3-12, and 3-14.

lb/hr = pounds per hour

kg/yr = kilograms per year

Table 3-19. CDD/CDF Air Emission Factors for a Crematorium

Congener/Congener Group	Mean Facility Emission Factor	
	Assuming ND = zero (ng/body)	Assuming ND = 1/2 det limit (ng/body)
2,3,7,8-TCDD	28.9	28.9
1,2,3,7,8-PeCDD	89.6	89.6
1,2,3,4,7,8-HxCDD	108	108
1,2,3,6,7,8-HxCDD	157	157
1,2,3,7,8,9-HxCDD	197	197
1,2,3,4,6,7,8-HpCDD	1,484	1,484
OCDD	2,331	2,331
2,3,7,8-TCDF	206	206
1,2,3,7,8-PeCDF	108	117
2,3,4,7,8-PeCDF	339	349
1,2,3,4,7,8-HxCDF	374	374
1,2,3,6,7,8-HxCDF	338	338
1,2,3,7,8,9-HxCDF	657	657
2,3,4,6,7,8-HxCDF	135	135
1,2,3,4,6,7,8-HpCDF	1,689	1,813
1,2,3,4,7,8,9-HpCDF	104	112
OCDF	624	624
Total 2,3,7,8-CDD	4,396	4,396
Total 2,3,7,8-CDF	4,574	4,725
Total I-TEQ_{DF}	501	508
Total TEQ_{DF}-WHO_{98}	543	550
Total TCDD	554	554
Total PeCDD	860	860
Total HxCDD	2,224	2,224
Total HpCDD	3,180	3,180
Total OCDD	2,331	2,331
Total TCDF	4,335	4,335
Total PeCDF	2,563	2,563
Total HxCDF	4,306	4,306
Total HpCDF	2,030	2,154
Total OCDF	624	624
Total CDD/CDF	23,007	23,131

ng/body = nanograms per body

Source: CARB (1990c)

Table 3-20. CDD/CDF Emission Factors for Sewage Sludge Incinerators

Congener	U.S. EPA (1987a) - 3 facilities Mean Emission Factor (ng/kg)		Green et al. (1995) - 11 facilities Mean Emission Factor (ng/kg)	
	Nondetects Set to Zero	Nondetects Set to 1/2 Det. Limit	Nondetects Set to Zero	Nondetects Set to 1/2 Det. Limit
2,3,7,8-TCDD	0.39	0.44	0.12	0.23
1,2,3,7,8-PeCDD	NR	NR	0.23	0.32
1,2,3,4,7,8-HxCDD	NR	NR	0.03	0.11
1,2,3,6,7,8-HxCDD	NR	NR	0.10	0.16
1,2,3,7,8,9-HxCDD	NR	NR	0.29	0.36
1,2,3,4,6,7,8-HpCDD	NR	NR	2.55	2.70
OCDD	46.2	46.2	13.60	14.00
2,3,7,8-TCDF	179	179	26.60	26.63
1,2,3,7,8-PeCDF	NR	NR	1.98	2.08
2,3,4,7,8-PeCDF	NR	NR	6.84	6.89
1,2,3,4,7,8-HxCDF	NR	NR	2.17	2.24
1,2,3,6,7,8-HxCDF	NR	NR	0.79	0.83
1,2,3,7,8,9-HxCDF	NR	NR	0.03	0.08
2,3,4,6,7,8-HxCDF	NR	NR	1.26	1.46
1,2,3,4,6,7,8-HpCDF	NR	NR	1.46	1.64
1,2,3,4,7,8,9-HpCDF	NR	NR	0.17	0.27
OCDF	109	109	1.22	1.62
Total TCDD	37.6	37.7	35.80	37.81
Total PeCDD	2.66	2.81	0.82	1.63
Total HxCDD	16.6	16.9	1.74	2.25
Total HpCDD	53.9	54.0	4.39	5.03
Total OCDD	46.2	46.2	13.60	14.00
Total TCDF	528	528	123.85	124.10
Total PeCDF	253	253	59.94	60.16
Total HxCDF	75.4	75.9	12.69	13.50
Total HpCDF	144	144	2.63	3.12
Total OCDF	109	109	1.22	1.62
Total I-TEQ_{DF}	NR	NR	6.94	7.19
Total TEQ_{DF}-WHO_{98}	NR	NR	7.04	7.33
Total CDD/CDF	1,266	1,268	257	263

ng/kg = nanograms per kilogram
NR = not reported
Sources: U.S. EPA (1987a); Green et al. (1995)

Table 3-21. CDD/CDF Air Emission Factors for Tire Combustion

Congener/Congener Group	Mean Facility Emission Factor	
	Assuming ND = zero (ng/kg)	Assuming ND = 1/2 det limit (ng/kg)
2,3,7,8-TCDD	0.149	0.149
1,2,3,7,8-PeCDD	0.006	0.026
1,2,3,4,7,8-HxCDD	0.018	0.023
1,2,3,6,7,8-HxCDD	0.055	0.062
1,2,3,7,8,9-HxCDD	0.036	0.048
1,2,3,4,6,7,8-HpCDD	0.379	0.379
OCDD	4.156	4.156
2,3,7,8-TCDF	0.319	0.319
1,2,3,7,8-PeCDF	0.114	0.118
2,3,4,7,8-PeCDF	0.086	0.091
1,2,3,4,7,8-HxCDF	0.103	0.111
1,2,3,6,7,8-HxCDF	0.059	0.090
1,2,3,7,8,9-HxCDF	0.036	0.068
2,3,4,6,7,8-HxCDF	0.100	0.148
1,2,3,4,6,7,8-HpCDF	0.000	0.166
1,2,3,4,7,8,9-HpCDF	0.027	0.095
OCDF	0.756	0.756
Total 2,3,7,8-CDD	4.799	4.843
Total 2,3,7,8-CDF	1.600	1.962
Total I-TEQ_{DF}	0.282	0.311
Total TEQ_{DF}-WHO_{98}	0.281	0.318
Total TCDD	0.153	0.153
Total PeCDD	0.032	0.032
Total HxCDD	0.391	0.391
Total HpCDD	0.695	0.695
Total OCDD	4.156	4.156
Total TCDF	1.204	1.204
Total PeCDF	0.737	0.737
Total HxCDF	0.710	0.710
Total HpCDF	0.119	0.186
Total OCDF	0.802	0.802
Total CDD/CDF	8.999	9.067

ng/kg = nanograms per kilogram
ND = not detected

Source: CARB (1991a)

Table 3-22. CDD/CDF Emission Factors for Combustion of Bleached-Kraft Mill Sludge in Wood Residue Boilers

Congener	Mean Emission Factors (ng/kg feed)	
	Nondetects Set to Zero	Nondetects Set to 1/2 Det. Limit
2,3,7,8-TCDD	0.005	0.013
1,2,3,7,8-PeCDD	0.005	0.012
1,2,3,4,7,8-HxCDD	0.012	0.022
1,2,3,6,7,8-HxCDD	0.050	0.056
1,2,3,7,8,9-HxCDD	0.035	0.043
1,2,3,4,6,7,8-HpCDD	0.301	0.302
OCDD	1.189	1.192
2,3,7,8-TCDF	0.104	0.107
1,2,3,7,8-PeCDF	0.022	0.029
2,3,4,7,8-PeCDF	0.019	0.027
1,2,3,4,7,8-HxCDF	0.069	0.071
1,2,3,6,7,8-HxCDF	0.043	0.046
1,2,3,7,8,9-HxCDF	0.036	0.041
2,3,4,6,7,8-HxCDF	0.004	0.012
1,2,3,4,6,7,8-HpCDF	0.274	0.275
1,2,3,4,7,8,9-HpCDF	0.081	0.083
OCDF	0.187	0.188
Total TCDD	0.101	0.108
Total PeCDD	0.030	0.109
Total HxCDD	0.599	0.600
Total HpCDD	0.956	0.958
Total OCDD	1.189	1.192
Total TCDF	0.560	0.560
Total PeCDF	0.469	0.470
Total HxCDF	0.748	0.748
Total HpCDF	1.102	1.102
Total OCDF	0.187	0.188
Total I-TEQ_{DF}	0.061	0.082
Total TEQ_{DF}-WHO_{98}	0.062	0.087
Total CDD/CDF	5.941	6.037

ng/kg = nanograms per kilogram

Source: NCASI (1995)

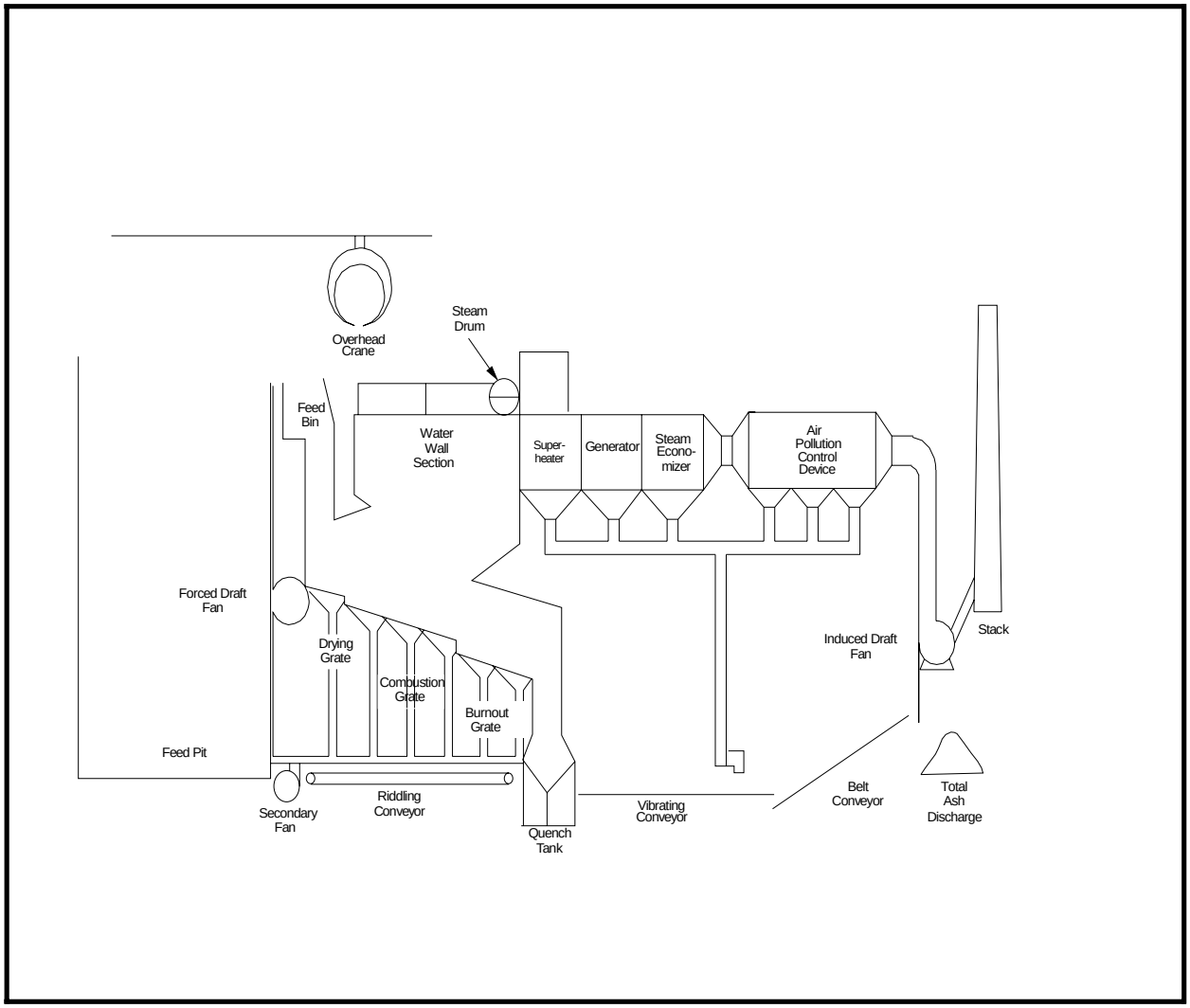


Figure 3-1. Typical Mass Burn Waterwall Municipal Solid Waste Incinerator

Source: U.S. EPA (1997b)

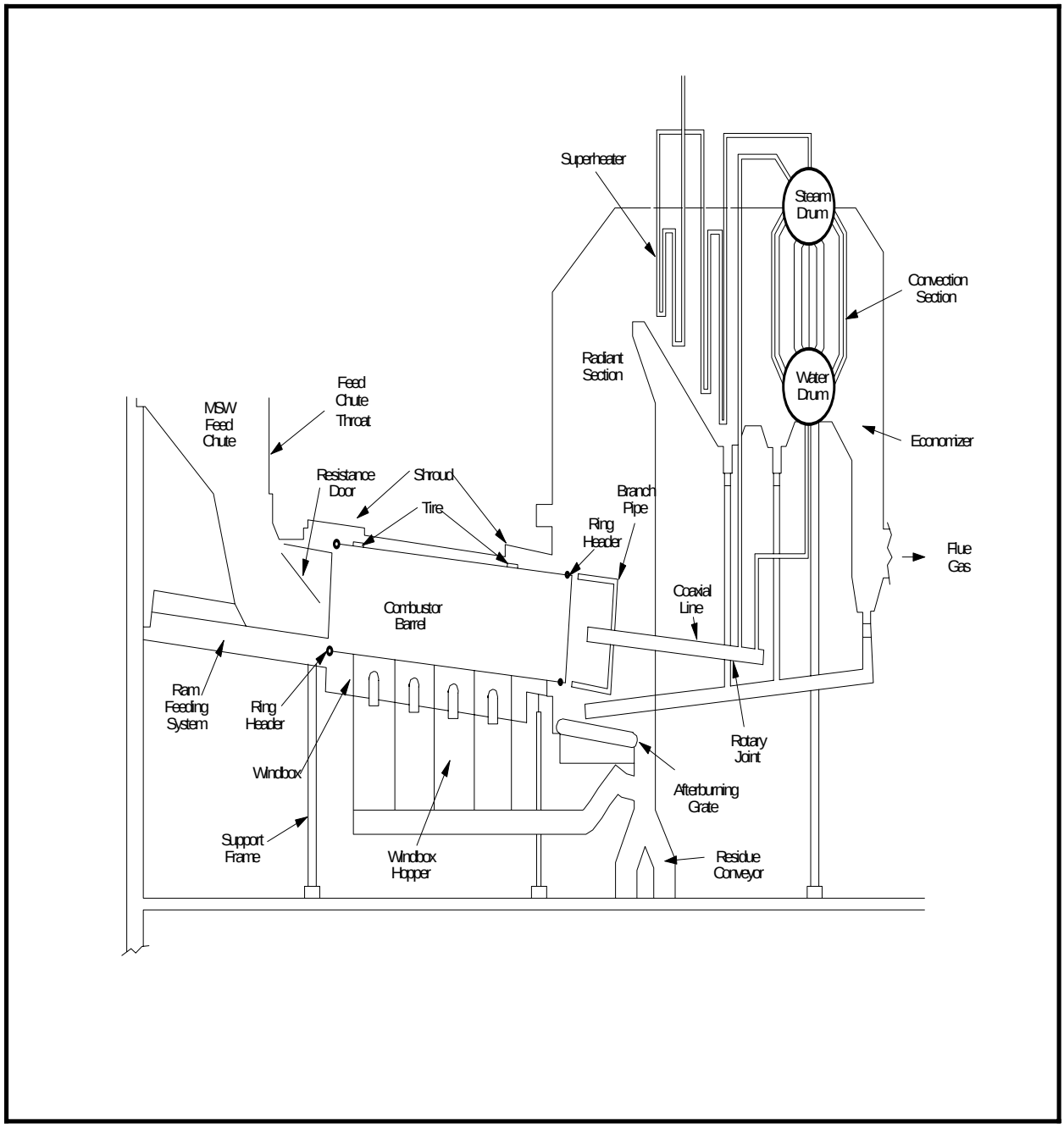


Figure 3-2. Typical Mass Burn Rotary Kiln Combustor

Source: U.S. EPA (1997b)

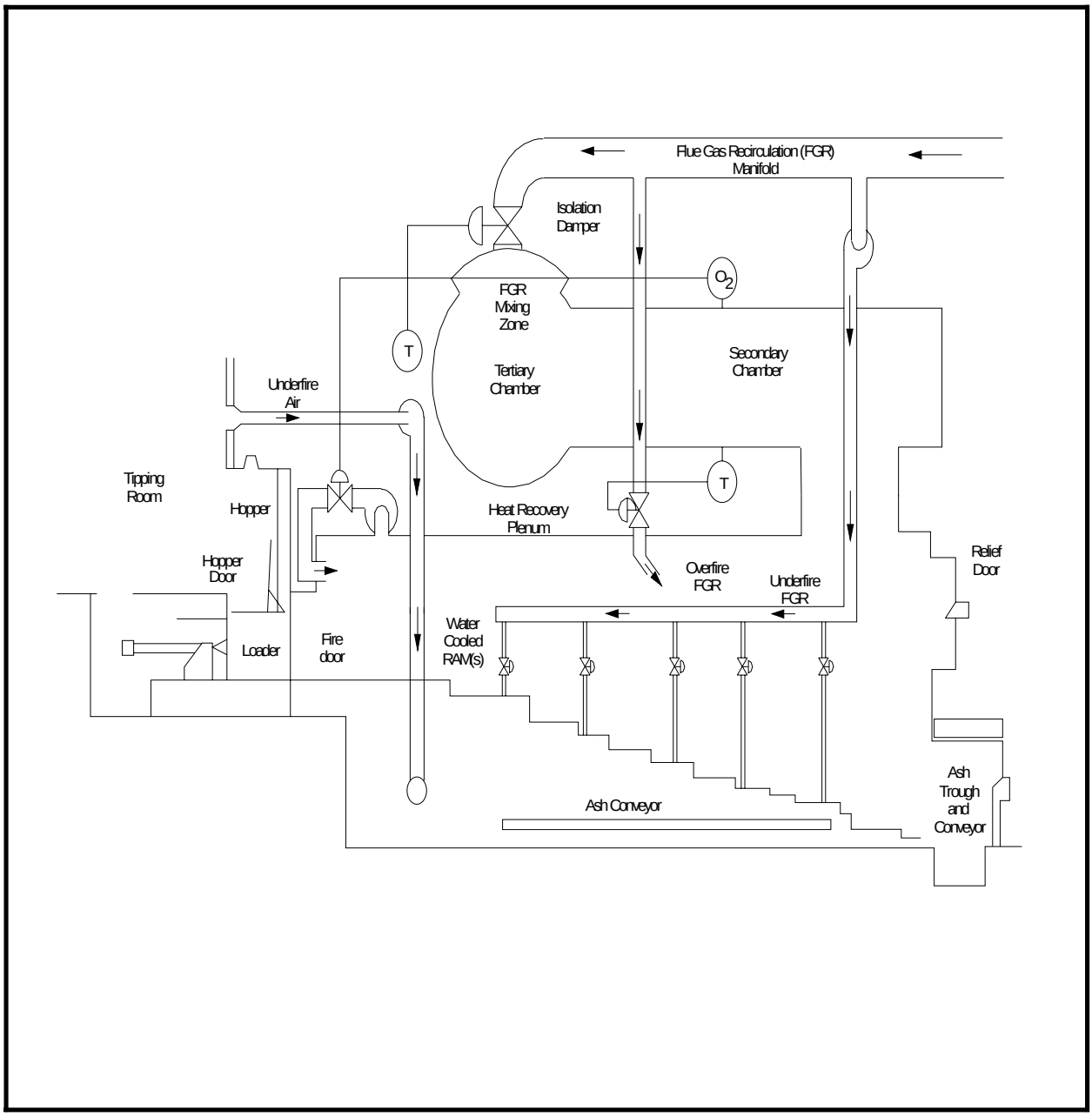


Figure 3-3. Typical Modular Excess-Air Combustor

Source: U.S. EPA (1997b)

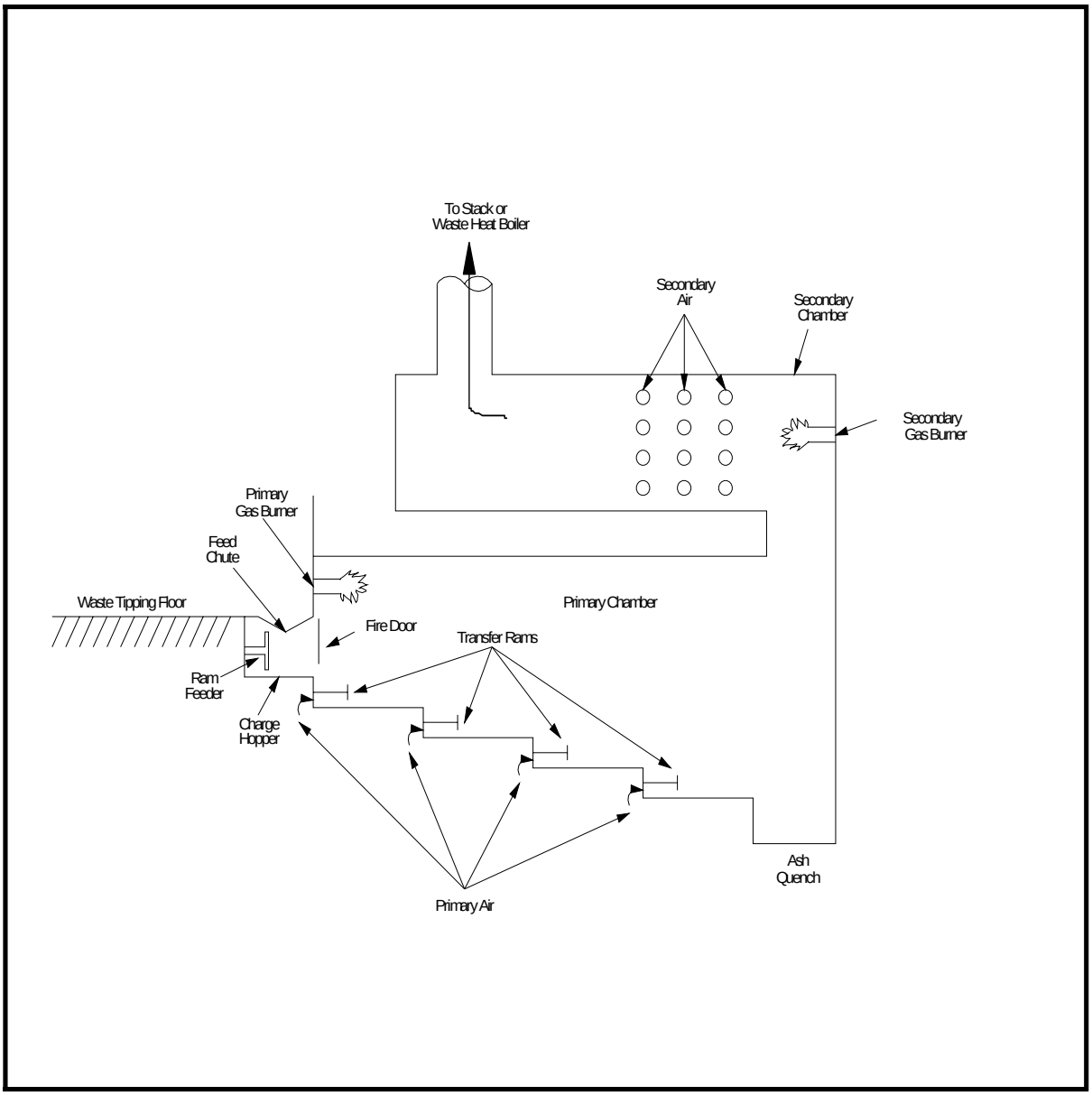


Figure 3-4. Typical Modular Starved-Air Combustor with Transfer Rams

Source: U.S. EPA (1997b)

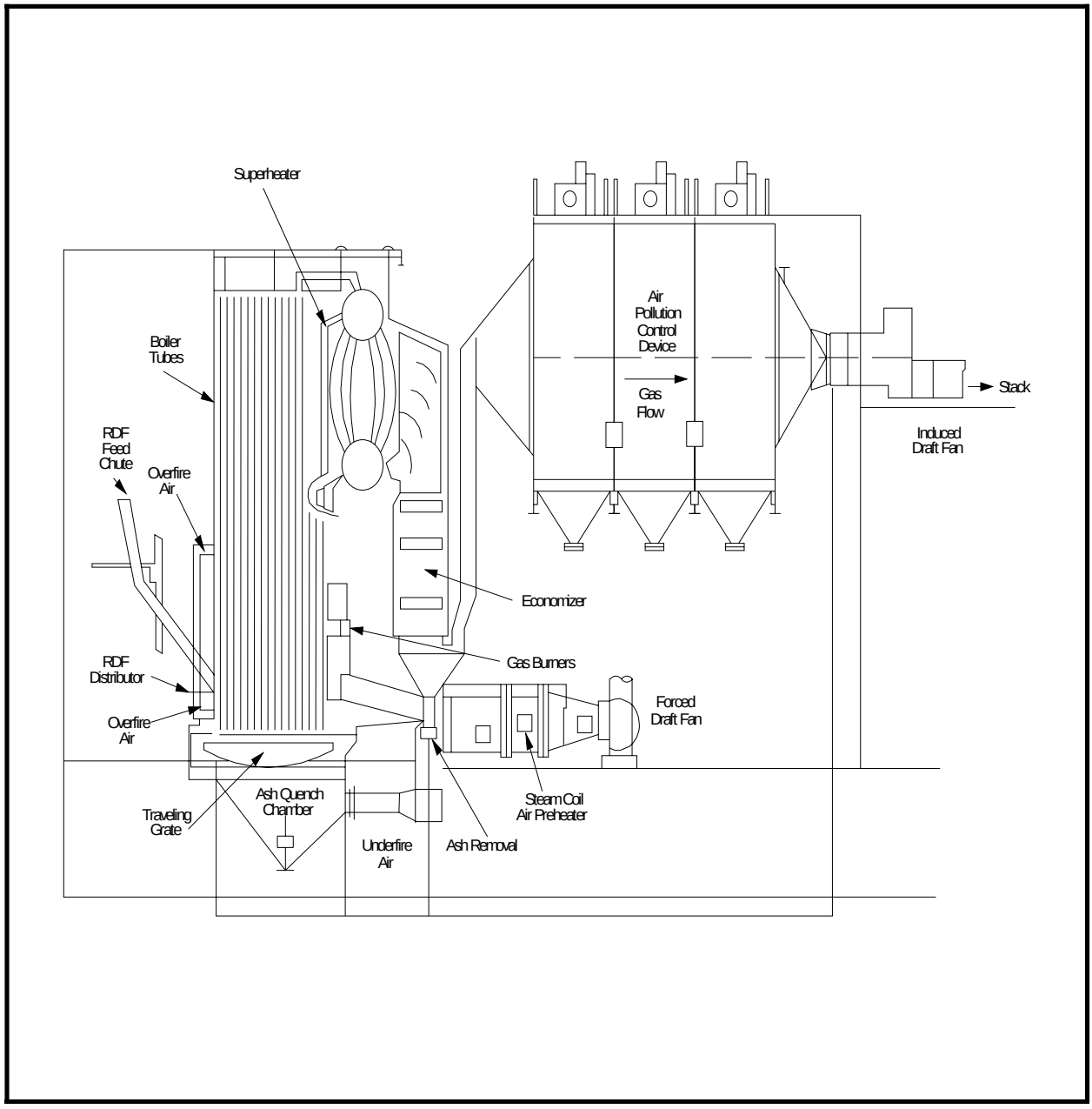


Figure 3-5. Typical Dedicated RDF-Fired Spreader Stoker Boiler

Source: U.S. EPA (1997b)

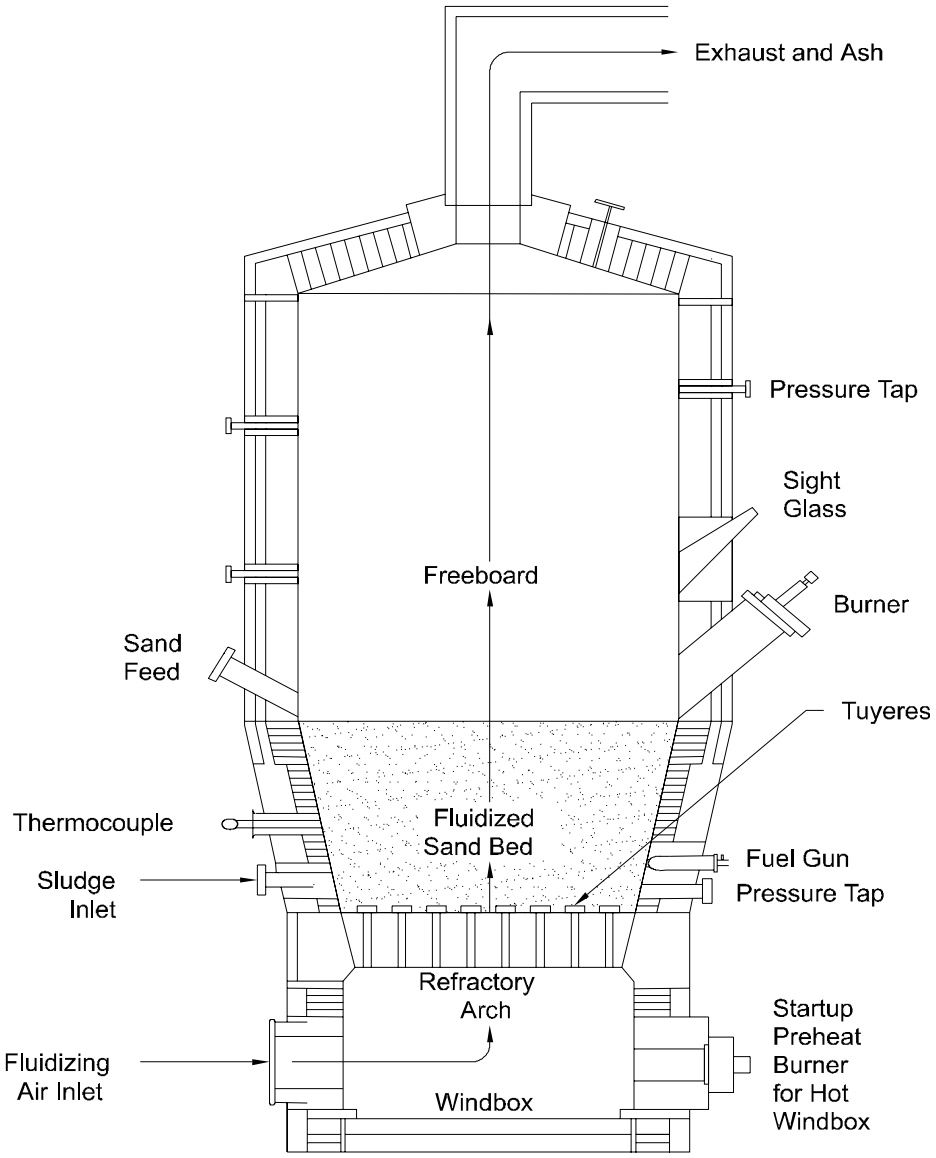
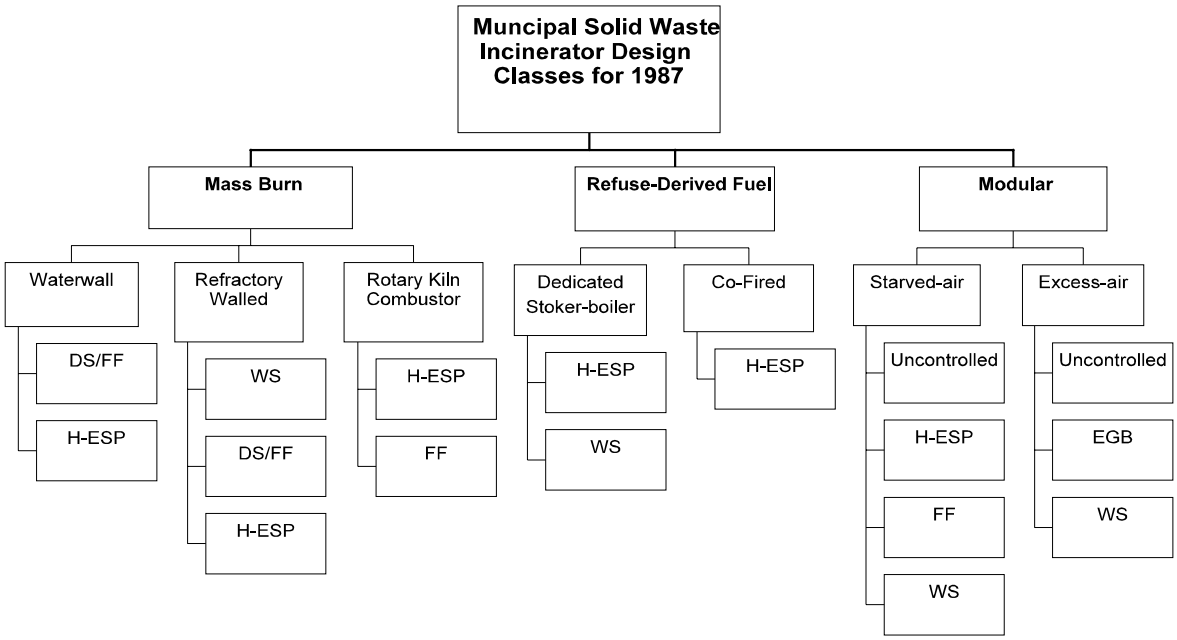


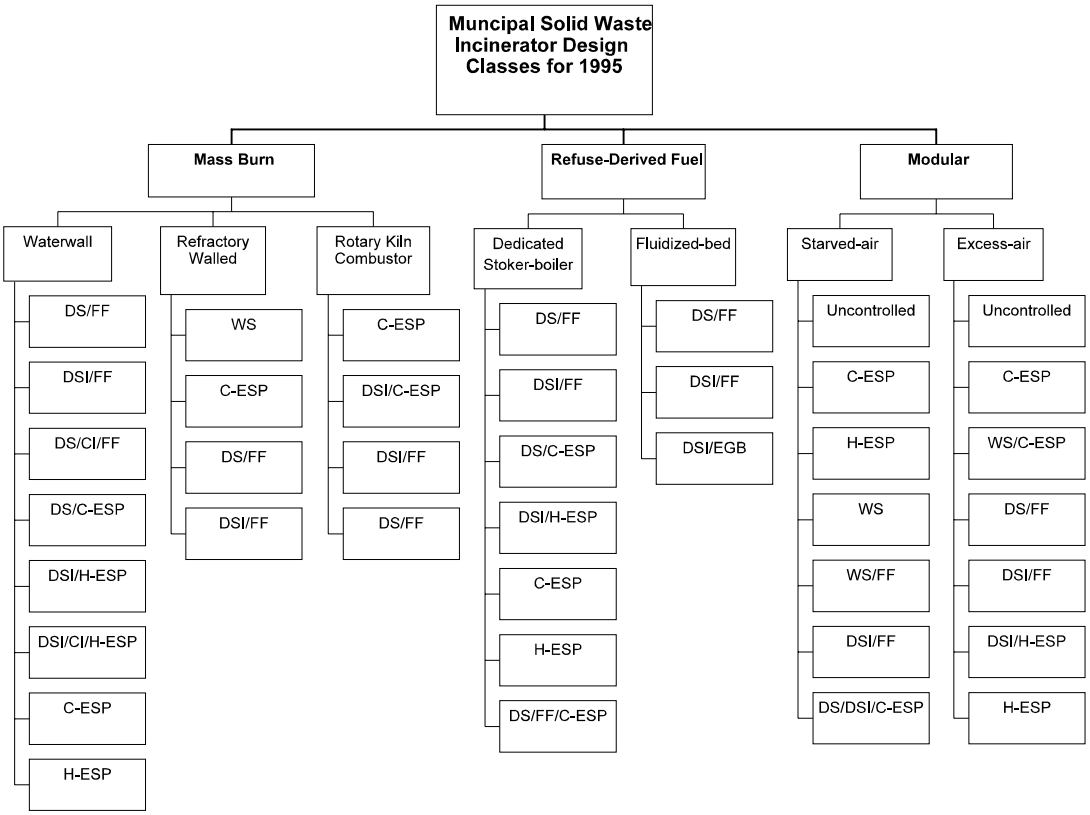
Figure 3-6. Fluidized-Bed RDF Incinerator

Source: U.S. EPA (1997b)



Key: DS/FF = Dry Scrubber combined with a Fabric Filter
H-ESP = Hot-side Electrostatic Precipitator (Temperature at control device is ≥230°C)
WS = Wet Scrubber
UNC = Uncontrolled (no APCD)
EGB = Electro Granular Activated Carbon Bed
FF = Fabric Filter

Figure 3-7. MSWI Design Classes for 1987



Key: DS/FF = Dry Scrubber combined with a Fabric Filter
DSI/FF = Dry Sorbent Injection coupled with a Fabric Filter
DS/CI/FF = Dry Scrubber -Carbon Injection-Fabric Filter
C-ESP = Cold-side Electrostatic Precipitator (Temperature at control device is below $\leq$230°C)
H-ESP = Hot-side Electrostatic Precipitator (Temperature at control device is $\geq$230°C)
WS = Wet Scrubber
UNC = Uncontrolled (no APCD)
EGB = Electro Granular Activated Carbon Bed

Figure 3-8. MSWI Design Classes for 1995

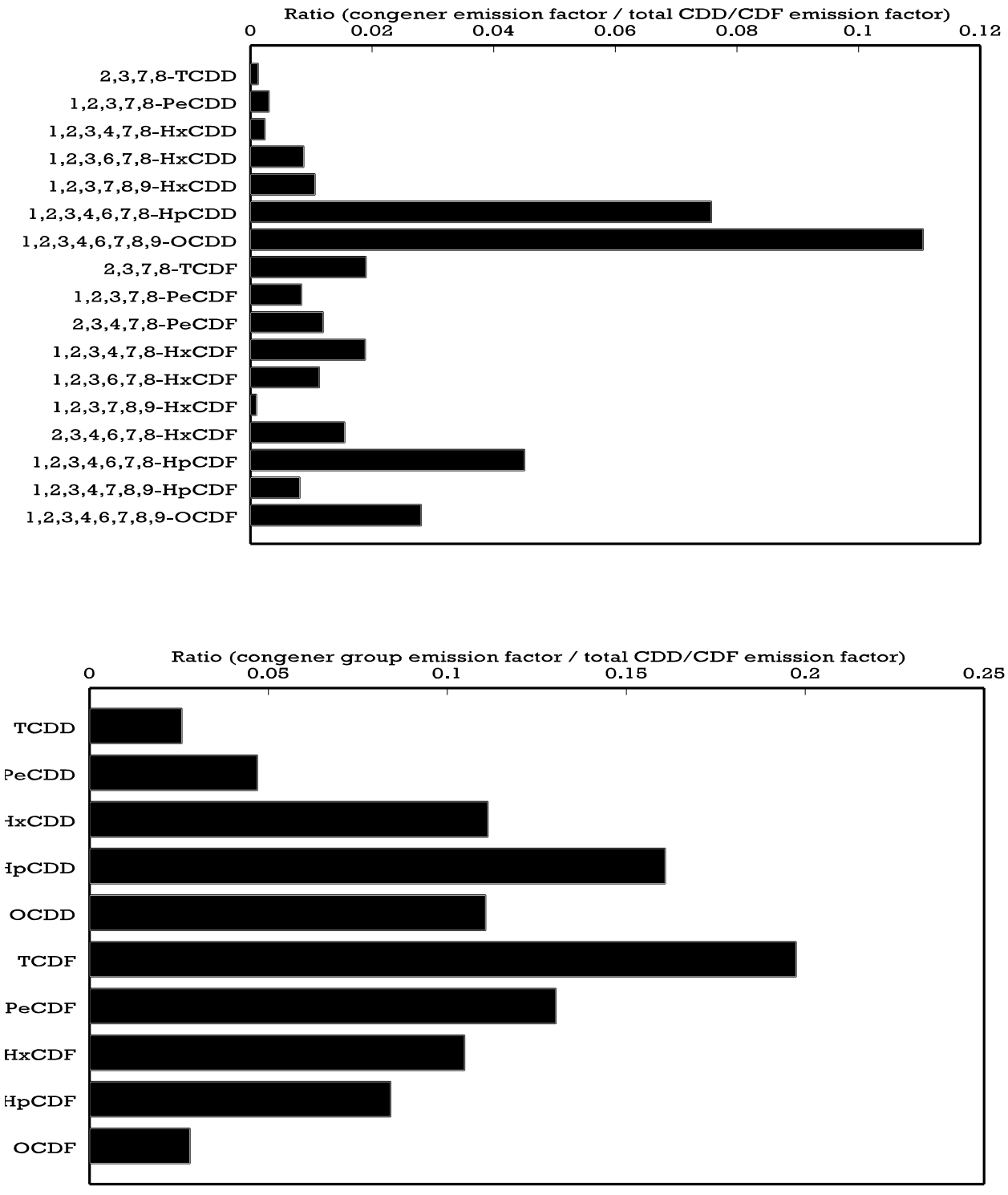


Figure 3-9. Congener and Congener Group Profiles for Air Emissions from a Mass-Burn Waterwall MSWI, Equipped with a Dry Scrubber and Fabric Filter

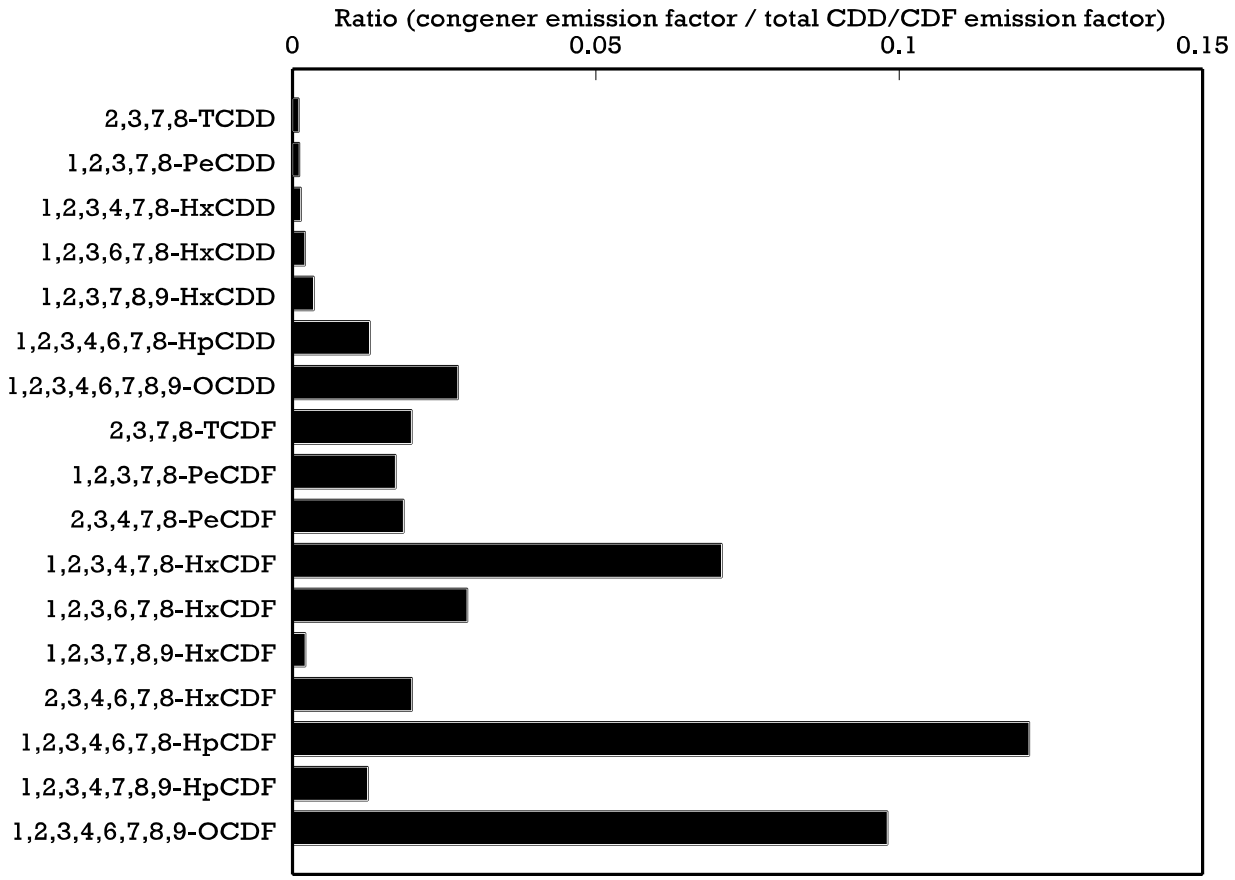


Figure 3-10. Congener Profile for Air Emissions from Hazardous Waste Incinerators

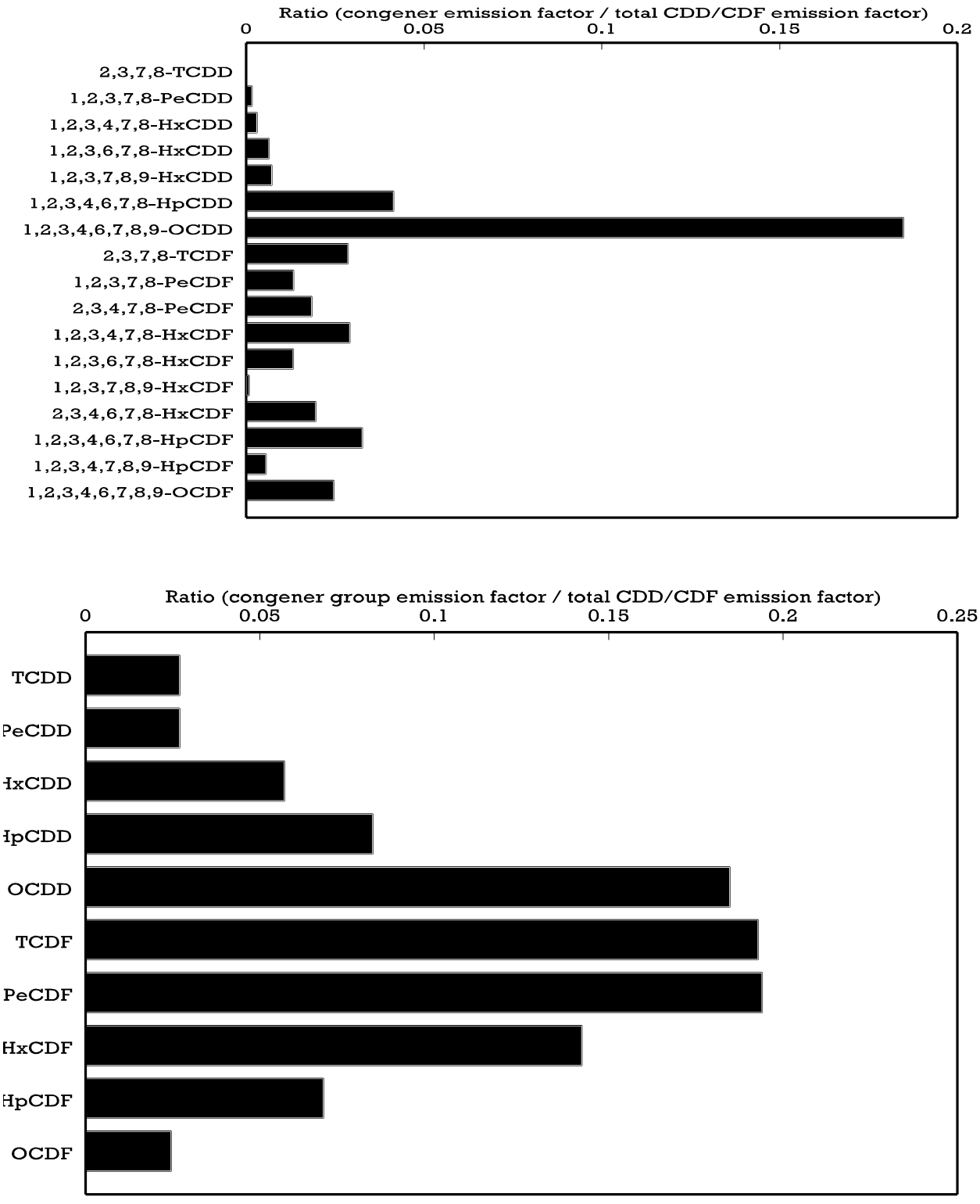


Figure 3-11. Congener and Congener Group Profiles for Air Emissions from Boilers and Industrial Furnaces Burning Hazardous Waste

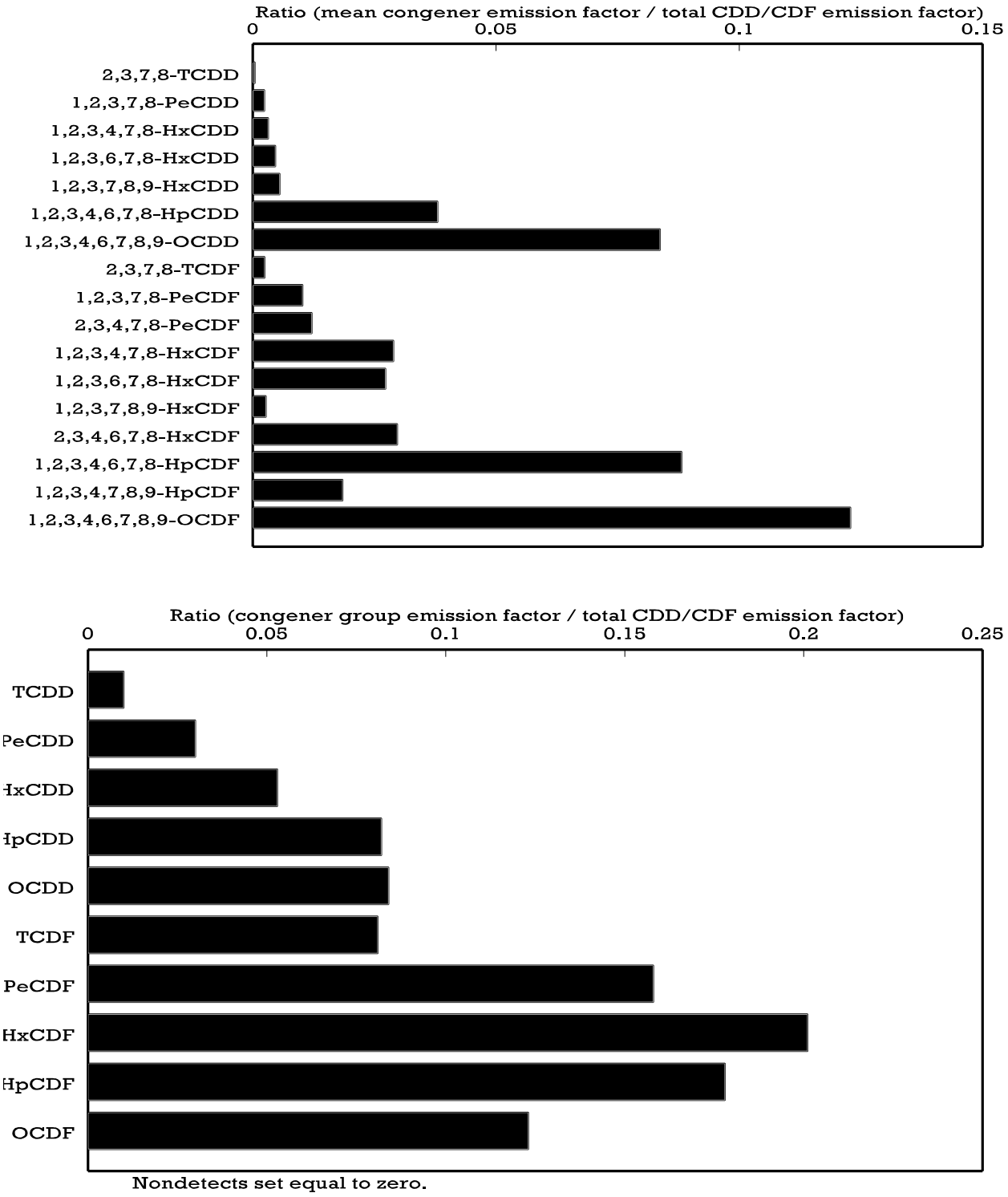


Figure 3-12. Congener and Congener Group Profiles for Air Emissions from Medical Waste Incinerators without APCD

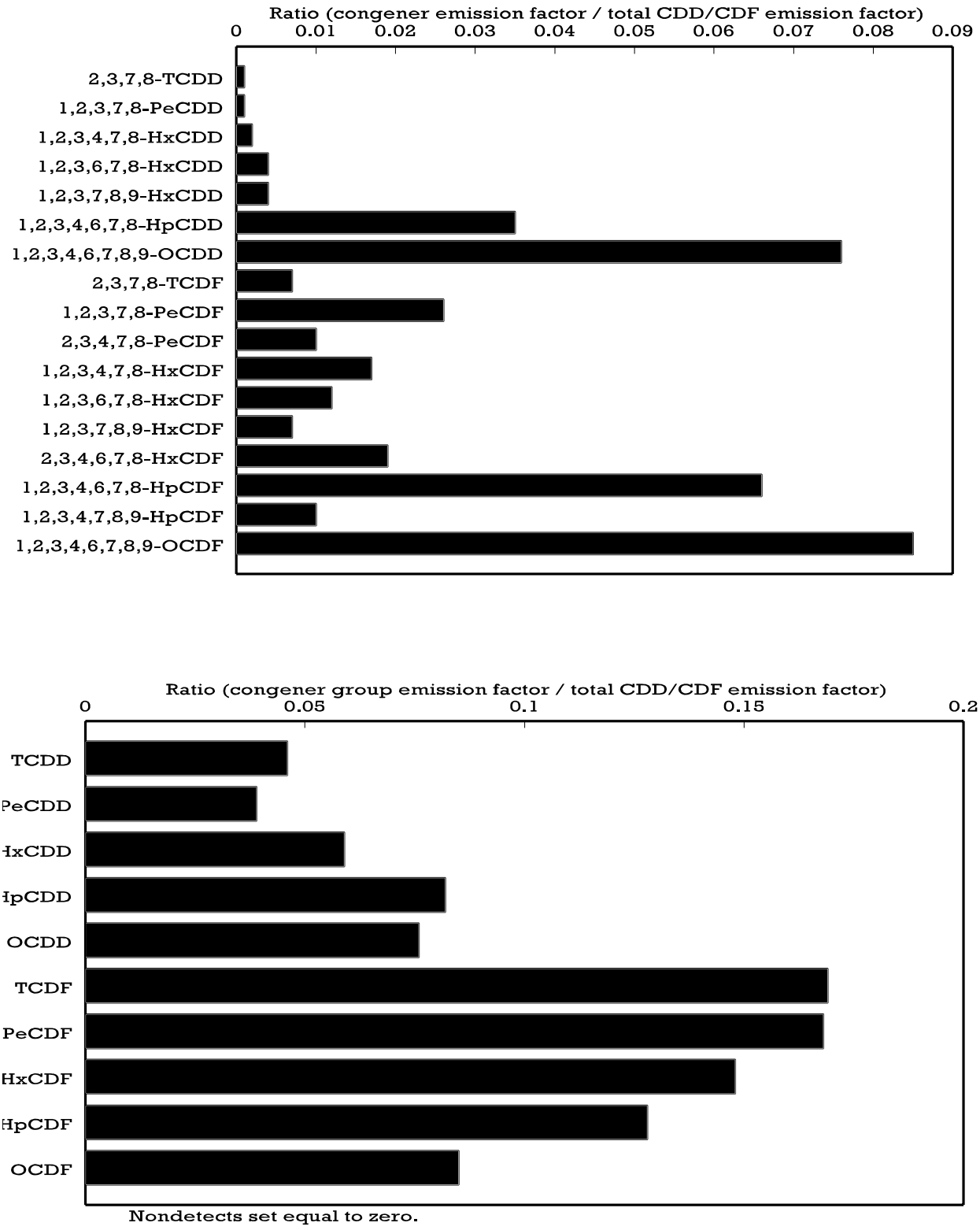
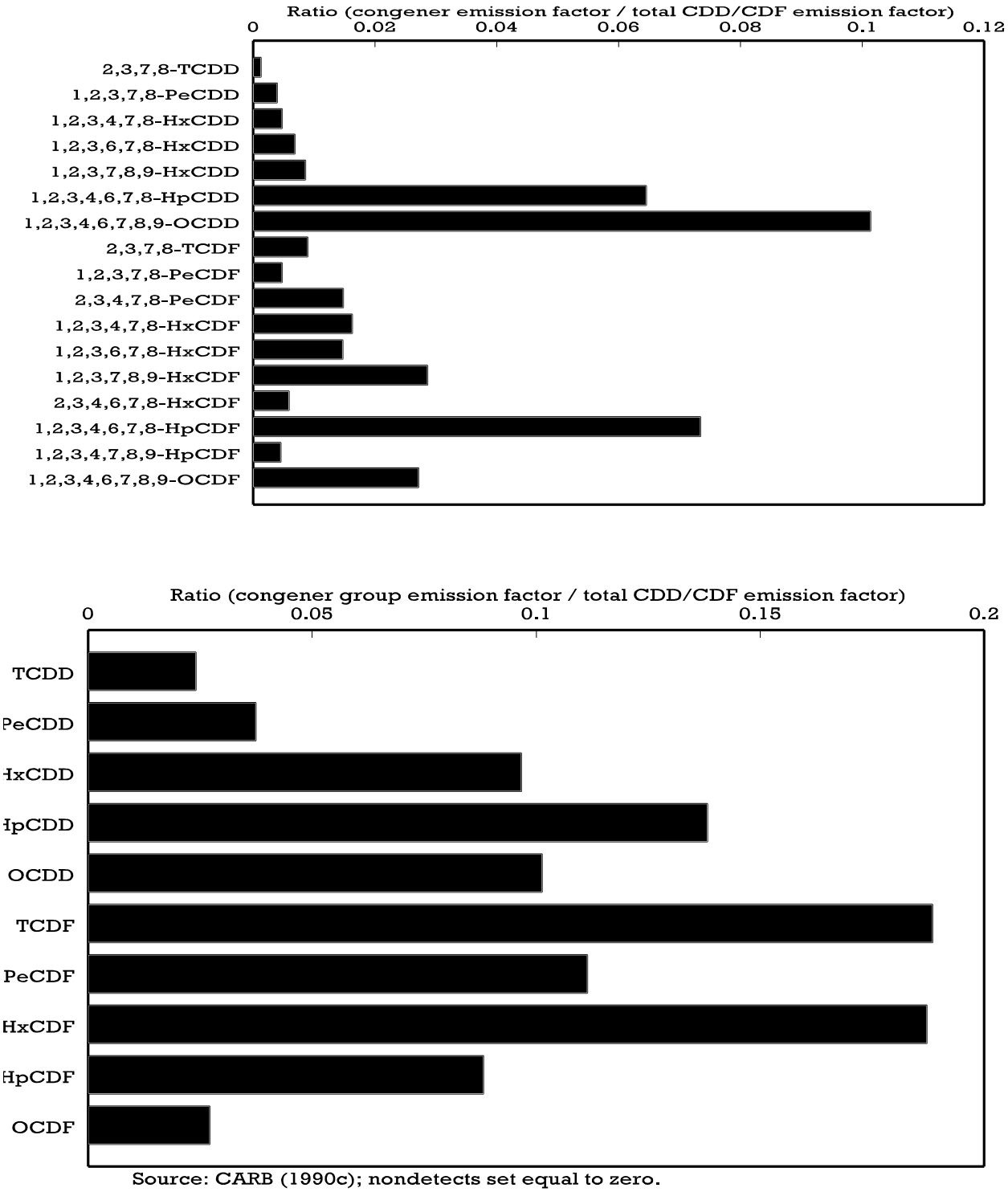


Figure 3-13. Congener and Congener Group Profiles for Air Emissions from Medical Waste Incinerators Equipped with a Wet Scrubber, Baghouse, and Fabric Filter



Source: CARB (1990c); nondetects set equal to zero.

Figure 3-14. Congener and Congener Group Profiles for Air Emissions from a Crematorium

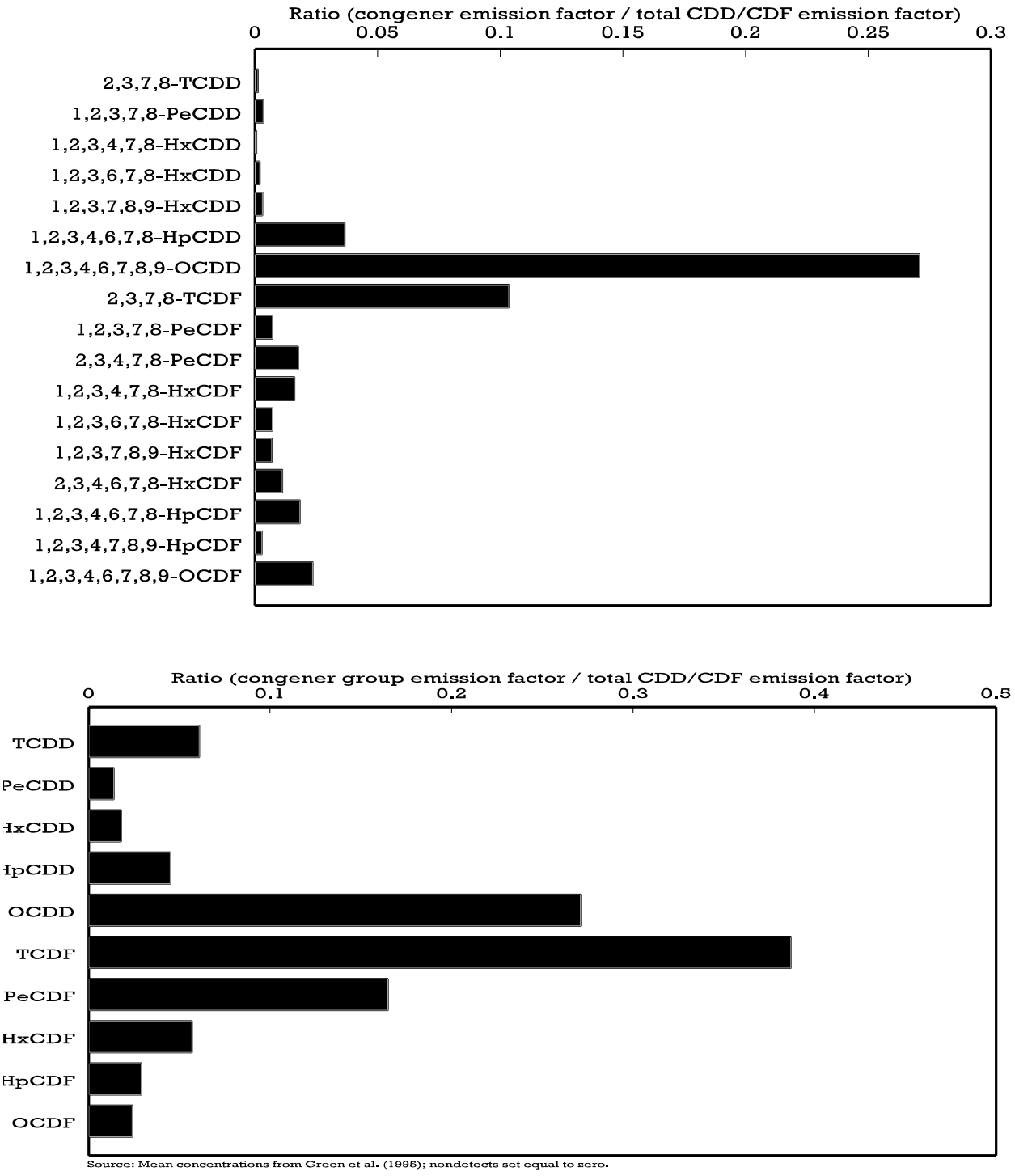
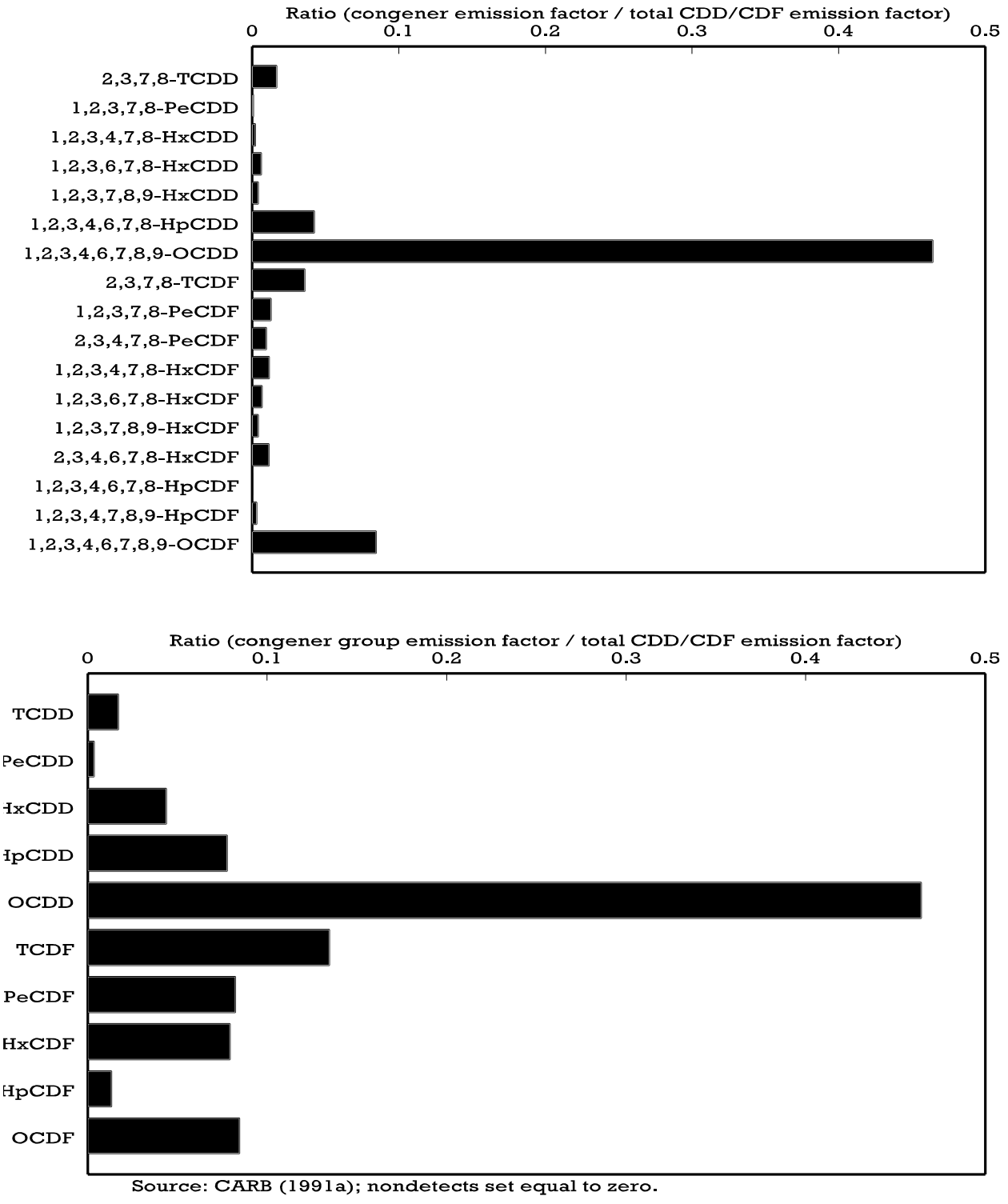


Figure 3-15. Congener and Congener Group Profiles for Air Emissions from Sewage Sludge Incinerators



Source: CARB (1991a); nondetects set equal to zero.

Figure 3-16. Congener and Congener Group Profiles for Air Emissions from a Tire Combustor

4. COMBUSTION SOURCES OF CDD/CDF: POWER/ENERGY GENERATION

4.1. MOTOR VEHICLE FUEL COMBUSTION

Ballschmiter et al. (1986) reported detecting CDD/CDFs in used motor oil and thus provided some of the first evidence that CDD/CDFs might be emitted by the combustion processes in gasoline- and diesel-fueled engines. Incomplete combustion and the presence of a chlorine source in the form of additives in the oil or the fuel (such as dichloroethane or pentachlorophenate) were speculated to lead to the formation of CDDs and CDFs. The congener patterns found in the used oil samples were characterized by Ballschmiter et al. (1986) as similar to the patterns found in fly ash and stack emissions from municipal waste incinerators.

Since 1986, several studies have been conducted to measure or estimate CDD/CDF concentrations in emissions from vehicles. Although there is no standard approved protocol for measuring CDD/CDFs in vehicle exhausts, researchers have developed and implemented several measurement approaches for collecting and analyzing vehicle exhausts. Other researchers have estimated vehicle exhaust emissions of CDD/CDFs indirectly from studies of tunnel air. The results of these two types of studies are summarized in chronological order in the following Section 4.1.1 and Section 4.1.2. Estimates of national annual CDD/CDF TEQ emissions from on-road motor vehicles fueled with leaded gasoline, unleaded gasoline, and diesel fuel are presented in Section 4.1.3 based on the results of these studies. It should be noted, however, that relatively few tests on emissions from diesel and unleaded gasoline fueled vehicles are available considering the variety and numbers of such vehicles currently in operation, and the range of operational, technical, and environmental conditions in which they are operated. As a result, the emission factors developed in this report for on-road motor vehicles are quite uncertain.

National emission estimates have not been generated in this report for off-road vehicles (i.e., construction and farm vehicles) or stationary sources using these fuel types because of lack of emission factor data; activity level information, however, is presented in this report for these potential source categories.

4.1.1. Tailpipe Emission Studies

Marklund et al. (1987) provided the first direct evidence of the presence of CDDs and CDFs in car emissions based on tailpipe measurements on Swedish cars. Approximately 20 to 220 pg of I-TEQ_{DF} from tetra- and penta-CDD/CDFs were reported per kilometer driven for four cars running on leaded gasoline. For this study, an unleaded gasoline was used to which was added tetramethyl lead (0.15 g/L or 0.57 grams per gallon) and dichloroethane (0.1 g/L as a scavenger). The fuel used may not have accurately represented commercial fuels at that time, which typically contained a mixture of chlorinated and brominated scavengers (Marklund et al., 1990). Also, the lead content of the fuel used (0.15 g lead/L), although the normal lead content for Swedish fuels at the time (Marklund et al., 1990), was higher than the lead content of leaded gasoline in the United States during the late 1980s (lowered to 0.10 g lead/gallon or 0.026 g lead/L effective January 1, 1986). Marklund et al. (1987) reported a striking similarity in the TCDF and PeCDF congener profiles in the car exhausts and those found in emissions from municipal waste incinerators. For two cars running on unleaded gasoline, CDD/CDF emissions were below the detection limit, which corresponded to approximately 13 pg of I-TEQ_{DF} per kilometer driven.

Table 4-1 presents a summary description of the results of the Marklund et al. (1987) study and subsequent studies (presented in chronological order) discussed below. Tables 4-2 and 4-3 present the results of tailpipe emission studies reported for diesel-fueled cars and trucks, respectively. Table 4-4 presents the results of studies using leaded gasoline-fueled cars, and Tables 4-5 and 4-6 present results of studies with cars fueled by unleaded gasoline. Figures 4-1, 4-2, and 4-3 present congener and congener group profiles for emissions from diesel-fueled vehicles, leaded gasoline-fueled vehicles, and unleaded gasoline-fueled vehicles, respectively.

Virtually no testing of vehicle emissions in the United States for CDD/CDFs has been reported. In 1987, the California Air Resources Board (CARB) produced a draft report on the testing of the exhausts of four gasoline-powered cars and three diesel fuel-powered vehicles (one truck, one bus, and one car) (CARB, 1987a). However, CARB indicated to EPA that the draft report should not be cited or quoted to support general conclusions about CDD/CDFs in motor vehicle exhausts because of the small sample size of the study and because the use of low rather than high resolution mass spectrometry in

the study resulted in high detection limits and inadequate selectivity in the presence of interferences (Lew, 1993). CARB did state that the results of a single sample from the heavy-duty diesel truck could be reported, because congeners from most of the homologue groups were present in the sample at levels that could be detected by the analytical method and there were no identified interferences in this sample. This test was conducted under steady state conditions (50 km/hr) for 6 hours with an engine with a fuel economy of 5.5 km/L. The TEQ emission factor of this one sample was equivalent to 7,290 pg I-TEQ_{DF}/L of fuel burned (7,190 pg TEQ_{DF}-WHO_{98}/L). Assuming a fuel economy of 5.5 km/L yields an emission factor of 1,325 pg I-TEQ_{DF}/km (1,307 pg TEQ_{DF}-WHO_{98}/km). Treating nondetected values as zeros yields TEQ emission factors of 3,720 pg I-TEQ_{DF}/L of fuel burned (or 676 pg I-TEQ_{DF}/km driven) and 3,280 pg TEQ_{DF}-WHO_{98}/L (or 596 pg TEQ_{DF}-WHO_{98}/km driven) (Lew, 1996).

Haglund et al. (1988) sampled exhaust gases from three different vehicles (two cars fueled with leaded and unleaded gasoline, respectively, and a heavy-duty diesel truck) for the presence of brominated dibenzo-p-dioxins (BDD) and brominated dibenzofurans (BDF). The authors concluded that the dibromoethane scavenger added to the tested gasoline probably acted as a halogen source. TBDF emissions measured 23,000 pg/km in the car with leaded gasoline and 240 pg/km in the car with unleaded gasoline. TBDD and PeBDF emissions measured 3,200 and 980 pg/km, respectively, in the car with leaded gasoline. All BDD/Fs were below detection limits in the diesel truck emissions.

Bingham et al. (1989) analyzed the exhausts of four cars using leaded gasoline (0.45 g/L tetramethyllead, 0.22 g/L dichloroethane, and 0.2 g/L dibromoethane), and the exhaust from one car using unleaded gasoline. Analytical results and detection limits were reported for only five of the 17 toxic CDD/CDF congeners. TEQ emission rates for the cars using leaded fuel, based on detected congeners only, ranged from 1 to 39 pg I-TEQ_{DF}/km. CDD/CDFs were not detected in the exhaust from the vehicle using unleaded fuel. The total I-TEQ_{DF} emission rate for this car using unleaded fuel, based on one-half the detection limits for the five reported congeners, was 20 pg I-TEQ_{DF}/km.

Marklund et al. (1990) tested Swedish cars fueled with commercial fuels, measuring CDD/CDF emissions before and/or after the muffler. Both new and old vehicles were tested. Three cars were tested using unleaded gasoline, and two cars were tested with leaded gasoline (0.15 g Pb/L and dichloroethane and dibromoethane scavengers).

CDD/CDFs were not detected in the fuels at a detection limit of 2 pg I-TEQ_{DF}/L, but were detected at a level of 1,200 pg I-TEQ_{DF}/L in the new semi-synthetic engine lube oil used in the engines. The test driving cycle employed (i.e., 31.7 km/hr as a mean speed; 91.2 km/hr as a maximum speed; and 17.9 percent of time spent idling) yielded fuel economies ranging from approximately 9 to 10 km/L or 22 to 24 miles/gallon in the various cars. The reported ranges of emission factors were:

- Leaded gas/before muffler: 2.4 to 6.3 pg I-TEQ_{DF}/km (or 21 to 60 pg I-TEQ_{DF}/L of fuel consumed);
- Leaded gas/in tailpipe: 1.1 to 2.6 pg I-TEQ_{DF}/km (or 10 to 23 pg I-TEQ_{DF}/L);
- Unleaded gas/catalyst-equipped/in tailpipe: 0.36 pg I-TEQ_{DF}/km (or 3.5 pg I-TEQ_{DF}/L); and
- Unleaded gas/before muffler: 0.36 to 0.39 pg I-TEQ_{DF}/km (or 3.5 pg I-TEQ_{DF}/L).

The TEQ levels in exhaust gases from older cars using leaded gasoline were up to six times greater when measured before the muffler than after the muffler. No muffler-related difference in new cars running on leaded gasoline or in old or new cars running on unleaded gasoline was observed.

Marklund et al. (1990) also analyzed the emissions from a heavy-duty diesel-fueled truck for CDD/CDFs. None were detected; however, the authors pointed out that the test fuel was a reference fuel and may not have been representative of commercial diesel fuel. Also, due to analytical problems, a much higher detection limit (about 100 pg I-TEQ_{DF}/L) was realized in this diesel fuel test than in the gasoline tests (5 pg I-TEQ_{DF}/L) conducted. Further uncertainty was introduced because the diesel emission samples were only collected prior to the muffler.

Hagenmaier et al. (1990) ran a set of tests using conditions comparable to the FTP-73 test cycle on gasoline- and diesel-fueled engines for light duty vehicles in Germany. The following average TEQ emission rates per liter of fuel consumed were reported:

- Leaded fuel: 1,080 pg I-TEQ_{DF}/L (1,287 pg TEQ_{DF}-WHO_{98}/L);
- Unleaded fuel (catalyst-equipped): 7.2 pg I-TEQ_{DF}/L (7.9 pg TEQ_{DF}-WHO_{98}/L);

- Unleaded fuel (not catalyst-equipped): 50.9 pg I-TEQ_{DF}/L (60.2 pg TEQ_{DF}-WHO_{98}/L); and
- Diesel fuel: 20.8 pg I-TEQ_{DF}/L (24.8 pg TEQ_{DF}-WHO_{98}/L).

The major findings of a German study of emissions of halogenated dibenzodioxins and dibenzofurans from internal combustion engines running on commercial fuels were published in 1991 (Schwind et al., 1991), and the full detailed report was published in 1992 (Hutzinger et al., 1992). The study was conducted by the Universities of Stuttgart, Tübingen, and Bayreuth for the Federal Ministry for Research and Technology, the Research Association for Internal Combustion Engines, and the German Association for the Petroleum Industry and Coal Chemistry. Tests were conducted using engine test benches and rolling test benches under representative operating conditions. Tests were performed on leaded gasoline engines, unleaded gasoline engines, diesel car engines, and diesel truck engines. The reported range of CDD/CDF emission rates across the test conditions in units of pg TEQ per liter of fuel consumed are presented below. The results from those tests conducted under normal operating conditions with commercial fuels and for which congener-specific emission results were presented in Hutzinger et al. (1992) are listed in Tables 4-2 through 4-6.

- Leaded fuel: 52 to 1,184 pg I-TEQ_{DF}/L (72 to 1,417 pg TEQ_{DF}-WHO_{98}/L);
- Unleaded fuel (not catalyst-equipped): 96 to 177 pg I-TEQ_{DF}/L (102 to 181 pg TEQ_{DF}-WHO_{98}/L);
- Unleaded fuel (catalyst-equipped): 10 to 26 pg I-TEQ_{DF}/L (9.6 to 28.0 pg TEQ_{DF}-WHO_{98}/L);
- Diesel fuel (cars): 10 to 130 pg I-TEQ_{DF}/L (12 to 140 pg TEQ_{DF}-WHO_{98}/L); and
- Diesel fuel (trucks): 70 to 81 pg I-TEQ_{DF}/L (79 to 82 pg TEQ_{DF}-WHO_{98}/L).

Although no specific details on the methodology used were provided, Hagenmaier (1994) reported that analyses of emissions of a diesel-fueled bus run either on steady state or on the "Berlin cycle" showed no CDD/CDF present at a detection limit of 1 pg/L of fuel consumed for individual congeners.

Gullett and Ryan (1997) recently reported the results of the first program to sample diesel engine emissions for CDD/CDFs during actual highway and city driving. The exhaust emissions from a 1991 Freightliner diesel tractor with a 10.3 L, 6-cylinder Caterpillar engine, representative of the first generation of computerized fuel controlled vehicles manufactured in the United States, were sampled during both highway and city driving routes. The average emission factor for the three highway tests conducted (15.1 pg I-TEQ_{DF}/km; range 11.7-18.7 pg I-TEQ_{DF}/km; standard deviation of 3.5 pg I-TEQ_{DF}/km) was a factor of three below the average of the two city driving tests (49.9 pg I-TEQ_{DF}/kg; range 3.0-96.8 pg I-TEQ_{DF}/km). Detection limits were considered as zeros in the calculation of these emission factors. The average of all five tests was 29.0 pg I-TEQ_{DF}/km with a standard deviation of 38.3 pg I-TEQ_{DF}/km; this standard deviation reflects the 30-fold variation in the two city driving route tests.

4.1.2. Tunnel Emission Studies

Several European studies and one recent U.S. study evaluated CDD/CDF emissions from vehicles by measuring the presence of CDD/CDFs in tunnel air. This approach has the advantage that it allows random sampling of large numbers of cars, including a range of ages and maintenance levels. The disadvantage of this approach is that it relies on indirect measurements (rather than tailpipe measurements), which may introduce unknown uncertainties and make interpretation of the findings difficult. Concerns have been raised that the tunnel monitors are detecting resuspended particulates that have accumulated over time, leading to overestimates of emissions. Also, the driving patterns encountered in these tunnel studies are more or less steady state driving conditions rather than the transient driving cycle and cold engine starts that are typical of urban driving conditions and that may affect emission levels. Each of these studies is summarized below in chronological order.

Rappe et al. (1988) reported the CDD/CDF content of two air samples (60 m^3 per sample) collected from a tunnel in Hamburg, Germany, during January of 1986 to be 0.42 and 0.58 pg I-TEQ_{DF}/m^3 (0.44 and 0.59 pg TEQ_{DF}-WHO_{98}/m^3. Each sample was collected over a period of about 60 hours. The tunnel handled 65,000 vehicles per day of which 17 percent were classified as "heavy traffic." The congener-specific results of the two samples are presented in Table 4-7. Measurement of ambient air conducted in September

of 1986 at a nearby highway in Hamburg was reported to contain CDD/CDF levels two to six times lower than those measured in the tunnel.

Larssen et al. (1990) and Oehme et al. (1991) reported the results of a tunnel study in Olso, Norway, performed during April/May of 1988. Oehme et al. (1991) estimated total vehicle emissions by measuring CDD/CDF concentrations in tunnel inlet and outlet air of both the uphill and downhill lanes. Emission rates for light-duty and heavy-duty vehicle classes in the uphill and downhill lanes were estimated by counting the number of light-duty vs. heavy-duty vehicles passing through the tunnel on workdays and a weekend and assuming a linear relationship between the percentage of the light- or heavy-duty traffic and the overall emission rate. Thus, the linear relationship for each emission rate was based on only two points (i.e., the weekday and weekend measurements). The emission rates, in units of Nordic TEQ, estimated in this study are:

- Light-duty vehicles using gasoline (approximately 70-75 percent using leaded gas): uphill = 520 pg TEQ/km; downhill = 38 pg TEQ/km; mean = 280 pg TEQ/km; and
- Heavy-duty diesel trucks: uphill = 9,500 pg TEQ/km; downhill = 720 pg TEQ/km; mean = 5,100 pg TEQ/km.

The mean values are the averages of the emission rates corresponding to the two operating modes: vehicles moving uphill on a 3.5 percent incline at an average speed of 37 miles per hour and vehicles moving downhill on a 3.5 percent decline at an average speed of 42 miles per hour. Although Oehme et al. (1991) reported results in units of Nordic TEQ, the results in I-TEQ_{DF} should be nearly identical (i.e., about 3 to 6 percent higher), because the only difference between the two TEQ schemes is the toxic equivalency factor assigned to 1,2,3,7,8-PeCDF (0.1 in Nordic and 0.05 in I-TEQ_{DF}), a minor component of the toxic CDD/CDFs measured in the tunnel air. Table 4-7 presents the congener-specific differences in concentrations between the tunnel inlet and outlet concentrations.

Wevers et al. (1992) measured the CDD/CDF content of air samples taken during the winter of 1991 inside a tunnel in Antwerp, Belgium. During the same period, background concentrations were determined outside the tunnel. Two to four samples were collected from each location with two devices: a standard high volume sampler with a glass fiber filter and a modified two-phase high volume sampler equipped with a glass

fiber filter and a polyurethane foam plug (PUF). The I-TEQ_{DF} concentration in the air sampled with the filter/PUF device was 74 to 78 percent of the value obtained with the high volume sampler. However, the results obtained from both sets of devices indicated that the tunnel air had a CDD/CDF TEQ concentration about twice as high as the outside air (filter and PUF: 80.3 fg I-TEQ_{DF}/m^3 for tunnel air vs. 35 fg I-TEQ_{DF}/m^3 for outside air; filter only: 100 fg I-TEQ_{DF}/m^3 for tunnel air vs. 58 fg I-TEQ_{DF}/m^3 for outside air). The authors presented the congener-specific results for only one tunnel air measurement; these results are presented in Table 4-7.

During October/November 1995, Gertler et al. (1996, 1998) conducted a study at the Fort McHenry Tunnel in Baltimore, Maryland, with the stated objective of measuring CDD/CDF emission factors from in-use vehicles operating in the United States, with particular emphasis on heavy-duty vehicles. The air volume entering and leaving the tunnel bore that services most of the heavy-duty vehicles (i.e., approximately 25 percent of the vehicles using the bore are heavy-duty) was measured, and the air was sampled for CDD/CDFs during 7 sampling periods of 12-hour duration. Three of the samples were collected during daytime (i.e., 6 am to 6 pm) and four samples were collected during the night (i.e., 6 pm to 6 am). The air volume and concentration measurements were combined with information on vehicle counts (obtained from videotapes) and tunnel length to determine average emission factors. A total of 33,000 heavy-duty vehicles passed through the tunnel during the seven sample runs. Heavy-duty vehicles accounted for 21.2 to 28.8 percent of all vehicles passing through the tunnel for the seven sample runs. The emission factors calculated, assuming that all CDD/CDF emitted in the tunnel were from heavy-duty vehicles, are presented in Table 4-8. The average I-TEQ_{DF} emission factor was reported to be 172 pg I-TEQ_{DF}/km (182 pg TEQ_{DF}-WHO_{98}/km). The major uncertainties identified by the authors in the study were tunnel air volume measurement, sampler flow volume control, and analytical measurement of CDD/CDF.

EPA's Office of Mobile Sources (OMS) reviewed the Gertler et al. (1996) study (Lorang, 1996) and found the study to be technologically well done, with no major criticisms or comments on the test methodology or protocol. OMS found no reason to doubt the validity of the emission factor determined by the study. OMS did note that the particulate emission rate for heavy-duty vehicles measured in the study (0.32 g/mile) is lower than the general particulate emission rate used by EPA (i.e., about 1 g/mile) and,

thus, may underestimate CDD/CDF emissions under different driving conditions. OMS cautioned that the reported emission factor should be regarded only as a conservative estimate of the mean emission factor for the interstate trucking fleet under the driving conditions of the tunnel (i.e., speeds on the order of 50 miles/hour with the entering traffic slightly higher and the exiting traffic slightly lower.

Figure 4-4 graphically presents the results of the studies by Rappe et al. (1988), Oehme et al. (1991), Wevers et al. (1992), and Gertler et al. (1996, 1998). The figure compares the congener profiles (i.e., congener concentrations or emission factors normalized to total concentration or emission factor of 2,3,7,8-substituted CDDs and CDFs) reported in the four studies. The dominant congeners in the Rappe et al. (1988), Wevers et al. (1992), and Gertler et al. (1996, 1998) studies are OCDD, 1,2,3,4,6,7,8-HpCDD, OCDF, and 1,2,3,4,6,7,8-HpCDF. With the exception of OCDD, these congeners are also major congeners reported by Oehme et al. (1991). The Oehme et al. (1991) study also differs from the other two studies in that the total of 2,3,7,8-substituted CDFs dominates total 2,3,7,8-substituted CDDs (by a factor of 2), whereas just the opposite is observed in Rappe et al. (1988), Wevers et al. (1992), and Gertler et al. (1996, 1998).

4.1.3. National Emission Estimates

Estimates of national CDD/CDF TEQ emissions are presented in this section only for on-road vehicles utilizing gasoline or diesel fuel. Because emission factors are lacking for off-road uses (i.e., construction vehicles, farm vehicles, and stationary industrial equipment), no emission estimates could be developed at this time; however, activity level information for off-road uses is presented below.

Activity Information for On-Road Vehicles: The U.S. Federal Highway Administration, as reported in U.S. Department of Commerce (DOC) (1997), reports that 1,586-billion total vehicle miles (2,552 billion km) were driven in the United States during 1994 by automobiles and motorcycles. Because 1994 is the last year for which data are available, these data are used as a surrogate for 1995 activity levels. Trucks accounted for 840-billion vehicle miles (1,351 billion km), and buses accounted for 6.4 billion vehicle miles (10 billion km) (U.S. DOC, 1997). In 1992, diesel-fueled trucks accounted for 14.4 percent of total truck vehicle km driven; gasoline-fueled trucks accounted for the

remaining 85.6 percent (U.S. DOC, 1995b). Applying this factor (i.e., 14.4 percent) to the 1994 truck km estimate (i.e., 1,351 billion km) indicates that an estimated 195 billion km were driven by diesel-fueled trucks in 1994. It is assumed that all other vehicle km driven (3,718 billion km) (i.e., non-diesel trucks, all automobiles, all buses, and all motorcycles) were those of gasoline-powered vehicles; although it is recognized that a fraction of the buses and automobiles use diesel fuel, the exact numbers are not known. It is further assumed that all of these km were driven by unleaded gasoline-powered vehicles because in 1992, only 1.4 percent of the gasoline supply were leaded fuel (EIA, 1993); usage should have further declined by 1995, because use of leaded fuel in motor vehicles for highway use in the United States was prohibited as of December 31, 1995 (Federal Register, 1985a).

Similar information for 1987 is as follows. An estimated 3,092 billion km were driven in the United States of which trucks accounted for 887 billion km (U.S. DOC, 1995a). In 1987, diesel-fueled trucks accounted for 17.2 percent of total truck km driven (U.S. DOC, 1995b). Applying this factor (i.e., 17.2 percent) to the 1987 truck km estimate (i.e., 887 billion km) indicates that an estimated 153 billion km were driven by diesel-fueled trucks. It is assumed that all other vehicle km driven (2,939 billion km) were those of gasoline-powered vehicles. Leaded gasoline accounted for 24.1 percent of the gasoline supply in 1987 (EIA, 1993). Thus, it can be estimated that 708 billion km (i.e., 24.1 percent of 2,939 billion km) were driven by leaded gasoline-fueled vehicles. The remaining 2,231 billion km are estimated to have been driven by unleaded gasoline-fueled vehicles. These mileage estimates are given a high confidence rating because they are based on recent U.S. Bureau of the Census transportation studies.

Activity Information for Off-Road Uses: Although on-road vehicles are the largest consumers of diesel fuel (accounting for about 50 percent of U.S. sales), other sectors of the economy use significant volumes: farm use, railroad use, vessel bunkering, and other off-highway uses. The following paragraphs define each of these uses and present volumes of distillate fuel sales in each sector for reference years 1987 and 1995. For these sectors, the majority of "distillate fuel" sales are diesel fuels; a small fraction are fuel oils.

Farm use includes sales for use in tractors, irrigation pumps and other agricultural machinery, as well as that used for crops drying, smudge pot fuel and space heating of buildings. Sales in 1987 and 1995 were 2,999 and 3,476 million gallons, respectively (EIA, 1992; EIA, 1997a).

Railroad use includes sales to railroads, for any use, including diesel fuel for railroad locomotive engines and fuel used for heating buildings operated by railroads. Sales in 1987 and 1995 were 2,850 and 3,429 million gallons, respectively (EIA, 1992; EIA, 1997a).

Vessel bunkering includes sales for the fueling of commercial or private boats, such as pleasure craft, fishing boats, tug boats, and ocean-going vessels, including vessels operated by oil companies. Excluded are volumes sold to the U.S. Armed Forces. Sales in 1987 and 1995 were 1,865 and 2,339 million gallons, respectively (EIA, 1992; EIA, 1997a).

Off-highway use includes sales for use in: (1) construction equipment including earthmoving equipment, cranes, stationary generators, air compressors, etc.; and (2) sales for non-construction other off-highway uses such as logging. Sales in 1987 and 1995 were 1,560 and 2,173 million gallons, respectively (EIA, 1992; EIA, 1997a).

Emission Estimates: Using the results of the studies discussed in Section 4.1.1, separate annual national emission estimates are developed below for vehicles burning leaded gasoline, unleaded gasoline, and diesel fuel. Estimates are provided for the years 1987 and 1995. The emission estimates for reference year 1995 are based on activity data (i.e., kilometers driven) for calendar year 1994.

Leaded Gasoline: Literature indicates that CDD/CDF emissions do occur from vehicles using leaded gasoline and that considerable variation occurs depending, at least in part, on the types of scavengers used. Marklund et al. (1987) reported emissions ranging from 20 to 220 pg I-TEQ_{DF}/km from four cars fueled with a reference unleaded fuel to which lead (0.5 gplg) and a chlorinated scavenger were added. Marklund et al. (1990)

reported much lower emissions in the exhaust of cars (1.1 to 6.3 pg I-TEQ_{DF}/km) using a commercial leaded fuel (0.5 g/L) containing both dichloroethane and dibromoethane as scavengers. Marklund et al. (1990) attributed the difference in the emission measurements of the 1987 and 1990 studies to the different mix of scavengers used in the two studies, which may have resulted in preferential formation of mixed chlorinated and brominated dioxins and furans. Hagenmaier et al. (1990) reported TEQ emissions of 1,080 pg I-TEQ_{DF}/L of fuel (approximately 108 pg I-TEQ_{DF}/km or 129 pg TEQ_{DF}-WHO_{98}/km) from a car fueled with a commercial leaded fuel (lead content not reported). Bingham et al. (1989) reported emissions from four cars using gasoline with a lead content of 1.7 g/L in New Zealand to range from 1 to 39 pg I-TEQ_{DF}/km. The German study reported by Schwind et al. (1991) and Hutzinger et al. (1992) measured emissions of 52 to 1,184 pg I-TEQ_{DF}/L (approximately 5.2 to 118 pg I-TEQ_{DF}/km or 7.2 to 142 pg TEQ_{DF}-WHO_{98}/km) for cars under various simulated driving conditions. The tunnel study by Oehme et al. (1991) estimated that emissions from cars running primarily on leaded gasoline (i.e., 70 to 75 percent of the cars) ranged from 38 to 520 pg Nordic TEQ/km.

As shown in Table 4-4, the average emission factor reported for the tailpipe emission studies performed using commercial leaded fuel which reported analytical results for all 17 toxic CDD/CDF congeners (i.e., Marklund et al., 1990; Hagenmaier et al., 1990; and Schwind et al., 1991) is 450 pg I-TEQ_{DF}/L or 532 pg TEQ_{DF}-WHO_{98}/L. Assuming an average fuel economy of 10 km/L, these emission factors are approximately 45 pg I-TEQ_{DF}/km and 53 pg TEQ_{DF}-WHO_{98}/km. A low confidence rating is assigned to this emission factor because it is based on European fuels and emission control technologies, which may have differed from U.S. leaded-fuels and engine technology, and also because the factor is based is based on tests with only nine cars.

Combining the average emission factor developed above (45 pg I-TEQ_{DF}/km or 53 pg TEQ_{DF}-WHO_{98}/km, assuming not detected values are zero) with the estimate for km driven by leaded fuel-powered vehicles in 1987 (708 billion km) suggests that 31.9 g I-TEQ_{DF} (or 37.5 pg TEQ_{DF}-WHO_{98}) were emitted from vehicles using leaded fuels in 1987. Although there likely was minor use of unleaded fuel in 1995 in on-road vehicles, further use of leaded fuel in motor vehicles for highway use in the United States was prohibited as of December 31, 1995 (Federal Register, 1985a). In 1992, the last year for which data are available on consumption of leaded gasoline by on-road vehicles, only 1.4 percent

of the gasoline supply was leaded gasoline (EIA, 1993). If it is conservatively assumed that 1 percent of the total vehicle km driven in 1995 (i.e., 37.2 billion km of a total of 3,718 billion km) were driven by leaded fuel-powered vehicles, then combining the emission factor of 45 pg I-TEQ_{DF}/km (or 53 pg TEQ_{DF}-WHO_{98}/km) with this activity level estimate yields an annual emission of 1.7 g I-TEQ_{DF} (or 2.0 g TEQ_{DF}-WHO_{98}) in 1995.

Unleaded Gasoline: The literature documenting results of European studies indicates that CDD/CDF emissions from vehicles burning unleaded fuels are less than the emissions from vehicles burning leaded gas with chlorinated scavengers. It also appears, based on the limited data available, that catalyst-equipped cars have lower emission factors than noncatalyst-equipped cars. Marklund et al. (1987) did not detect CDD/CDF in emissions from two catalyst-equipped cars running on unleaded gasoline at a detection limit of 13 pg I-TEQ_{DF}/km. Marklund et al. (1990) reported emission factors of 0.36 and 0.39 pg I-TEQ_{DF}/km for two noncatalyst-equipped cars and an emission factor of 0.36 pg I-TEQ_{DF}/km for one catalyst-equipped car. Hagenmaier et al. (1990) reported an emission factor of 5.1 pg I-TEQ_{DF}/km for one noncatalyst-equipped car and 0.7 pg I-TEQ_{DF}/km for one catalyst-equipped car. Schwind et al. (1991) and Hutzinger et al. (1992) reported emission factors of 9.6 to 17.7 pg I-TEQ_{DF}/km for several noncatalyst-equipped cars tested under various conditions; the reported emission factor range for catalyst-equipped cars was 1.0 to 2.6 pg I-TEQ_{DF}/km.

All automobiles running on unleaded gasoline in the United States are equipped with catalysts. As shown in Table 4-6, the average emission factor reported for the tailpipe emission studies performed on catalyst-equipped cars (i.e., Hagenmaier et al. 1990; Schwind et al., 1991; and Hutzinger et al., 1992) is 14.9 pg I-TEQ_{DF}/L or 15.6 pg TEQ_{DF}-WHO_{98}/L. Assuming an average fuel economy of 10 km/L yields emission factors of 1.5 pg I-TEQ_{DF}/km and 1.6 pg TEQ_{DF}-WHO_{98}/km. A low confidence rating is assigned to this emission factor because the European fuels and emission control technology used may have differed from U.S. fuels and technology and also because the emission factor range is based on tests with only three catalyst-equipped cars.

Combining the calculated mean emission factor of 1.5 pg I-TEQ_{DF}/km (or 1.6 pg TEQ_{DF}-WHO_{98}/km) with the estimate derived above for vehicle km driven in 1995 by all gasoline-powered vehicles (3,718 billion km) suggests that 5.6 g of I-TEQ_{DF} (or 5.9 g

TEQ_{DF}-WHO_{98}) were emitted from vehicles using unleaded fuels in 1995. Applying the same emission factors to the estimate derived above for vehicle km driven in 1987 by unleaded gasoline-powered vehicles (2,231 billion km), suggests that 3.3 g of I-TEQ_{DF} (or 3.6 g TEQ_{DF}-WHO_{98}) may have been emitted in 1987.

Diesel Fuel: Few data are available upon which to base an evaluation of the extent of CDD/CDF emissions resulting from diesel fuel combustion. The limited data available address emissions only from on-road vehicles; no emissions data are available for off-road diesel uses (i.e., construction vehicles, farm vehicles, and stationary equipment). Two U.S. tailpipe studies are available: CARB (1987a) and Gullett and Ryan (1997). CARB (1987a) reported a relatively high emission factor of 676 pg I-TEQ_{DF}/km (not detected values assumed to be zero) for one tested heavy-duty truck with a fuel economy at 50 km/hr of 5.5 km/L. Gullett and Ryan (1997) reported a range of emission factors for one diesel truck tested on six highway or city driving routes, 3.0 to 96.8 pg I-TEQ_{DF}/km (mean of 29.0 pg I-TEQ_{DF}/km).

The results of several tailpipe studies conducted in Europe have also been published. Marklund et al. (1990) reported no emissions at a detection limit of 100 pg I-TEQ_{DF}/L (or 18 pg I-TEQ_{DF}/km assuming a fuel economy of 5.5 km/L) for one tested truck. Schwind et al. (1991) and Hutzinger et al. (1992) reported emission factors of 32 to 81 pg I-TEQ_{DF}/L (or 6 to 15 pg I-TEQ_{DF}/km assuming a fuel economy of 5.5 km/L) for a truck engine run under various simulated driving conditions. Hagenmaier (1994) reported no emissions from a bus at a detection limit of 1 pg/L of fuel consumed for individual congeners. For diesel-fueled cars, Hagenmaier et al. (1990) reported an emission factor of 24 pg I-TEQ_{DF}/L (or approximately 2.4 pg I-TEQ_{DF}/km) for one tested car. Schwind et al. (1991) and Hutzinger et al. (1992) reported emission factors of 5 to 13 pg I-TEQ_{DF}/km for a car engine run under various simulated driving conditions.

The tunnel study by Oehme et al. (1991) generated an estimated mean emission factor of 5,100 pg TEQ/km and a range of 720 to 9,500 pg TEQ/km (in units of Nordic TEQ) for diesel-fueled trucks. Insufficient information was provided in Oehme et al. (1991) to enable an exact calculation of emission in units of I-TEQ_{DF} or TEQ_{DF}-WHO_{98}. However, based on the information that was provided, the mean emission factor in units of I-TEQ is approximately 5,250 to 5,400 pg I-TEQ_{DF}/km. These indirectly estimated

emission factors are considerably larger than those reported from engine studies by Marklund et al. (1990), Schwind et al. (1991), and Hutzinger et al. (1992); the CARB (1987a) diesel truck emission factor falls at the low end of the range. Although aggregate samples were collected in this study representing several thousand heavy duty diesel vehicles, several characteristics of this study introduce considerable uncertainty with regard to using the study's results as a basis for estimating emissions in the United States. These factors include: (1) heavy-duty vehicles comprised only 3 to 19 percent of total vehicle traffic in the tunnel; (2) the majority of the light-duty vehicles were fueled with leaded gasoline the combustion of which, as noted above in Table 4-4, can release considerable amounts of CDD/CDFs; and (3) technology differences likely existed between the 1988 Norwegian and the 1987 and 1995 U.S. vehicle fleets.

The recent tunnel study conducted in Baltimore, Maryland, by Gertler et al. (1996, 1998) has the same disadvantages shared by all tunnel studies relative to tailpipe studies. Specifically, tunnel studies rely on indirect measurements (rather than tailpipe measurements), which may introduce unknown uncertainties, and the emission factors calculated from these studies reflect driving conditions by the vehicle fleet using the tunnel and not necessarily the overall vehicle fleet under other driving conditions. However, the Gertler et al. (1996, 1998) study does have strengths lacking in the Oehme et al. (1991) tunnel study. Also, the Gertler et al. (1996, 1998) study has benefits over the two U.S. diesel truck tailpipe studies. These include (1) the study is a recent study conducted in the United States and thus reflects current U.S. fuels and technology, (2) virtually no vehicle using the tunnel used leaded gasoline, (3) the tunnel walls and streets were cleaned 1 week prior to the start of sampling and, in addition, the study analyzed road dust and determined that resuspended road dust contributed only about 4 percent of the estimated emission factors, (4) heavy-duty vehicles comprised, on average, a relatively large percentage (25.7 percent) of vehicles using the tunnel, and (5) a large number of heavy-duty vehicles, approximately 33,000, passed through the tunnel during the sampling period, which generates confidence that the emission factor is representative of interstate trucks.

In consideration of the strengths and weaknesses of the available emission factor data from the tailpipe and tunnel studies, the mean TEQ emission factor reported by Gertler et al. (1996, 1998), 172 pg I-TEQ_{DF}/km (or 182 pg TEQ_{DF}-WHO_{98}/km), is assumed

to represent the best current estimate of the average emission factor for on-road diesel-fueled trucks. Because it may not be representative of emission rates for the entire fleet of diesel-fueled trucks under the wide array of driving conditions encountered on the road, this emission factor is assigned a low confidence rating.

Combining the calculated mean emission factors from Gertler et al. (1996, 1998) with the above estimate for vehicle kms driven in 1995 in the United States by diesel-fueled trucks (195 billion km) suggests that 33.5 g of I-TEQ_{DF} (or 35.5 g TEQ_{DF}-WHO_{98}) were emitted from trucks using diesel fuel in 1995. Combining the same emission factors to the estimate derived above for vehicle km driven in 1987 by diesel-fueled trucks (153 billion km) suggests that 26.3 g of I-TEQ_{DF} (or 27.8 g TEQ_{DF}-WHO_{98}) were emitted from diesel-fueled trucks in 1987.

4.2. WOOD COMBUSTION

In 1995, wood fuel (including black liquor solids) provided about 2.6 percent (or 2,350-trillion Btu) of the total primary energy consumed in the United States (EIA, 1997b). During 1987, wood energy consumption is estimated to have been 2,437 trillion Btu, or 3.2 percent of total primary energy consumed (EIA, 1997b). The industrial sector is the largest consumer of wood fuel, accounting for almost 72 percent of total wood fuel consumption in 1995 and 65 percent in 1987. The residential sector accounted for 25 percent of consumption in 1995 and 35 percent in 1987. The electric utility sector accounted for less than 1 percent of total consumption in both years. There are no accurate sources to provide reliable estimates of commercial wood energy use; consumption is thought to be between 20 and 40 trillion Btu, or 2 to 4 percent of total wood consumption (EIA, 1994, 1997b).

These energy consumption estimates, however, appear to include the energy value of black liquor solids, which are combusted in recovery boilers by wood pulp mills. In 1987 and 1995, the energy value of combusted black liquor solids were 950 trillion Btu and 1,078 trillion Btu, respectively (American Paper Institute, 1992; American Forest & Paper Association, 1997). Subtracting these black liquor energy value estimates from the national totals for wood fuel yields 1,487 trillion Btu in 1987 and 1,272 trillion Btu in 1995. Assuming that 1 kg of oven-dried wood (i.e., 2.15 kg of green wood) provides approximately 19,000 Btu (EIA, 1994), then an estimated 66.9 million and 78.3 million

metric tons of oven-dried wood equivalents were burned for energy purposes in 1995 and 1987, respectively. Of these totals, an estimated 31.4 million metric tons and 44.8 million metric tons were consumed by the residential sector in 1995 and 1987, respectively. An estimated 35.5 million metric tons and 33.5 million metric tons were consumed by the industrial sector in 1995 and 1987, respectively.

The following two subsections discuss the results of relevant emission studies for the residential and industrial sectors, respectively, and present annual TEQ emission estimates for the reference years 1987 and 1995.

4.2.1. Residential Wood Combustion

Four studies have provided direct measurement of CDD/CDFs in flue gas emissions from wood stoves and/or fireplaces (Schatowitz et al., 1993; Vikelsoe et al., 1993; Bremmer et al., 1994; Broker et al., 1992). The findings of each of these studies are summarized in the following paragraphs.

Schatowitz et al. (1993) measured the CDD/CDF content of flue gas emissions from several types of wood burners used in Switzerland: a household stove (6 kW), automatic chip furnaces (110 to 1,800 kW), and a wood stick boiler (35 kW). The emissions from combustion of a variety of wood fuels were measured (natural beech wood, natural wood chips, uncoated chipboard chips, waste wood chips from building demolition, and household paper and plastic waste). The results from the testing of the household stove are most relevant for assessing releases from residential combustion. The household stove was tested with the stove door both open and closed. The open door stove can be assumed to be representative of fireplaces because both have an uncontrolled draft. Although the congener/congener group analytical results were not reported, the following emission factors (dry weight for wood; wet weight for household waste) and emission rates (corrected to 13 volume% oxygen) for the household stoves and furnaces were reported.

Stoves

- Open door burn of beech wood sticks: 0.77 ng I-TEQ_{DF}/kg (0.064 ng I-TEQ_{DF}/Nm^3);

- Closed door burn of beech wood sticks: 1.25 ng I-TEQ$_{DF}$/kg (0.104 ng I-TEQ$_{DF}$/Nm^3); and
- Closed door burn of household waste: 3,230 ng I-TEQ$_{DF}$/kg (114.4 ng I-TEQ$_{DF}$/Nm^3).

Furnaces

- Natural wood chips: 0.79 to 2.57 ng I-TEQ$_{DF}$/kg
- Chipboard chips (uncoated): 0.29 to 0.91 ng I-TEQ$_{DF}$/kg
- Waste wood chips from building demolition: 26.0 to 173.3 ng I-TEQ$_{DF}$/kg

Vikelsoe et al. (1993) studied emissions of CDD/CDF congener groups from residential wood stoves in Denmark. The wood fuels used in the experiments were seasoned birch, beech, and spruce, equilibrated to 18 percent absolute moisture. Four different types of stoves (including one experimental stove) were evaluated under both normal and optimal (i.e., well controlled with CO emission as low as possible) operating conditions. Widely varying total CDD/CDF emissions were found for the 24 different fuel/stove type/operating condition combinations. The emissions from spruce were about twice as high as the emissions from birch and beech. Surprisingly, the optimal operating condition led to significantly higher CDD/CDF emissions for two stove types, but not for the other stoves. The predominant congener group for all experiments was TCDF. The weighted average (considering wood and stove types) emission factor and flue gas concentration for wood stoves were reported to be 1.9 ng Nordic-TEQ/kg and 0.18 ng Nordic-TEQ/Nm^3, respectively. Because Vickelsoe et al. (1993) did not measure congener levels, the reported emission factor and emission rate were estimated by assuming the same congener distribution in each congener group that had been found for municipal waste incinerators.

Bremmer et al. (1994) reported results of testing performed with a cast-iron, wood burning stove with a combustion chamber lined with fire refractory clay. Measurements were conducted at three loads (maximum, average, and minimum) using clean wood as fuel. The emission factors ranged from 1.0 to 3.3 ng I-TEQ$_{DF}$/kg (average of about 2.2 ng I-TEQ$_{DF}$/kg). Bremmer et al. (1994) also reported results of testing conducted at a

fireplace of a type that is common in The Netherlands. The measured emission factors from burning of clean wood ranged from 13.0 to 28.5 ng I-TEQ_{DF}/kg (average of about 20 ng I-TEQ_{DF}/kg). Bremmer et al. (1994) noted that the measured emission factors for fireplaces were considerably higher than those reported by others (see Broker et al., 1992, below) and they, therefore, assigned "great uncertainty" to the emission factors.

Broker et al. (1992) reported results of a series of three tests with a wood stove and a fireplace. The average of the minimum and maximum emission factors measured for the woodstove tests ranged from 0.53 to 0.94 ng I-TEQ_{DF}/kg, respectively. The geometric mean of these two average values is 0.71 ng I-TEQ_{DF}/kg. The average of the minimum and maximum emission factors measured for the fireplace tests ranged from 0.20 to 1.06 ng I-TEQ_{DF}/kg, respectively. The geometric mean of these two average values is 0.46 ng I-TEQ_{DF}/kg.

Based on the results reported by Schatowitz et al. (1993), Vikelsoe et al. (1993), Bremmer et al. (1994), and Broker et al. (1992), 2 ng I-TEQ_{DF}/kg appear to be a reasonable average emission factor for residential burning of clean wood in fireplaces and stoves. Although the cited studies were conducted in Europe, residential wood burning practices are probably sufficiently similar to apply to the United States. Nevertheless, a low confidence rating was assigned to this estimate on the basis that it is derived from only four direct measurement studies. With the exception of the Broker et al. (1992) study, none of the cited studies presented results for the individual 2,3,7,8-substituted congeners. The Broker et al. (1992) study reported congener-specific results for only one of the test runs. Consequently, the data are not available from which to derive a corresponding emission factor for TEQ_{DF}-WHO_{98}. For purposes of this inventory, an emission factor of 2 ng TEQ_{DF}-WHO_{98}/kg is assumed.

Several studies have reported that combustion of non-clean wood in stoves and fireplaces can result in significantly higher CDD/CDF emission factors. The results of Schatowitz et al. (1993) for combustion of household waste in stoves and demolition waste in wood furnaces are presented above. A few researchers (e.g., Vikelsoe et al, 1993) have reported high CDD/CDF emission rates when PCP-contaminated wood is combusted in residential wood stoves and furnaces. The European Inventory (Quab and Fermann, 1997) used the results of these studies to derive best estimates of CDD/CDF emission factors for combustion of "slightly contaminated wood (excluding PCP)" and

"PCP-contaminated wood" to be 50 and 500 ng I-TEQ_{DF}/kg, respectively. Although it is likely that there is some residential combustion of these types of wood in the United States, there are no corresponding activity level data upon which to base a national annual estimate of emissions.

In 1987, 22.5 million households in the United States burned wood (EIA, 1991). Of these households, wood was used in 1987 as the primary heating fuel in 5 million households and as a secondary source for aesthetic purposes (i.e., fireplaces) in 17.4 million households (EIA, 1991; EIA, 1997b). Lower numbers were reported for 1995; wood was reported to be used as the primary fuel in 3.53 million households (EIA, 1997b). More rural low-income households consume wood as a primary heating fuel than do other sectors of the population. The majority of these households use wood-burning stoves as the primary heating appliance. Although fireplaces are the most common type of wood-burning equipment in the residential sector, only 7 percent of fireplace users report use of fireplaces for heating an entire home (EIA, 1991; EIA, 1994).

Residential wood consumption in 1995 was 596 trillion Btu (31.4 million metric tons), or 25 percent of total U.S. wood energy consumption (EIA, 1997b). In 1987, residential wood consumption was 852 trillion Btu (44.8 million metric tons), or 35 percent of total U.S. consumption (EIA, 1997b). These production estimates are given high confidence ratings because they are based on recent government survey data.

Combining the best estimate of the emission factor (2 ng I-TEQ_{DF}/kg wood) with the mass of wood consumed by residences in the years 1995 and 1987 indicates that the annual I-TEQ_{DF} air emissions from this source were approximately 62.8 grams in 1995 and 89.6 grams in 1987.

4.2.2. Industrial Wood Combustion

Emissions Data - Congener-specific measurements of CDD/CDFs in stack emissions from industrial wood-burning furnaces were measured by the California Air Resources Board at four facilities in 1988 (CARB, 1990b; CARB, 1990e; CARB, 1990f; CARB, 1990g). Measurements of CDD/CDF congener groups and 2,3,7,8-TCDD and 2,3,7,8-TCDF were reported for one facility by EPA (U.S. EPA, 1987a). The National Council of the Paper Industry for Air and Stream Improvement (NCASI) (1995) presented congener-specific emission factors for five boilers tested during burns of bark/wood residue. The

average congener emission factors derived from the four CARB and five NCASI studies are presented in Table 4-9. Average congener and congener group profiles are presented in Figure 4-5a for the four CARB studies and in Figure 4-5b for the five NCASI studies.

In CARB (1990b), CDD/CDFs were measured in the emissions from a quad-cell wood-fired boiler used to generate electricity. The fuel consisted of coarse wood waste and sawdust from nonindustrial logging operations. The exhaust gas passed through a multicyclone before entering the stack. From this study, average emission factors for total CDD/CDF and I-TEQ_{DF} are calculated to be 48.1 and 0.64 ng/kg of wood burned, respectively.

In CARB (1990e), CDD/CDFs were measured in the emissions from two spreader stoker wood-fired boilers operated in parallel by an electric utility for generating electricity. The exhaust gas stream from each boiler is passed through a dedicated ESP after which the gas streams are combined and emitted to the atmosphere through a common stack. Stack tests were conducted both when the facility burned fuels allowed by existing permits and when the facility burned a mixture of permitted fuel supplemented by urban wood waste at a ratio of 70:30. From this study, average emission factors for total CDD/CDF and I-TEQ_{DF} are calculated to be 29.2 and 0.82 ng/kg of wood burned, respectively.

In CARB (1990f), CDD/CDFs were measured in the emissions from a twin fluidized bed combustors designed to burn wood chips for the generation of electricity. The air pollution control device (APCD) system consisted of ammonia injection for controlling nitrogen oxides, and a multiclone and electrostatic precipitator for controlling particulate matter. During testing, the facility burned wood wastes and agricultural wastes allowed by existing permits. From this study, average emission factors for total CDD/CDF and I-TEQ_{DF} are calculated to be 47.9 and 1.32 ng/kg of wood burned, respectively.

In CARB (1990g), CDD/CDFs were measured in the emissions from a quad-cell wood-fired boiler. During testing, the fuel consisted of wood chips and bark. The flue gases passed through a multicyclone and an ESP before entering the stack. From this study, average emission factors for total CDD/CDF and I-TEQ_{DF} are calculated to be 27.4 and 0.50 ng/kg of wood burned, respectively.

NCASI (1995) presented stack emission test results for five boilers burning bark or wood residues. One of these facilities, equipped with a multicyclone, normally burns bark

in combination with sludge and coal. One other facility, equipped with an ESP, normally fires pulverized coal. The other three facilities were spreader stokers equipped with multicyclones or ESPs. Although stack gas flow rates were obtained during these tests, accurate measurements of the amounts of bark/wood fired were not made and had to be estimated by NCASI (1995) from steam production rates. The average TEQ emission factor for these facilities was 0.40 ng I-TEQ_{DF}/kg of feed (or 0.46 ng TEQ_{DF}-WHO_{98}/kg).

The mean of the emission factors derived from the four CARB studies and five NCASI studies, 0.56 ng I-TEQ_{DF}/kg wood (assuming nondetected values are zero) (or 0.60 ng TEQ_{DF}-WHO_{98}/kg wood), is used in this report as most representative of industrial wood combustion. This emission factor was assigned a medium confidence rating.

It should be noted, however, that these mean emission factors may not be appropriate emission factors to apply to the combustion of waste wood containing elevated chlorine content. NCASI (1995) concluded that CDD/CDF emissions from facilities burning salt-laden wood residue may be considerably higher than from those burning salt-free wood. Similarly, Umweltbundesamt (1996) reported the results of stack gas testing at approximately 30 facilities of varying design type as well as type of wood fuel combusted and noted that elevated CDD/CDF emissions were observed when the combustion conditions were poor, as evidenced by elevated carbon monoxide emissions, and/or when the fuel contained elevated chlorine levels. Umweltbundesamt (1996) attributed the correlation between elevated CDD/CDF emissions and elevated chlorine content of the fuel to the fire retardant effects of chlorine, which may have inhibited complete combustion. The chlorine content of untreated wood and bark were reported to range from 0.001 to 0.01 percent by weight and 0.01 to 0.02 percent by weight, respectively. Chipboard can contain up to 0.2 percent chlorine by weight because of binding agents used to manufacture the chipboard. Preservative-treated wood and PVC-coated wood were reported to contain chlorine contents as high as 1.2 and 0.3 percent by weight, respectively.

The facility tested by EPA in 1987 was located at a lumber products plant that manufactures overlay panels and other lumber wood products. Nearly all the wood fed to the lumber plant had been stored in sea water adjacent to the facility and, therefore, had a significant concentration of inorganic chloride. The wood-fired boiler tested was a three-cell dutch oven equipped with a waste heat boiler. The feed wood was a mixture of bark,

hogged wood, and green and dry planar shavings. The exhausted gases from the boiler passed through a cyclone and fabric filter prior to discharge from the stack. From this study, an average emission factor for total CDD/CDF of 1,020 ng/kg of wood burned (range: 552 to 1,410 ng/kg) was reported for the three collected samples. An average emission factor for I-TEQ_{DF} of 17.1 ng/kg of wood burned (range: 7.34 to 22.8 ng/kg) was estimated by EPA using measured congener group concentrations and concentrations of 2,3,7,8-TCDD and 2,3,7,8-TCDF. Similar emission factors were reported by Lutke et al. (1998) for testing conducted during the 1990s at four Canadian coastal, salt-laden wood power boilers: 1.4, 2.6, 17.4, and 27.6 ng I-TEQ_{DF}/kg wood combusted. The overall average of the five tested Canadian and U.S. facilities is 13.2 ng I-TEQ_{DF}/kg of wood combusted. The confidence rating assigned to this emission factor is low because it is based on reporting of limited congener data at one U.S. facility and testing at four non-U.S. sources and because the fraction of salt-laden wood combusted across facilities is likely to be highly variable.

Activity Level Information - As discussed in Section 4.2, industrial wood consumption in 1995 totaled 35.5 million metric tons. A similar amount, 33.5 million metric tons, was burned for fuel in industrial furnaces in 1987. The majority of wood fuel consumed in the industrial sector consists of wood waste (i.e., chips, bark, sawdust, and hogged fuel). Consumption in the industrial sector is dominated by two industries: the Paper and Allied Products industry and the Lumber and Wood Products industry (EIA, 1994). These activity level estimates are assigned a high confidence rating because they are based on recent government survey data.

As noted above, the emission factor associated with combustion of salt-laden wood appears to be greater than that associated with combustion of non-salt-laden wood. However, activity level data on combustion of salt-laden wood are not normally collected. Nonetheless, attempts have been made to estimate this activity level. NCASI combined the results from a 1995 survey of combustion units in the pulp and paper industry with an ad hoc telephone survey of mills in the Pacific Northwest (i.e., Oregon and Washington) to produce a conservative (i.e., high end) estimate of the amount of salt-laden wood combusted at U.S. pulp and paper mills in 1995: 254,000 metric tons (or 0.7 percent of the estimated 35.5 million metric tons of industrial wood consumed that year). NCASI

suspects that a similar fraction of industrial wood combustion in 1987 by pulp and paper mills was salt-laden (Gillespie, 1998).

For purposes of the NCASI survey, salt-laden wood was defined as wood that had been transported, stored, or otherwise exposed to saltwater prior to being processed as fuel. None of the three responding mills in Oregon reported use of salt-laden wood. Eight of the 13 responding mills in Washington reported some combustion of salt-laden wood. The estimated percentage of salt-laden wood to total wood consumption in the Washington mills was 17 percent.

As noted above, the majority of industrial wood combustion (i.e., 97 percent) occurs in two industries: the Paper and Allied Products industry and the Lumber and Wood Products industry. The relative amounts of wood combusted by each of these two industries were the same in 1990 and 1992, the only years for which these statistics are readily available (EIA, 1991, 1994). Therefore, it can be assumed that the percentage of total wood combusted nationally by the Lumber and Wood Products industry that is salt-laden is the same percentage as that reported by the Paper and Allied Products industry, 0.7 percent. Therefore, the total percentage of wood combusted by industry that is salt-laden is 1.4 percent. On a mass basis, this equates to 0.5 million metric tons in 1995 and 0.5 million metric tons in 1987. These activity level estimates are assigned a low confidence rating.

Emission Estimates - Applying the average TEQ emission factor from the four CARB and five NCASI studies (0.56 ng I-TEQ_{DF}/kg wood or 0.60 ng TEQ_{DF}-WHO_{98}/kg wood) to the estimated quantities of non-salt-laden wood burned by industrial facilities in 1995 (35 million metric tons) and 1987 (33 million metric tons) yields estimated TEQ emissions to air of 19.6 g I-TEQ_{DF} (or 21.0 g TEQ_{DF}-WHO_{98}) in 1995 and 18.5 g I-TEQ_{DF} (or 19.8 g TEQ_{DF}-WHO_{98}) in 1987.

Applying the average TEQ emission factor from the five studies on boilers combusting salt-laden wood (13.2 ng I-TEQ_{DF}/kg wood) to the estimated quantities of salt-laden wood burned by industrial facilities in 1995 (0.5 million metric tons) and 1987 (0.5 million metric tons) yields estimated TEQ emissions to air of 6.6 g TEQ in both 1995 and 1987.

Total emissions are estimated to have been 26.2 and 25.1 g I-TEQ_{DF} in 1995 and 1987, respectively. Total emissions of TEQ_{DF}-WHO_{98} are estimated to have been 27.6

and 26.4 g in 1995 and 1987, respectively. As noted above, these emissions are based on tests conducted at nine facilities in two industries. These two industries account for 97 percent of total industrial wood fuel combustion. The remaining 3 percent of industrial combustion and the combustion of wood by the commercial sector (for which no reliable activity level estimates are available) may not be well represented by the emission factors used above, particularly if poorly controlled combustors or treated wood (e.g., treated with PCP or plastics) are combusted.

4.2.3. Solid Waste from Wood Combustion

The measurement of CDDs and CDFs in chimney soot and bottom ash from wood-burning stoves and fireplaces has been reported by several researchers (Bumb et al., 1980; Nestrick and Lamparski, 1982 and 1983; Clement et al., 1985b; Bacher et al., 1992; Van Oostam and Ward, 1995; and Dumler-Gradl et al., 1995a).

Bumb et al. (1980) detected TCDDs (ND to 0.4 μg/kg), HxCDDs (0.2 to 3 μg/kg), HpCDDs (0.7 to 16 μg/kg), and OCDD (0.9 to 25 μg/kg) in residues from the wall of a home fireplace and from the firebrick of another home fireplace; for lack of a suitable analytical method, analysis was not performed for PeCDDs. Neither of the fireplaces sampled by Bumb et al. (1980) had burned preservative-treated wood.

Nestrick and Lamparski (1982, 1983) expanded the research of Bumb et al. (1980) by conducting a survey of CDD concentrations in chimney soot from residential wood-burning units in three different rural areas of the United States. Samples were collected from the base of six chimneys in each of the three study areas. Samples were not collected from units where any type of treated or manufactured wood had been burned. For lack of a suitable analytical method, analysis was not performed for PeCDDs. The results of this survey are summarized in Table 4-10. There was wide variation in the results across soot samples with standard deviations for congeners and congener groups often equal to or exceeding the mean value; however, CDDs in each congener group were detected in the soot from almost all sampled units. Nestrick and Lamparski (1982, 1983) concluded that the results do not appear to present any easily discernible patterns with respect to geographic region, furnace operational parameters, or wood fuel type. Nestrick and Lamparski (1982, 1983) attribute the wide variability observed to differences in

design of the different units, which affected the sampling point and/or the conditions at the sampling point, and/or possible contamination of the fuel wood.

Clement et al. (1985b) analyzed chimney soot and bottom ash from residential woodstoves and fireplaces in Canada. The CDD/CDF congener concentrations are presented in Table 4-10 (soot) and Table 4-11 (bottom ash). CDD/CDF congeners were detected in all samples analyzed, although the relative amounts of the different congener groups varied considerably and inconsistently within the type of wood burning unit and between ash and soot samples from the same unit. Clement et al. (1985b) also presents total CDD/CDF concentration data for bottom ashes from outside open-air burning of wood. No analyses were reported for individual congeners. The results for the congener groups are presented below. Clement et al. (1985b) did not present the quantities of ashes produced by the outside open-air burning test, hence it is not possible to readily determine the quantities of CDD/CDF disposed.

Congener group	Concentration (μg/kg)	Congener group	Concentration (μg/kg)
TCDDs	0.8	TCDFs	2.2
PeCDDs	4.2	PeCDFs	7.6
HxCDDs	7.2	HxCDFs	8.2
HpCDDs	11	HpCDFs	11
OCCDs	10	OCDFs	1.7

Bacher et al. (1992) characterized the full spectrum (i.e., mono- through octa-substitution) of chlorinated and brominated dibenzo-p-dioxin and dibenzofuran congeners in the soot from an old farmhouse in southern Germany. The chimney carried smoke from an oven that had used untreated wood at the rate of about 5 m^3 per year for more than 10 years. The sample was taken during the annual cleaning by a chimney sweep. The only BDF detected was mono-BDF (230 ng/kg). No BDDs, BCDDs, or BCDFs were detected at a detection limit of 20 ng/kg. The results for the tetra- through octa- CDDs and CDFs are presented in Table 4-10. The results indicate that CDFs dominate the CDDs in each congener group except octa. Also, the lower chlorinated congener groups dominate the higher chlorinated congener groups for both the CDDs and CDFs. The TEQ

content of the chimney soot was 720 ng I-TEQ_{DF}/kg (755 ng TEQ_{DF}-WHO_{98}/kg) of which less than 30 percent was due to CDDs.

Van Oostdam and Ward (1995) analyzed soot from two wood stoves in British Columbia, Canada. The average TEQ concentrations were 211 ng I-TEQ_{DF}/kg and 246 ng TEQ_{DF}-WHO_{98}/kg. The congener-specific results are presented in Table 4-10. The soot from a wood stove burning salt-laden wood in a coastal area was found to have an I-TEQ_{DF} content of 7,706 ng I-TEQ_{DF}/kg or 20 to 90 times greater than the concentrations found in the soot from the other two tested stoves.

Dumler-Gradl et al. (1995a) analyzed chimney soot samples collected by chimney sweeps from 188 residences in Bavaria. The summary results of the survey, the largest published survey of its kind to date, are presented in Table 4-12. As was observed by Nestrick and Lamparski (1982, 1983) and Clement et al. (1985b), CDD/CDFs were detected in all samples; however, there was wide variability in total TEQ concentrations within and across unit type/fuel type combinations.

Washington (1998) reports CDD/CDF congener data for ash from hog fuel boilers at three paper mills. The data are compiled and evaluated to determine a total I-TEQ concentrations and loading. Non-detect values were included as either zero, ½ DL or at the DL. The results are as follows, assuming that non-detect values are at zero concentration:

Location	Type of Residual	I-TEQ_{DF} (ng/kg)	I-TEQ_{DF} (mg/day)
Daishowa America, Port Angeles	Mixed Ash	0.31	0.012
Ft. James	Fly Ash	35.4	0.544
Rayonier	Filter Ash Vacuum Filter & Grate Filter Ash Fly Ash	12,640 1,150 2,299 225	68.9 6.27 12.5 1.23

Pohlandt (1994) presents CDD/CDF concentration data for various ashes ("bottom", "furnace", "boiler", "fly") from 12 wood burning boilers. The "fly ash" samples from two wood working industry boilers appear to have the greatest concentrations of CDD/CDF. Table 4-13 list the average congener concentration for those two boilers.

Three boiler bottom ash samples contain detectable amounts of only total HpCDD/HpCDF and OCDD/OCDF. All the other boiler samples were from boilers that burned copper/chrome/boron impregnated woods. These samples had total TEQs (assumed to be I-TEQs) ranging from 0.07 - 89 ppt, the highest being the fly ash samples (52 and 89). Pohlandt (1994) did not report the quantities produced by the boilers that were tested, hence it is not possible to readily determine the quantities of CDD/CDF disposed.

Carpenter (2001) reported the results of analyses of two ash samples from wood burning facilities in New Hampshire. Both samples are from the burning of clean (i.e., untreated) wood chips, sawdust and bark. The first sample is a combination of fly ash and bottom ash. The second sample is only fly ash, but it is a combination of fly ash from two wood burning boilers. For the first sample, none of the 2,3,7,8-substituted congeners were detected at detection limits that ranged from 0.98 ng/kg for 2,3,7,8-TCDD and 2,3,7,8-TCDF to 9.80 ng/kg for OCDD and OCDF. (All other congeners had a detection limit of 4.90 ng/kg.) For the second sample, except for two congeners, all congeners were below detection limits (which ranged from 0.379 to 0.831 ng/kg). The two congeners that exceeded detection limits were OCDD at 1.261 ng/kg, and 1,2,3,4,6,7,8-HpCDF at 1.022 ng/kg. For this sample, assuming that the non-detect congeners are not present, I-TEQ_{DF} concentration is 0.011 ng/kg. The quantities of the ash produced were not reported.

In a CARB report of emissions from a wood waste fired incinerator (CARB, 1990b) data are given for CDDs and CDFs for four ash samples. The concentrations of 2,3,7,8-substituted CDD/CDF congeners for each of those four tests were *all* below the method detection limits (MDLs) except for OCDD, which was detected in three samples at concentrations of 14,18, and 32 ng/kg, and 2,3,7,8-TCDF, which was detected in one sample at a concentration of 2.2 ng/kg. The method detection limits for each CDD and CDF congener ranged from 0.63 ppt (for 2,3,7,8-TCDD) to 9.5 ppt (for HpCDF congeners). Total CDD and total CDF values are given for each of the four samples. However, those values assume that non-detected congeners are at the MDL level. Consequently, the total CDD and total CDF values are biased high. The average of the four total CDD values is 28.8 ng/kg (with a range of 20.3 - 44.0). The average of the four total CDF values is 21.9 ng/kg (with a range of 16.0 - 26.9).

In another CARB report (CARB, 1990e), data are presented for CDDs and CDFs for several samples of Electrostatic Precipitator (ESP) waste ash from a wood-fired boiler. The report provides sample results for two weeks of sampling conducted at the facility. During the first week, the boiler burned fuels that were allowed by the facility permit; during the second week, the boiler burned a mixture containing 70 percent permitted fuel and 30 percent urban wood wastes. For the six samples collected over the three days of the first week, many of the concentrations of CDD/CDF congeners in the ESP ash were below the detection limits. CARB reports the CDD concentrations in ESP waste ash ranged from 24 to 264 ng/kg, and the CDF concentrations ranged from 12 to 151 ng/kg. However, those values assume that non-detected congeners are present at the detection level. One sample does not have any non-detect values for CDDs. The total CDD concentration for this sample is 264 ng/kg, or about 8.3 ng/kg I-TEQ_{DF} and 11.4 ng/kg WHO-TEQs. The I-TEQ_{DF} and TEQ_{DF}-WHO_{98} CDF concentrations for this sample are both less than 1.5 ng/kg. These values are less than 1 ng/kg for the other five samples. All of the samples have some non-detects for the CDF analysis.

Six samples were also collected over three days during the second week of sampling, when the 70/30 permitted/urban wood waste mix was burned. For the samples from the second week, the CDD concentrations in ESP waste ash ranged from 1,365 to 3,190 ng/kg, and the CDF concentrations ranged from 2,866 to 11,282 ng/kg. CARB (1990e) assumes that non-detected congeners are present at the detection level. However, this is a reasonable estimate for this data set because there is only one non-detect value. Table 4-14 presents the average congener concentrations for these samples.

CARB (1990e) did not present quantities of ESP ashes produced by the boiler, therefore, it is not possible to readily determine the quantities of CDD/CDF disposed.

Appendix II of Luthe (1998) reports TEQ concentrations (assumed to be I-TEQ_{DF}) in ashes collected from air pollution control devices from "salt-laden" wood steam boilers. The I-TEQ_{DF} content of ashes from three for primary multiclone hoppers varied significantly, 0.0978, 0.186, and 9.375 μg/kg. For the secondary multiclone hoppers, two samples of ash were taken. The secondary multiclone removes dust from the primary multiclone emissions; and therefore, the ash is finer than primary dust). The I-TEQ_{DF} for the ash were 1.073 and 20.879 μg/kg. The I-TEQ_{DF} for two samples taken from the

electrostatic precipitator, which collects dust from the secondary multiclone emissions, and is, therefore, finer than multiclone dust, are 3.926 and 8.044 μg/kg. No data are given for individual congeners. In fact, because the reference discusses only "dioxins", it is unclear whether the TEQ data are for CDDs, or CDDs plus CDFs. Quantities of collected ash are not given.

Also for the burning of salt-laden wood in paper mill boilers, Table II of Luthe (1996) presents data for the "TEQs [assumed to be I-TEQs] on particulates from secondary collection device" for four different paper mills. Eight data points are given (two for each mill), the average of which is 3.6 μg/kg. The range of values is 1.3 to 8.0 μg/kg. As with Luthe (1998), no data are given for individual congeners. It is also unclear whether the TEQ data are for CDDs, or CDDs plus CDFs. Quantities of collected ash are not given.

Table 5-16 of U.S.EPA (1987a) contains data indicating that the bottom ash from wood combustion (it is not indicated whether the combustion source was a boiler) from one source contained 140 ng/kg of 2,3,7,8-TCDD, 138,200 ng/kg of CDDs, and 7,400 ng/kg of CDFs. For a second wood combustion source, the ash contained no detectable 2,3,7,8-TCDD, but did contain about 125 ng/kg of CDDs and non detectable levels of CDFs. The baghouse dust from the second source contained 100 ng/kg of 2,3,7,8-TCDD, 1,143,600 ng/kg of CDDs, and 315,600 ng/kg of CDFs. Specific data for congeners and for ash/dust quantities were not given.

4.3. OIL COMBUSTION

Two major categories of fuel oil are burned by combustion sources: distillate oils and residual oils. These oils are further distinguished by grade numbers, with Nos. 1 and 2 being distillate oils; Nos. 5 and 6 being residual oils; and No. 4 either distillate oil or a mixture of distillate and residual oils. No. 6 fuel oil is sometimes referred to as Bunker C. Distillate oils are more volatile and less viscous than residual oils. They have negligible nitrogen and ash contents and usually contain less than 0.3 percent sulfur (by weight). Distillate oils are used mainly in domestic and small commercial applications. Being more viscous and less volatile than distillate oils, the heavier residual oils (Nos. 5 and 6) must be heated for ease of handling and to facilitate proper atomization. Because residual oils are produced from the residue remaining after the lighter fractions (gasoline, kerosene, and

distillate oils) are removed from the crude oil, they contain significant quantities of ash, nitrogen, and sulfur. Residual oils are used mainly in utility, industrial, and large commercial application (U.S. EPA, 1995b).

4.3.1. Residential/Commercial Oil Combustion

No testing of the CDD/CDF content of air emissions from residential/commercial oil-fired combustion units in the United States could be located. However, U.S. EPA (1997b) has estimated CDD/CDF congener group and I-TEQ$_{DF}$ emission factors based on average CDD/CDF concentrations reported for soot samples from 21 distillate fuel oil-fired furnaces used for central heating in Canada, and a particulate emission factor for distillate fuel oil combustors (300 mg/L of oil) obtained from AP-42 (U.S. EPA, 1995b). The I-TEQ$_{DF}$ emission factor estimate in U.S. EPA (1997b) was derived using the calculated emission factors for 2,3,7,8-TCDD, 2,3,7,8-TCDF, and the 10 congener groups. These emission factors are presented in Table 4-15, and the congener group profile is presented in Figure 4-6.

Because there are no direct measurements of CDD/CDF emissions in stack gases from U.S. residential oil-fired combustors and because of uncertainties associated with using chimney soot data to estimate stack emissions, no national emission estimates for this category are proposed at this time. However, a preliminary estimate of potential national TEQ emissions from this source category can be made using the emission factor presented in Table 4-13 (150 pg I-TEQ$_{DF}$/L of oil combusted). Distillate fuel oil sales to the residential/commercial sector totaled 39.7 billion liters in 1995 (EIA, 1997a). Application of the emission factor of 150 pg I-TEQ$_{DF}$/L to this fuel oil sales estimate results in estimated emissions of 6.0 g I-TEQ$_{DF}$ in 1995. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of the emissions.

4.3.2. Utility Sector and Industrial Oil Combustion

Preliminary CDD/CDF emission factors for oil-fired utility boilers developed from boiler tests conducted over the past several years are reported in U.S. EPA (1997b). The data are a composite of various furnace configurations and APCD systems. Table 4-16 lists the median emission factors presented in U.S. EPA (1997b). The congener and

congener group profiles based on these data are presented in Figure 4-7. The median I-TEQ_{DF} emission factor was reported to be 314 pg/L of oil burned (or 366 pg TEQ_{DF}-WHO_{98}/L).

In 1993, the Electric Power Research Institute (EPRI) sponsored a project to gather information of consistent quality on power plant emissions. This project, the Field Chemical Emissions Measurement (FCEM) project, included testing of two cold side ESP-equipped oil-fired power plants for CDD/CDF emissions (EPRI, 1994). The averages of the congener and congener group emission factors reported for these two facilities are presented in Table 4-16. The average TEQ emission factors are 83.1 pg I-TEQ_{DF}/L and 93.6 pg TEQ_{DF}-WHO_{98}/L of oil burned (when nondetected values are treated as zero).

The TEQ emission factors reported in EPRI (1994) are a factor of three to four less than the median TEQ emission factor reported in U.S. EPA (1997b). For purposes of this assessment, emission factors of 200 pg I-TEQ_{DF}/L and 230 pg TEQ_{DF}-WHO_{98}/L (i.e., the average of the EPA median and EPRI mean emission factors) are assumed to be current best estimates of the average TEQ emission factors for utility/industrial oil burning. These estimated emission factors are assigned a low confidence rating.

The emission factors derived above were based on combustion of virgin oil by utility boilers. Significantly greater emission factors have been reported by Bremmer et al. (1994) for combustion of used oil by smaller combustion units in The Netherlands. Flue gases from a garage stove consisting of an atomizer fueled by spent lubricating oil from diesel engines (35 mg Cl^-/kg) were reported to contain 0.1 ng I-TEQ_{DF}/Nm^3 (or 2,000 pg I-TEQ_{DF}/kg of oil burned). The flue gases from a hot water boiler consisting of a rotary cup burner fueled with the organic phase of rinse water from oil tanks (340 mg Cl^-/kg) contained 0.2 ng I-TEQ_{DF}/Nm^3 (or 4,800 pg I-TEQ_{DF}/kg of oil burned). The flue gases from a steam boiler consisting of a rotary cup burner fueled by processed spent oil (240 mg Cl^-/kg) contained 0.3 ng I-TEQ_{DF}/Nm^3 (or 6,000 pg I-TEQ_{DF}/kg of oil burned). The emission factor for a ferry burning heavy fuel oil containing 11 ng/kg organic chlorine was 3,200 to 6,500 pg I-TEQ_{DF}/kg of oil burned. From these data, Bremmer et al. (1994) derived an average emission factor for combustion of used oil of 4,000 pg I-TEQ_{DF}/kg of oil burned. Bremmer et al. (1994) also reported measuring CDD/CDF emissions from a river barge and a container ship fueled with gas oil (less than 2 ng/kg of organic chlorine). The exhaust gases contained from 0.002 to 0.2 ng I-TEQ_{DF}/Nm^3. From these data, Bremmer et al.

(1994) derived an average emission factor for inland oil-fueled vessels of 1,000 pg I-TEQ_{DF}/kg oil burned. The applicability of these emission factors to used oil combustors in the United States is uncertain. Therefore, estimates of potential emissions from used oil combustion in the United States are not being developed at this time.

Residual fuel oil sales totaled 46.6 billion liters in 1995 and 77.3 billion liters in 1987 (EIA, 1992, 1997a). Vessel bunkering was the largest consumer (48 percent of sales) followed by electric utilities and the industrial sector. A high confidence rating is assigned to these production estimates. Application of the TEQ emission factor of 200 pg I-TEQ_{DF}/L (230 pg TEQ_{DF}-WHO_{98}/L) to these residual fuel oil sales results in estimated TEQ emissions of 9.3 g I-TEQ_{DF} (10.7 g TEQ_{DF}-WHO_{98}) in 1995 and 15.5 g I-TEQ_{DF} 1987 (17.8 g TEQ_{DF}-WHO_{98}) in 1987.

4.4. COAL COMBUSTION

During 1995, coal consumption accounted for approximately 22 percent of the energy consumed from all sources in the United States (U.S. DOC, 1997). In 1995, 872 million metric tons of coal were consumed in the United States. Of this total, 88.4 percent (or 771 million metric tons) were consumed by electric utilities, 11.0 percent (or 96 million metric tons) were consumed by the industrial sector (including consumption of 30 million metric tons by coke plants), and 0.6 percent (or 5.3 million metric tons) were consumed by residential and commercial sources (EIA, 1997b). Comparable figures for 1987 are: total consumption, 759 million metric tons; consumption by electric utilities, 651 million metric tons; consumption by coke plants, 33.5 million metric tons; consumption by other industries, 68.2 million metric tons; and consumption by the residential and commercial sectors, 6.3 million metric tons (EIA, 1995c). These production estimates are assigned a high confidence rating because they are based on detailed studies specific to the United States.

The following two subsections discuss the results of relevant emission studies for the utility/industrial and residential sectors, respectively, and present annual TEQ emission estimates for the reference years 1987 and 1995.

4.4.1. Utilities and Industrial Boilers

Until fairly recently, few studies had been performed to measure CDD/CDF concentrations in emissions from coal-fired plants, and several of these studies did not have the congener specificity and/or detection limits necessary to fully characterize this potential source (U.S. EPA, 1987a; NATO, 1988; Wienecke et al., 1992). The results of more recent testing of coal-fired utility and industrial boilers in The Netherlands (Bremmer et al., 1994), the United Kingdom (Cains and Dyke, 1994; CRE, 1994), Germany (Umweltbundesamt, 1996), and the United States (Riggs et al., 1995; EPRI, 1994) have achieved lower detection limits.

Bremmer et al. (1994) reported the results of emission measurements at two coal-fired facilities in The Netherlands. The emission factor reported for a pulverized coal electric power plant equipped with an ESP and a wet scrubber for sulfur removal was 0.35 ng I-TEQ_{DF}/kg of coal fired (or 0.02 ng I-TEQ_{DF}/Nm^3 at 11 percent O_2). The emission factor reported for a grass drying chain grate stoker equipped with a cyclone APCD was 1.6 ng I-TEQ_{DF}/kg of coal fired (or 0.16 ng I-TEQ_{DF}/Nm^3 at 11 percent O_2).

Cains and Dyke (1994) reported an emission factor of 102 to 109 ng I-TEQ_{DF}/kg of coal at a small-scale facility in the United Kingdom that was equipped with an APCD consisting only of a grit arrestor. CRE (1994) reported results of testing at 13 commercial/ industrial coal-fired boilers in the United Kingdom. The I-TEQ_{DF} emission factors ranged from 0.04 to 4.8 ng I-TEQ_{DF}/kg coal combusted (mean value of 0.6 ng I-TEQ_{DF}/kg). CRE (1994) also reported testing results for one coal-fired power plant, 0.06 ng I-TEQ_{DF}/kg coal combusted.

Umweltbundesamt (1996) reported that the I-TEQ_{DF} content of stack gases from 16 coal-burning facilities in Germany ranged from 0.0001 to 0.04 ng I-TEQ_{DF}/m^3; the data provided in that report did not enable emission factors to be calculated.

The U.S. Department of Energy sponsored a project in 1993 to assess emissions of hazardous air pollutants at coal-fired power plants. As part of this project, CDD/CDF stack emissions were measured at seven U.S. coal-fired power plants. The preliminary results of this project (i.e., concentrations in stack emissions) were reported by Riggs et al. (1995) and are summarized in Table 4-17. The levels reported for individual 2,3,7,8-substituted congeners were typically very low (i.e., $\leq$0.033 ng/Nm^3) or not detected. In general, CDF levels were higher than CDD levels. OCDF and 2,3,7,8-TCDF were the most

frequently detected congeners (i.e., at four of the seven plants). Table 4-18 presents characteristics of the fuel used and APCD employed at each plant. Variation in emissions between plants could not be attributed by Riggs et al. (1995) to any specific fuel or operational characteristic.

During the early 1990s, EPRI also sponsored a project to gather information of consistent quality on power plant emissions. This project, the Field Chemical Emissions Measurement (FCEM) project, included testing of four cold-side ESP-equipped coal-fired power plants for CDD/CDF emissions. Two plants burned bituminous coal and two burned subbituminous coal. The final results of the DOE project discussed above (Riggs et al., 1995) were integrated with the results of the EPRI testing and published in 1994 (EPRI, 1994). The average congener and congener group emission factors derived from this 11 facility data set, as reported in EPRI (1994), are presented in Table 4-19. Congener and congener group profiles for the data set are presented in Figure 4-8. The average I-TEQ_{DF} and TEQ_{DF}-WHO_{98} emission factors, assuming nondetected values are zero, are 0.079 ng I-TEQ_{DF}/kg of coal combusted and 0.078 ng TEQ_{DF}-WHO_{98}/kg. A medium confidence rating is assigned to these emission factors derived from the DOE and EPRI studies because they are based on recent testing at U.S. utilities.

Because the EPRI and DOE data only characterized emissions from units with cold-side ESPs, there has been uncertainty regarding the applicability of the emission factors derived from these data to units with hot-side ESPs. In July 1999, EPA conducted testing of stack emissions at a coal-fired utility equipped with a hot-side ESP. The preliminary results of this testing indicate that the TEQ emission factor for hot-sided ESPs is of the same order of magnitude as the average TEQ emission factors derived above.

As stated above, consumption of coal by the U.S. utility sectors was 771 million metric tons in 1995 and 651 million metric tons in 1987. Applying the TEQ emission factors of 0.079 ng I-TEQ_{DF}/kg of coal combusted and 0.078 ng TEQ_{DF}-WHO_{98}/kg to these production factors yields estimated annual emissions of 60.9 g I-TEQ_{DF} and 60.1 g TEQ_{DF}-WHO_{98} in 1995 and 51.4 g I-TEQ_{DF} and 50.8 TEQ_{DF}-WHO_{98} in 1987 by the utility sector.

No testing of the CDD/CDF content of air emissions from commercial/industrial coal-fired combustion units in the United States could be located. However, as noted above, several studies have been performed in European countries (Bremmer et al., 1994; CRE, 1994). It is uncertain whether the data collected in these European studies

accurately represent U.S. sources, but the data suggest that emission factors for commercial/industrial sources can be higher than those reported above for U.S. coal-fired utilities. Therefore, no national emission estimate for this category is being derived at this time. However, a preliminary estimate of potential national TEQ emissions from this source category can be derived using the average emission factor reported in CRE (1994), 0.6 ng I-TEQ_{DF}/kg coal combusted. As noted above, 66 million metric tons of coal were consumed by the industrial sector (excluding 30 million metric tons consumed by coke plants). Applying the emission factor of CRE (1994) to this activity level estimate yields an estimated national emission of 39.6 g I-TEQ_{DF} in 1995. This estimate should be regarded as a preliminary indication of possible emissions from commercial/industrial coal-fired boilers; further testing is needed to confirm the true magnitude of these emission.

4.4.2. Residential/Commercial Coal Combustion

Coal is usually combusted in underfeed or hand-stoked furnaces in the residential sector. Other coal-fired heating units include hand-fed room heaters, metal stoves, and metal and masonry fireplaces. Stoker-fed units are the most common design for warm-air furnaces and for boilers used for steam or hot water production. Most coal combusted in these units are either bituminous or anthracite. These units operate at relatively low temperatures and do not efficiently combust the coal. Coal generally contains small quantities of chlorine and CDD/CDF; therefore, the potential for CDD/CDF formation exists. Typically, coal-fired residential furnaces are not equipped with particulate matter or gaseous pollutant control devices that may limit emissions of any CDD/CDFs formed (U.S. EPA, 1997b). No testing of the CDD/CDF content of air emissions from residential/commercial coal-fired combustion units in the United States could be located. However, several relevant studies have been performed in European countries.

Thub et al. (1995) measured flue gas concentrations of CDD/CDF from a household heating system in Germany, fired either with salt lignite coal (i.e., total chlorine content of 2,000 ppm) or normal lignite coal (i.e., total chlorine content of 300 ppm). CDD/CDFs were detected in the flue gases generated by combustion of both fuel types. (See Table 4-20.) The congener profiles and patterns were similar for both fuel types, with OCDD the dominant congener and TCDF the dominant congener group. However, the emissions were higher for the "salt" coal (0.109 ng I-TEQ_{DF}/m^3 or 2.74 ng I-TEQ_{DF}/kg of

coal) by a factor of eight than for the "normal" coal (0.015 ng I-TEQ_{DF}/m^3 or 0.34 ng I-TEQ_{DF}/kg of coal).

Eduljee and Dyke (1996) used the results of testing performed by the Coal Research Establishment in the United Kingdom to estimate emission factors for residential coal combustion units as follows:

- Anthracite coal: 2.1 ng I-TEQ_{DF}/kg of coal; and
- Bituminous coal: 5.7 to 9.3 ng I-TEQ_{DF}/kg of coal (midpoint of 7.5 ng I-TEQ_{DF}/kg).

CDD/CDF emission factors for coal-fired residential furnaces were estimated in U.S. EPA (1997b) based on average particulate CDD/CDF concentrations from chimney soot samples collected from seven coal ovens, and particulate matter emission factors specific to anthracite and bituminous coal combustion obtained from AP-42 (U.S. EPA, 1995b). The I-TEQ_{DF} emission factors estimated in U.S. EPA (1997b) (i.e., 60.0 and 98.5 ng I-TEQ_{DF}/kg of anthracite and bituminous coal, respectively) were derived using the calculated emission factors for 2,3,7,8-TCDD 2,3,7,8-TCDF, and the 10 congener groups. U.S. EPA (1997b) stated that the estimated factors should be considered to represent maximum emission factors, because soot may not be representative of the particulate matter actually emitted to the atmosphere. These emission factors are presented in Table 4-20, and congener group profiles are presented in Figure 4-9.

Although the congener group profiles of the Thub et al. (1995) measurements and the U.S. EPA (1997b) estimates are similar, the I-TEQ_{DF} emission factors differ by factors of 175 to 289 between the two studies. The emission factors used by Eduljee and Dyke (1996) to estimate national annual emissions of I-TEQ_{DF} from residential coal combustion in the United Kingdom fall in between those other two sets of estimates but are still about one to two orders of magnitude greater than the estimated emission factor for industrial/ utility coal combustors. (See Section 4.4.1.)

Because there are no direct measurements of CDD/CDF emissions from U.S. residential coal-fired combustors and because of uncertainties regarding the comparability of U.S. and German and British coal combustion units, no national emission estimate for this category is being derived at this time. However, a preliminary estimate of potential

national TEQ emissions from this source category can be derived using the emission factors of Eduljee and Dyke (1996). As noted above, 5.3 million metric tons of coal were consumed by the residential/commercial sector in 1995 (U.S. DOC, 1997). U.S. EPA (1997b) reports that 72.5 percent of the coal consumed by the residential sector in 1990 were bituminous and 27.5 percent were anthracite. Assuming that these relative proportions reflect the actual usage in 1995, then application of the emission factors from Eduljee and Dyke (1996) (i.e., 2.1 ng I-TEQ_{DF}/kg of anthracite coal and 7.5 ng I-TEQ_{DF}/kg of bituminous coal) to the consumption value of 5.3 million metric tons results in an estimated I-TEQ_{DF} emission of 32.0 g TEQ in 1995. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions.

4.4.3. Solid Wastes from Coal Combustion

A limited amount of CDD/CDF concentration data have been developed for utility industry solid wastes (U.S.EPA, 1999b). These data are for utility industry solid wastes that are comanaged (i.e., combinations of fly ash, bottom ash, boiler slag, and flue gas desulfurization [FGD] wastes). Samples were taken from 11 disposal sites. A total of 15 samples were taken from the 11 sites. The average concentrations for each of the CDD and CDF congeners are presented in the second column of Table 4-21. It should be noted that most of the concentration values shown in Table 4-21 represent limits of detection. Consequently, the values overestimate the actual concentration.

Section 3.3 of U.S.EPA (1999c) indicates that there were approximately 63 million tons (assumed to be short tons, i.e., 2,000 pounds) of large-volume utility coal combustion solid wastes produced in 1995. Of this amount, about 67 percent was landfilled, and the balance was disposed of in surface impoundments. The concentration data presented in Table 4-21 is only for the 53 million tons that were comanaged (or about 84 percent of the total wastes). For purposes of this analysis it will be assumed that the CDD/CDF concentrations in the comanaged wastes are the same as for the entire waste quantity. Combining the concentration data with the 63 million tons of total waste yields the total quantities of each congener disposed of in 1995. These data are presented in the fourth column of Table 4-21. Section 4.4 of this document indicates that total consumption of coal for electric utility boilers in 1987 was 98.4 percent of 1995

consumption. Consequently, the quantities of CDD/CDF disposed of in 1987 is assumed to be 98.4 percent of the 1995 values. These values are presented in column 3 of Table 4-21.

The 1995 congener quantities are converted into I-TEQ_{DF} and TEQ_{DF}-WHO_{98} values in columns 5 and 6 of Table 4-21 respectively. The values for 1987 are assumed to be 98.4 percent of the 1995 values based on the assumptions stated in the above paragraph.

Table 4-1. Descriptions and Results of Vehicle Emission Testing Studies for CDDs and CDFs

Study	Country	Fuel Type	Scavenger[a]	Catalyst Equipped	Number of Test Vehicles	TEQ Emission Factor[g] (pg/km driven)	Driving Cycle; Sampling Location
CARB (1987a); Lew (1996)	United States	Diesel (truck)	No	NR	1	676-1,325[b] [597-1,307]	6-hr dynamometer test at 50 km/hr
Marklund et al. (1987)	Sweden	Unleaded Leaded	No Yes	Yes No	2 4	not detected (<13) approx. 20-220	A10 (2 cycles); muffler exhaust A10 (2 cycles); muffler exhaust
Bingham et al. (1989)	New Zealand	Unleaded Leaded	No Yes	NR NR	1 4	not detected (<20) 1-39	A10 (3 or 4 cycles); muffler exhaust A10 (3 or 4 cycles); muffler exhaust
Marklund et al. (1990)	Sweden	Unleaded Leaded Unleaded Leaded Diesel (truck)	No Yes No Yes No	No No Yes No NR	2 2 1 2 1	0.36-0.39 2.4-6.3 0.36 1.1-2.6[e] not detected (<18)[b]	FTP-73 test cycle; before muffler FTP-73 test cycle; before muffler FTP-73 test cycle; in tailpipe FTP-73 test cycle; in tailpipe U.S. Federal mode 13 cycle; before muffler
Hagenmaier et al. (1990)	Germany	Unleaded Unleaded Leaded Diesel (car)	No No Yes No	No Yes No NR	1 1 1 1	5.1[b] [6.0] 0.7[b] [0.8] 108[b] [129] 2.1[b] [2.5]	Comparable to FTP-73 test cycle; in tailpipe Comparable to FTP-73 test cycle; in tailpipe Comparable to FTP-73 test cycle; in tailpipe Comparable to FTP-73 test cycle; in tailpipe
Oehme et al. (1991) (tunnel study)	Norway	---	---	---	(c)	520[d] 38[d] avg = 280 9,500[d] 720[d] avg = 5,100	Cars moving uphill (3.5% incline) at 60 km/hr Cars moving downhill (3.5% decline) at 70 km/hr Car average Trucks moving uphill (3.5% incline) at 60 km/hr Trucks moving downhill (3.5% decline) at 70 km/hr Truck average
Schwind et al. (1991) Hutzinger et al. (1992)	Germany	Leaded Unleaded Unleaded Diesel (car) Diesel (truck)	Yes No No No No	No No Yes No No	1 1 1 1 1	5.2-118[b] [7.2-142] 9.6-17.7[b] [10.2-18.1] 1.0-2.6[b] [1.0-2.8] 1.0-13[b] [1.2-14] 13-15[b] [14-15]	Various test conditions (i.e., loads and speeds) Various test conditions (i.e., loads and speeds) Various test conditions (i.e., loads and speeds) Various test conditions (i.e., loads and speeds) Various test conditions (i.e., loads and speeds)
Gertler et al. (1996, 1998) (tunnel study)	United States	Diesel (truck)	---	---	(f)	mean = 172	Mean of seven 12-hour samples
Gullett and Ryan (1997)	United States	Diesel (truck)	No	---	1	mean - 29.0	Mean of five sample routes

[a] Dichloroethane and dibromoethane, except for Marklund et al. (1987), used as scavengers.

[b] Results reported were in units of pg TEQ/liter of fuel. For purposes of this table, the fuel economy factor used by Marklund et al. (1990), 10 km/L or 24 miles/gal, was used to convert the emission rates into units of pg TEQ/km driven for the cars. For the diesel-fueled truck, the fuel economy factor reported in CARB (1987a) for a 1984 heavy-duty diesel truck, 5.5 km/L (or 13.2 miles/gal), was used.

[c] Tests were conducted over portions of 4 days, with traffic rates of 8,000-14,000 vehicles/day. Heavy duty vehicles (defined as vehicles over 7 meters in length) ranged from 4-15% of total.

[d] Emission factors are reported in units of pg Nordic TEQ/km driven; the values in units of I-TEQ_{DF}/km are expected to be about 3 to 6 percent higher.

[e] Table reflects the range of summary results reported in Marklund et al. (1990); however, the congener-specific results for the single run reported indicate an emission rate of about 7.3 pg I-TEQ_{DF}/km.

[f] Tests were conducted over 5 days with heavy-duty vehicle rates of 1,800-8,700 vehicles per 12-hour sampling event. Heavy-duty vehicles accounted for 21-28 percent of all vehicles.

[G] Values listed are in units of I-TEQ_{DF}. Values in brackets are in units of TEQ_{DF}-WHO_{98}.

NR = Not Reported

Table 4-2. Diesel-Fueled Automobile CDD/CDF Congener Emission Factors

Congener/Congener Group	Automobile Tailpipe Emission Study Results				Mean Emission Factors	
	63 km/hr (Ref. A) (pg/L)	Idling (test no. 25) (Ref. B) (pg/L)	57 km/hr (test no. 24) (Ref. B) (pg/L)	57 km/hr (full load) (test no. 28) (Ref. B) (pg/L)	Assuming ND = zero (pg/L)	Assuming ND = ½ det limit (pg/L)
2,3,7,8-TCDD	7.9	13.1	2.4	22	11.4	11.4
1,2,3,7,8-PeCDD	9.0	6.3	4.1	23	10.6	10.6
1,2,3,4,7,8-HxCDD	ND (5.1)	21.4	1.0	7.8	7.6	8.2
1,2,3,6,7,8-HxCDD	ND (5.1)	36	1.4	21	14.6	15.2
1,2,3,7,8,9-HxCDD	ND (5.1)	28	2.0	10	10.0	10.6
1,2,3,4,6,7,8-HpCDD	44.1	107	22.9	166	85.0	85.0
OCDD	440	635	525	560	540	540
2,3,7,8-TCDF	20.5	79	18.1	236	88.4	88.4
1,2,3,7,8-PeCDF	ND (5.1)	171	1.8	111	71.0	71.6
2,3,4,7,8-PeCDF	7.1	58.7	3.4	85	38.6	38.6
1,2,3,4,7,8-HxCDF	6.5	121	4.1	68	49.9	49.9
1,2,3,6,7,8-HxCDF	6.7	75	3.0	55	34.9	34.9
1,2,3,7,8,9-HxCDF	ND (5.1)	17.1	0.8	4.7	5.7	6.3
2,3,4,6,7,8-HxCDF	ND (5.1)	52	ND (0.4)	31	20.8	21.4
1,2,3,4,6,7,8-HpCDF	40.7	159	18.9	214	108.2	108.2
1,2,3,4,7,8,9-HpCDF	8.5	11.9	7.1	7.8	8.8	8.8
OCDF	94.4	214	101	305	178.6	178.6
Total 2,3,7,8-CDD	501.0	846.8	558.8	809.8	679.1	681.0
Total 2,3,7,8-CDF	184.4	958.7	158.2	1117.5	604.7	606.7
Total I-TEQ_{DF} (ND = zero)	20.8	100.7	10.4	129.6	65.4	
Total I-TEQ_{DF} (ND = ½ det limit)	22.2*	100.7	10.4	129.6		65.7
Total TEQ_{DF}-WHO_{98} (ND = zero)	24.8	103.1	11.9	140.4	70.0	
Total TEQ_{DF}-WHO_{98} (ND = ½ det limit)	26.2	103.1	1.9	140.4		70.4
Total TCDD	37.4	317	31	394	195	195
Total PeCDD	19.7	214	22	228	121	121
Total HxCDD	23.6	256	20	164	116	116
Total HpCDD	88.5	187	77	356	177	177
Total OCDD	440.5	635	525	560	540	540
Total TCDF	76.7	436	58	3093	916	916
Total PeCDF	39.3	821	36	1205	525	525
Total HxCDF	25.6	556	26	472	270	270
Total HpCDF	80.6	321	72	241	179	179
Total OCDF	94.4	214	101	305	179	179
Total CDD/CDF (ND = zero)	926.3	3,957	968	7,018	3,217	
Total CDD/CDF (ND = ½ det limit)	926.3	3,957	968	7,018		3,217

ND = Not detected; value in parentheses is the detection limit.

* = An I-TEQ_{DF} emission factor of 23.6 pg/L is reported in Ref. A; however, an I-TEQ_{DF} emission factor of 22.2 pg/L is calculated based on reported congener levels.

Ref. A: Hagenmaier et al. (1990)

Ref. B: Schwind et al. (1991); Hutzinger et al. (1992)

Table 4-3. Diesel-Fueled Truck CDD/CDF Congener Emission Factors

Congener/Congener Group	Truck Tailpipe Study Results			Mean Emission Factors	
	50 km/hr (test no. 40) (Ref. A) (pg/L)	90 km/hr (full load) (test no. 42) (Ref. A) (pg/L)	50 km/hr (Ref. B) (pg/L)	Assuming ND = zero (pg/L)	Assuming ND = ½ det lim (pg/L)
2,3,7,8-TCDD	25	16	ND (560)	13.7	107
1,2,3,7,8-PeCDD	5	18	ND (1,340)	7.7	231
1,2,3,4,7,8-HxCDD	14.0	5.7	ND (2,160)	6.6	367
1,2,3,6,7,8-HxCDD	28	6	ND (1,770)	11.3	307
1,2,3,7,8,9-HxCDD	14	6	ND (2,640)	6.7	446
1,2,3,4,6,7,8-HpCDD	119	74	116,000	38,731	38,731
OCDD	1,355	353	344,400	115,369	115,369
2,3,7,8-TCDF	87	53	ND (605)	46.7	148
1,2,3,7,8-PeCDF	45	34	ND (4,750)	26.3	819
2,3,4,7,8-PeCDF	18	51	ND (5,190)	23.0	887
1,2,3,4,7,8-HxCDF	56	29	ND (8,210)	28.3	1,397
1,2,3,6,7,8-HxCDF	84	31	ND (6,480)	38.3	1,119
1,2,3,7,8,9-HxCDF	4.7	5.1	13,400	4,469	4,469
2,3,4,6,7,8-HxCDF	63	23	ND (7,780)	28.7	1,325
1,2,3,4,6,7,8-HpCDF	375	71	73,460	24,636	24,636
1,2,3,4,7,8,9-HpCDF	40	5.4	ND (11,700)	15.1	1,960
OCDF	397	104	140,400	46,981	46,981
Total 2,3,7,8-CDD	1,560	478.7	460,400	154,146	155,558
Total 2,3,7,8-CDF	1,170	406.5	227,300	76,292	83,739
Total I-TEQ_{DF} (ND = zero)	81	70	3,720	1,290	
Total I-TEQ_{DF} (ND = ½ det limit)	81	70	7,290		2,480
Total TEQ_{DF}-WHO_{98} (ND = zero)	82	79	3,280	1,150	
Total TEQ_{DF}-WHO_{98} (ND = ½ det limit)	82	79	7,190		2,450
Total TCDD	200	208	ND (3,760)	136	762
Total PeCDD	32	117	ND (3,020)	49.7	553
Total HxCDD	130	67	ND (45,300)	65.7	7,620
Total HpCDD	200	155	203,300	67,892	67,892
Total OCDD	1355	353	344,000	115,252	115,252
Total TCDF	763	694	25,000	8,831	8,831
Total PeCDF	230	736	47,900	16,294	16,294
Total HxCDF	524	268	169,200	56,670	56,670
Total HpCDF	509	76	150,700	50,414	50,414
Total OCDF	397	104	140,300	46,932	46,932
Total CDD/CDF (ND = zero)	4,340	2,778	1,080,500	362,538	
Total CDD/CDF (ND = ½ det limit)	4,340	2,778	1,104,700		370,596

ND = Not detected; value in parentheses is the detection limit.

Ref. A: Schwind et al. (1991); Hutzinger et al. (1992)
Ref. B: Lew (1993, 1996)

Table 4-4. Leaded Gasoline-Fueled Automobile CDD/CDF Congener Emission Factors

Congener/Congener Group	Automotive Tailpipe Emission Study Results							Mean Emission Factors	
	FTP cycle (Ref. A) (pg/L)	63 km/hr (Ref. B) (pg/L)	Idling (test no. 12) (Ref. C) (pg/L)	Full load (test no. 13) (Ref. C) (pg/L)	64 km/hr (test no. 14) (Ref. C) (pg/L)	Rated power (test no. 15) (Ref. C) (pg/L)	FTP cycle (test no. 22) (Ref. C) (pg/L)	Assuming ND = zero (pg/L)	Assuming ND = ½ det limit (pg/L)
2,3,7,8-TCDD	ND	128	NR	60	141	NR	5	67	68
1,2,3,7,8-PeCDD	(14.4)	425	43	106	468	40	73	165	168
1,2,3,4,7,8-HxCDD	ND (36)	188	17	15	206	16	41	69	73
1,2,3,6,7,8-HxCDD	ND (54)	207	32	35	228	30	62	85	89
1,2,3,7,8,9-HxCDD	ND (54)	188	NR	NR	206	NR	35	107	114
1,2,3,4,6,7,8-HpCDD	ND (54)	503	119	136	554	111	518	277	281
OCDD	ND (54) ND (90)	498	380	513	549	1166	1,581	670	676
2,3,7,8-TCDF	432	1,542	NR	678	1,697	78	214	774	774
1,2,3,7,8-PeCDF	21.6	1,081	49	367	1,190	45	218	425	425
2,3,4,7,8-PeCDF	43.2	447	26	156	492	24	225	202	202
1,2,3,4,7,8-HxCDF	ND (54)	856	33	70	942	31	381	330	334
1,2,3,6,7,8-HxCDF	ND (54)	856	22	60	942	20	375	325	329
1,2,3,7,8,9-HxCDF	ND (54)	ND (76)	NR	NR	NR	NR	85	28	50
2,3,4,6,7,8-HxCDF	ND (54)	273	NR	25	301	NR	1,033	326	332
1,2,3,4,6,7,8-HpCDF	ND (54)	4,051	170	NR	4,460	158	2,301	1857	1861
1,2,3,4,7,8,9-HpCDF	ND (54)	ND (76)	NR	NR	NR	NR	109	36	58
OCDF	ND (90)	230	1115	NR	253	447	1,128	529	536
Total 2,3,7,8-CDD	ND	2,137	≥ 591	≥ 865	2,352	≥ 1,363	2,315	1,440	1,469
Total 2,3,7,8-CDF	496.8	9,336	≥ 1,415	≥ 1,356	≥ 10,277	≥ 803	6,069	4,832	4,900
Total I-TEQ_{DF} (ND = zero)	65.9	1,075	≥ 52	≥ 300	≥ 1,184	≥ 56	419	≥ 450	
Total I-TEQ_{DF} (ND = ½ det limit)	102	1,080	≥ 52	≥ 300	≥ 1,184	≥ 56	419		≥ 456
Total TEQ_{DF}-WHO_{98} (ND = zero)	65.9	1,287	≥ 72	≥ 352	≥ 1,417	≥ 75	454	≥ 532	
Total TEQ_{DF}-WHO_{98} (ND = ½ det limit)	111	1,291	≥ 72	≥ 352	≥ 1,417	≥ 75	454		≥ 539
Total TCDD	5,220	4,555	517	8,134	5,012	4,558	921	4,131	4,131
Total PeCDD	ND (360)	3,338	658	2,161	3,675	6,389	359	2,369	2,394
Total HxCDD	ND (540)	1,868	354	623	2,056	1,973	996	1,124	1,163
Total HpCDD	ND (90)	1,164	194	297	1,281	2,374	988	900	906
Total OCDD	ND (90)	498	380	513	549	1,166	1,581	670	676
Total TCDF	15,300	50,743	2,167	20,513	55,857	29,353	4,290	25,460	25,460
Total PeCDF	2,430	11,591	452	3,608	12,757	10,580	3,165	6,369	6,369
Total HxCDF	ND (540)	6,308	192	477	6,947	12,553	3,132	4,230	4,268
Total HpCDF	ND (270)	5,642	170	NR	6,210	4,767	2,920	3,285	3,307
Total OCDF	ND (90)	230	1,115	NR	253	447	1,128	529	536
Total CDD/CDF (ND = zero)	22,950	85,937	6,199	≥ 36,326	94,597	74,160	19,480	≥ 49,066	
Total CDD/CDF (ND = ½ det limit)	23,940	85,937	6,199	≥ 36,326	94,597	74,160	19,480		≥ 49,212

NR = Not reported.
ND = Not detected; value in parentheses is the reported detection limit.

Ref. A: Marklund et al. (1990); values in the table were calculated from the reported units of pg/km to pg/L using a fuel economy of 9 km/L for leaded gas as reported in Marklund et al. (1990).
Ref. B: Hagenmaier et al. (1990)

Table 4-5. Unleaded Gasoline-Fueled (Without Catalytic Converters) Automobile CDD/CDF Congener Emission Factors

Congener/Congener Group	Automotive Tailpipe Emission Study Results						Mean Emission Factors	
	FTP cycle (Ref. A) (pg/L)	63 km/hr (Ref. B) (pg/L)	FTP cycle (test no. 21) (Ref. C) (pg/L)	64 km/hr (test no. 17) (Ref. C) (pg/L)	64 km/hr (test no. 20) (Ref. C) (pg/L)	64 km/hr (test no. 31/2) (Ref. C) (pg/L)	Assuming ND = zero (pg/L)	Assuming ND = ½ det limit (pg/L)
2,3,7,8-TCDD	ND (5)	2.6	24	44	7	8.9	14.4	14.8
1,2,3,7,8-PeCDD	ND (3)	19.1	14	31	11	14.1	14.9	15.1
1,2,3,4,7,8-HxCDD	ND (40)	16.6	24	26	25	16.3	18.0	21.3
1,2,3,6,7,8-HxCDD	ND (40)	17.1	84	28	42	60.1	38.5	41.9
1,2,3,7,8,9-HxCDD	ND (40)	17.6	15	29	23	17.1	17.0	20.3
1,2,3,4,6,7,8-HpCDD	ND (40)	40.4	192	66	121	197.8	103	106
OCDD	ND (50)	176	868	280	685	2,634	774	778
2,3,7,8-TCDF	64	44.0	70	71	77	295.2	104	104
1,2,3,7,8-PeCDF	ND (7)	44.5	40	72	69	161.8	64.6	65.1
2,3,4,7,8-PeCDF	ND (7)	20.7	30	34	184	135.2	67.3	67.9
1,2,3,4,7,8-HxCDF	ND (40)	41.9	68	68	88	129.1	65.8	69.2
1,2,3,6,7,8-HxCDF	ND (40)	21.2	62	34	35	113.2	44.2	47.6
1,2,3,7,8,9-HxCDF	ND (40)	37.8	47	61	ND (1)	36.9	30.5	33.9
2,3,4,6,7,8-HxCDF	ND (40)	54.3	55	88	42	82.1	53.6	56.9
1,2,3,4,6,7,8-HpCDF	ND (40)	27.9	278	45	22	418.0	132	135
1,2,3,4,7,8,9-HpCDF	ND (40)	16.6	ND (1)	27	24	54.5	20.4	23.8
OCDF	ND (70)	119	374	194	288	991	328	334
Total 2,3,7,8-CDD	ND	289.4	1,221	504	914	2,948	979	998
Total 2,3,7,8-CDF	64	427.9	1,024	694	829	2,417	909	936
Total I-TEQ_{DF} (ND = zero)	6.4	50.9	96.4	122	144	177	99.5	
Total I-TEQ_{DF} (ND = ½ det limit)	26.2	50.9	96.4	122	144	177		103
Total TEQ_{DF}-WHO_{98} (ND = zero)	6.4	60.2	102	138	148	181	106	
Total TEQ_{DF}-WHO_{98} (ND = ½ det limit)	26.9	60.2	102	138	148	181		109
Total TCDD	13	435	429	706	500	304	398	398
Total PeCDD	ND (3)	481	837	784	542	170	469	469
Total HxCDD	ND (40)	305	484	496	563	114	327	330
Total HpCDD	ND (10)	93	392	147	225	301	193	194
Total OCDD	ND (5)	176	868	280	685	2,634	774	774
Total TCDF	170	569	718	923	478	6,379	1540	1540
Total PeCDF	ND (7)	931	531	1,513	437	1,969	897	897
Total HxCDF	ND (40)	378	165	615	258	1,226	440	444
Total HpCDF	ND (20)	476	278	773	445	1,088	510	512
Total OCDF	ND (7)	119	374	194	288	991	328	328
Total CDD/CDF (ND = zero)	183	3,963	5,076	6,431	4,421	15,176	5875	
Total CDD/CDF (ND = ½ det limit)	249	3,963	5,076	6,431	4,421	15,176		5886

ND = Not detected; value in parentheses is the reported detection limit.

Ref. A: Marklund et al. (1990); the pg/L values in the table were calculated from the reported units of pg/km assuming a fuel economy of 10 km/L for unleaded gas.

Table 4-6. Unleaded Gasoline-Fueled (With Catalytic Converters) Automobile CDD/CDF Congener Emission Factors

Congener/Congener Group	Automotive Tailpipe Emission Study Test Results				Mean Emission Factors	
	63 km/hr (Ref. A) (pg/L)	64 km/hr (test no. 29I) (Ref. B) (pg/L)	64 km/hr (test no. 30/2) (Ref. B) (pg/L)	64 km/hr (test no. 18) (Ref. B) (pg/L)	Assuming ND = zero (pg/L)	Assuming ND = ½ det limit (pg/L)
2,3,7,8-TCDD	1.6	3.0	ND (7.9)	14	4.7	5.6
1,2,3,7,8-PeCDD	1.6	2.6	ND (7.9)	4	2.1	3.0
1,2,3,4,7,8-HxCDD	2.4	5.3	ND (7.9)	1	2.2	3.2
1,2,3,6,7,8-HxCDD	3.5	6.0	6.4	2	4.5	4.5
1,2,3,7,8,9-HxCDD	3.1	6.0	ND (7.9)	2	2.8	3.8
1,2,3,4,6,7,8-HpCDD	15.3	27.8	78.1	14	33.8	33.8
OCDD	170	275	427	197	267	267
2,3,7,8-TCDF	4.3	10.6	12.7	35	15.7	15.7
1,2,3,7,8-PeCDF	3.3	8.7	5.1	13	7.5	7.5
2,3,4,7,8-PeCDF	2.4	7.2	6.2	6	5.5	5.5
1,2,3,4,7,8-HxCDF	4.8	10.6	4.5	5	6.2	6.2
1,2,3,6,7,8-HxCDF	6.3	9.1	3.9	7	6.6	6.6
1,2,3,7,8,9-HxCDF	0.2	ND (3.8)	2.1	5	1.8	2.3
2,3,4,6,7,8-HxCDF	4.6	18.1	8.2	ND (1)	7.7	7.9
1,2,3,4,6,7,8-HpCDF	16.3	54.3	154.2	51	69.0	69.0
1,2,3,4,7,8,9-HpCDF	ND (0.2)	ND (3.8)	7.9	1	2.2	2.7
OCDF	27.9	38	106	140	78.0	78.0
Total 2,3,7,8-CDD	197.5	325.7	511.5	234	317	321
Total 2,3,7,8-CDF	70.1	156.6	310.8	263	200	201
Total I-TEQ_{DF} (ND = zero)	7.2	16.0	10.1	26.3	14.9	
Total I-TEQ_{DF} (ND = ½ det limit)	7.2	16.2	16.8	26.4		16.6
Total TEQ_{DF}-WHO_{98} (ND = zero)	7.8	17.1	9.6	28.0	15.6	
Total TEQ_{DF}-WHO_{98} (ND = ½ det limit)	7.8	17.3	18.3	28.1		17.9
Total TCDD	28.6	51	13	82	43.7	43.7
Total PeCDD	25.5	51	ND (15)	101	44.4	46.3
Total HxCDD	26.3	56	36	50	42.1	42.1
Total HpCDD	38.7	50	163	25	69.2	69.2
Total OCDD	170	275	427	197	267.3	267.3
Total TCDF	52.6	152	79	332	153.9	153.9
Total PeCDF	53.4	122	29	84	72.1	72.1
Total HxCDF	33.3	71	60	39	50.8	50.8
Total HpCDF	27.1	62	174	83	86.5	86.5
Total OCDF	27.9	38	106	140	78.0	78.0
Total CDD/CDF (ND = zero)	483.4	928	1,095	1,133	910	
Total CDD/CDF (ND = ½ det limit)	483.4	928	1,087	1,133		945

ND = Not detected; value in parentheses is the reported detection limit.
Ref. A: Hagenmaier et al. (1990)
Ref. B: Schwind et al. (1991); Hutzinger et al. (1992)

Table 4-7. European Tunnel Study Test Results

Congener/Congener Group	Tunnel Air Germany (Ref. A) (pg/m3)	Tunnel Air Germany (Ref. A) (pg/m3)	Tunnel Air Belgium (Ref. B) (pg/m3)	Tunnel Air Norway (workdays)[a] (Ref. C) (pg/m3)	Tunnel Air Norway (weekend)[a] (Ref. C) (pg/m3)
2,3,7,8-TCDD	ND (0.01)	0.06	0.002	0.02	0.02
1,2,3,7,8-PeCDD	0.31	0.28	0.025	0.18	0.04
1,2,3,4,7,8-HxCDD	0.37	ND (0.17)	0.025	0.06	0.03
1,2,3,6,7,8-HxCDD	1.19	0.66	0.042	0.29	0.03
1,2,3,7,8,9-HxCDD	0.44	ND (0.17)	0.030	0.25	0.06
1,2,3,4,6,7,8-HpCDD	1.9	2.0	0.468	1.41	0.16
OCDD	6.3	6.4	2.190	0.10	0.50
2,3,7,8-TCDF	0.17	0.72	0.013	0.58	0.07
1,2,3,7,8-PeCDF	0.40	0.36	0.143	0.83	0.75
2,3,4,7,8-PeCDF	0.19	NR	0.039	0.78	0.58
1,2,3,4,7,8-HxCDF	0.26	0.13	0.073	0.79	0.34
1,2,3,6,7,8-HxCDF	0.16	0.15	0.093	0.62	0.31
1,2,3,7,8,9-HxCDF	ND (0.04)	ND (0.05)	0.143	0.04	0.03
2,3,4,6,7,8-HxCDF	0.12	ND (0.05)	0.004	0.74	0.13
1,2,3,4,6,7,8-HpCDF	1.2	0.98	0.499	1.78	0.93
1,2,3,4,7,8,9-HpCDF	ND (0.16)	ND (0.17)	0.074	0.22	0.14
OCDF	ND (1.3)	ND (1.0)	0.250	1.62	2.54
Total 2,3,7,8-CDD	10.51	9.40	2.782	2.31	0.84
Total 2,3,7,8-CDF	2.50	2.34	1.330	7.98	5.82
Total I-TEQ_{DF} (ND = zero)	0.58	0.42	0.096	0.91	0.48
Total I-TEQ_{DF} (ND = 1/2 det limit)	0.59	0.44	0.096	0.91	0.48
Total TEQ_{DF}-WHO_{98} (ND = zero)	0.73	0.55	0.106	1.00	0.49
Total TEQ_{DF}-WHO_{98} (ND = 1/2 det limit)	0.74	0.58	0.106	1.00	0.49
Total TCDD	0.23	0.22	NR	0.26	0.16
Total PeCDD	2.5	1.3	NR	1.78	0.41
Total HxCDD	7.8	2.7	NR	1.32	0.12
Total HpCDD	3.4	3.4	NR	1.31	0.23
Total OCDD	6.3	6.4	NR	0.10	0.50
Total TCDF	3.5	6.2	NR	13.20	1.70
Total PeCDF	3.6	4.1	NR	10.17	7.91
Total HxCDF	2.0	1.1	NR	6.42	2.08
Total HpCDF	1.9	1.2	NR	2.62	1.41
Total OCDF	ND (1.3)	ND (1.0)	NR	1.62	2.54
Total CDD/CDF (ND = zero)	31.2	26.6	NR	38.80	17.06
Total CDD/CDF (ND = 1/2 det limit)	31.9	27.1	NR	38.80	17.06

ND = Not detected; value in parentheses is the detection limit.

Ref. A: Rappe et al. (1988)
Ref. B: Wevers et al. (1992)
Ref. C: Oehme et al. (1991)

[a] Listed values are the differences between the concentrations at the inlet and outlet of the northbound tunnel lanes.

Table 4-8. Baltimore Harbor Tunnel Study: Estimated Emission Factors for Heavy-Duty (HD) Diesel Vehicles

Congener/Congener Group	Run-Specific Emission Factors							Mean Emission Factors (pg/km)
	Run No. 2 (pg/km)	Run No. 3 (pg/km)	Run No. 5 (pg/km)	Run No. 6 (pg/km)	Run No. 8 (pg/km)	Run No. 9 (pg/km)	Run No. 10 (pg/km)	
2,3,7,8-TCDD	24.5	61.6	0.0	21.2	37.8	40.1	54.9	34.3
1,2,3,7,8-PeCDD	40.2	20.6	15.4	5.6	38.4	0.0	83.0	29.0
1,2,3,4,7,8-HxCDD	18.2	25.2	46.5	8.3	64.5	0.0	123	40.8
1,2,3,6,7,8-HxCDD	37.5	28.2	64.3	19.6	153	71.1	186	80.0
1,2,3,7,8,9-HxCDD	53.6	56.5	91.6	48.4	280	126	370	147
1,2,3,4,6,7,8-HpCDD	0	401	729	111	2,438	963	2,080	960
OCDD	0	3,361	3,382	1,120	9,730	5,829	7,620	4,435
2,3,7,8-TCDF	0	94.3	67.6	152.8	155.8	73.4	61.7	86.5
1,2,3,7,8-PeCDF	0	48.9	72.6	23.6	53.3	0.0	43.3	34.5
2,3,4,7,8-PeCDF	24.5	75.7	131	46.6	85.0	63.9	108	76.4
1,2,3,4,7,8-HxCDF	15.4	139	204	93.8	124	164	166	129
1,2,3,6,7,8-HxCDF	0.3	75.1	73.7	51.0	61.3	54.4	95.5	58.8
1,2,3,7,8,9-HxCDF	27.7	14.8	75.6	0	20.6	37.2	63.5	34.2
2,3,4,6,7,8-HxCDF	15.2	82.5	152	55.7	93.0	86.8	111	85.2
1,2,3,4,6,7,8-HpCDF	12.6	280	445	154	313	354	308	267
1,2,3,4,7,8,9-HpCDF	0	58.5	60.8	31.1	25.0	2.3	34.9	30.4
OCDF	0	239	401	175	416	534	370	305
Total 2,3,7,8-CDD	174	3,954	4,328	1,335	12,743	7,028	10,515	5,725
Total 2,3,7,8-CDF	95.7	1,108	1,684	784	1,347	1,371	1,362	1,107
Total I-TEQ_{DF}	73.8	175	170	96	235	153	303	172
Total TEQ_{DF}-WHO_{98}	93.8	182	175	97	245	147	337	182
Total TCDD	245	0	140	165	311	109	97.3	152
Total PeCDD	110	21.9	83.3	35.6	174	0.0	165	84.2
Total HxCDD	677	0	753	54.5	2,009	1,666	2,971	1,162
Total HpCDD	0	802	1,498	142	5,696	1,933	4,377	2,064
Total OCDD	0	3361	3,382	1,120	9,730	5,829	7,620	4,435
Total TCDF	0	901	1,314	656	2,416	1,007	687	997
Total PeCDF	124	119	1,152	78.4	1,055	282	626	491
Total HxCDF	136	319	852	67.6	444	719	619	451
Total HpCDF	0	223	814	144	513	354	637	384
Total OCDF	0	239	401	175	416	534	370	305
Total CDD/CDF	1,291	5,987	10,390	2,638	22,766	12,434	18,168	10,525
HD vehicles as % of total vehicles	21.2	22.0	22.6	34.0	28.8	24.2	27.4	25.7

Source: Gertler et al. (1996, 1998)

Notes:
1) Listed values are based on the difference between the calculated chemical mass entering the tunnel and the mass exiting the tunnel.
2) All calculated negative emission factors were set equal to zero.
3) All CDD/CDF emissions were assumed to result from heavy-duty diesel fueled vehicles. The table presents in the last row the percent of total traffic that was heavy-duty vehicles.

Table 4-9. CDD/CDF Emission Factors for Industrial Wood Combustors

Congener	Four Facilities Tested by CARB Mean Emission Factors (ng/kg wood)		Five Facilities Tested by NCASI Mean Emission Factors (ng/kg wood)		Nine Facilities Tested by CARB and NCASI Mean Emission Factors (ng/kg wood)	
	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit
2,3,7,8-TCDD	0.007	0.016	0.066	0.068	0.040	0.046
1,2,3,7,8-PeCDD	0.044	0.054	0.110	0.112	0.079	0.084
1,2,3,4,7,8-HxCDD	0.042	0.055	0.179	0.183	0.115	0.123
1,2,3,6,7,8-HxCDD	0.086	0.096	0.191	0.193	0.138	0.143
1,2,3,7,8,9-HxCDD	0.079	0.132	0.522	0.524	0.321	0.342
1,2,3,4,6,7,8-HpCDD	0.902	0.905	0.635	0.637	0.745	0.748
OCDD	6.026	6.026	1.317	1.317	3.329	0.329
2,3,7,8-TCDF	0.673	0.673	0.707	0.719	0.684	0.690
1,2,3,7,8-PeCDF	0.790	0.790	0.145	0.149	0.406	0.409
2,3,4,7,8-PeCDF	0.741	0.741	0.159	0.164	0.389	0.392
1,2,3,4,7,8-HxCDF	0.761	0.768	0.108	0.111	0.375	0.379
1,2,3,6,7,8-HxCDF	0.941	0.941	0.071	0.073	0.418	0.419
1,2,3,7,8,9-HxCDF	0.343	0.350	0.064	0.067	0.178	0.183
2,3,4,6,7,8-HxCDF	0.450	0.491	0.015	0.017	0.192	0.209
1,2,3,4,6,7,8-HpCDF	2.508	2.749	0.072	0.074	1.062	1.155
1,2,3,4,7,8,9-HpCDF	0.260	0.344	0.017	0.020	0.113	0.152
OCDF	1.587	1.590	0.049	0.060	0.674	0.681
Total TCDD	0.151	0.154	1.628	1.629	0.969	0.970
Total PeCDD	1.039	1.039	1.958	1.980	1.521	1.533
Total HxCDD	1.748	1.748	1.792	1.796	1.663	1.665
Total HpCDD	2.936	2.936	1.120	1.132	1.821	1.823
Total OCDD	6.026	6.026	1.317	1.317	3.329	0.329
Total TCDF	4.275	4.275	4.532	4.552	4.353	4.364
Total PeCDF	9.750	9.750	1.548	1.549	4.930	4.930
Total HxCDF	7.428	7.428	0.536	0.543	3.316	3.320
Total HpCDF	3.747	3.988	0.111	0.116	1.580	1.674
Total OCDF	1.588	1.590	0.049	0.060	0.674	0.681
Total I-TEQ_{DF}	0.82	0.85	0.40	0.41	0.56	0.58
Total TEQ_{DF}-WHO_{98}	0.84	0.87	0.46	0.46	0.60	0.62
Total CDD/CDF	38.69	38.93	14.593	14.674	24.155	24.294

Sources: CARB (1990b); CARB (1990e); CARB (1990f); CARB (1990g); NCASI (1995)

Table 4-10. CDD/CDF Concentrations in Residential Chimney Soot from Wood Stoves and Fireplaces

Congener/Congener Group	U.S. East Region (Ref. A) (ng/kg)	U.S. West Region (Ref. A) (ng/kg)	U.S. Central Region (Ref. A) (ng/kg)	German Farmhouse (Ref. B) (ng/kg)	Canadian Wood Stove (Ref. C) (ng/kg)	Canadian Fireplace (Ref. C) (ng/kg)	Canadian Wood Stove (Ref. D) (ng/kg)
2,3,7,8-TCDD	66	13.3	66	150	NR	NR	ND (12)
1,2,3,7,8-PeCDD	NR	NR	NR	70	NR	NR	70
1,2,3,4,7,8-HxCDD	250*	522*	1,831*	35	NR	NR	ND (10)
1,2,3,6,7,8-HxCDD	250*	522*	1,831*	60	NR	NR	625
1,2,3,7,8,9-HxCDD	208	282	1,450	30	NR	NR	281
1,2,3,4,6,7,8-HpCDD	1,143	1,653	6,160	90	NR	NR	948
OCDD	2,033	2,227	13,761	90	NR	NR	530
2,3,7,8-TCDF	NR	NR	NR	930	NR	NR	235
1,2,3,7,8-PeCDF	NR	NR	NR	560	NR	NR	58
2,3,4,7,8-PeCDF	NR	NR	NR	590	NR	NR	68
1,2,3,4,7,8-HxCDF	NR	NR	NR	330	NR	NR	51
1,2,3,6,7,8-HxCDF	NR	NR	NR	400	NR	NR	57
1,2,3,7,8,9-HxCDF	NR	NR	NR	70	NR	NR	8
2,3,4,6,7,8-HxCDF	NR	NR	NR	200	NR	NR	24
1,2,3,4,6,7,8-HpCDF	NR	NR	NR	490	NR	NR	97
1,2,3,4,7,8,9-HpCDF	NR	NR	NR	40	NR	NR	20
OCDF	NR	NR	NR	70	NR	NR	41
Total 2,3,7,8-CDD	3,450	4,175	21,437	525	NR	NR	2,454
Total 2,3,7,8-CDF	NR	NR	NR	3,680	NR	NR	659
Total I-TEQ_{Df}	≥125	≥112	≥479	720	NR	NR	211
Total TEQ_{DF}-WHO_{98}	≥123	≥110	≥467	755	NR	NR	246
Total TCDD	1,987	269	1,511	3,900	ND (10)	ND (10)	11
Total PeCDD	NR	NR	NR	880	ND (10)	500	608
Total HxCDD	2,183	4,273	14,243	600	ND (50)	1,700	3,450
Total HpCDD	2,104	3,243	12,603	200	100	500	1,550
Total OCDD	2,033	2,227	13,761	90	200	400	530
Total TCDF	NR	NR	NR	13,400	ND (10)	300	1,010
Total PeCDF	NR	NR	NR	6,100	ND (10)	1,400	948
Total HxCDF	NR	NR	NR	3,200	ND (50)	1,700	482
Total HpCDF	NR	NR	NR	720	ND (50)	400	154
Total OCDF	NR	NR	NR	70	ND (50)	100	41
Total CDD/CDF	8,307	10,012	42,118	29,160	300	7,000	8,783

NR = Not reported.
* = Analytical method could not distinguish between congeners; listed value is the sum of both congeners.

Ref. A: Nestrick and Lamparski (1982, 1983); mean values listed - six samples collected in each Region.
Ref. B: Bacher et al. (1992)
Ref. C: Clement et al. (1985b)
Ref. D: Van Oostdam and Ward (1995); mean of two samples - nondetected values assumed to be zero.

Table 4-11. CDD/CDF Concentrations in Residential Bottom Ash from Wood Stoves and a Fireplace

Congener/Congener Group	Canadian Wood Stove Ash (ng/kg)	Canadian Wood Stove Ash (ng/kg)	Canadian Wood Stove Ash (ng/kg)	Canadian Fireplace Ash (ng/kg)
2,3,7,8-TCDD	NR	NR	NR	NR
1,2,3,7,8-PeCDD	NR	NR	NR	NR
1,2,3,4,7,8-HxCDD	NR	NR	NR	NR
1,2,3,6,7,8-HxCDD	NR	NR	NR	NR
1,2,3,7,8,9-HxCDD	NR	NR	NR	NR
1,2,3,4,6,7,8-HpCDD	NR	NR	NR	NR
OCDD	NR	NR	NR	NR
2,3,7,8-TCDF	NR	NR	NR	NR
1,2,3,7,8-PeCDF	NR	NR	NR	NR
2,3,4,7,8-PeCDF	NR	NR	NR	NR
1,2,3,4,7,8-HxCDF	NR	NR	NR	NR
1,2,3,6,7,8-HxCDF	NR	NR	NR	NR
1,2,3,7,8,9-HxCDF	NR	NR	NR	NR
2,3,4,6,7,8-HxCDF	NR	NR	NR	NR
1,2,3,4,6,7,8-HpCDF	NR	NR	NR	NR
1,2,3,4,7,8,9-HpCDF	NR	NR	NR	NR
OCDF	NR	NR	NR	NR
Total 2,3,7,8-CDD	NR	NR	NR	NR
Total 2,3,7,8-CDF	NR	NR	NR	NR
Total TEQ	NR	NR	NR	NR
Total TCDD	ND (10)	100	100	ND (10)
Total PeCDD	ND (10)	3,000	200	ND (10)
Total HxCDD	ND (50)	10,000	700	300
Total HpCDD	300	1,200	500	2,000
Total OCDD	2,600	900	100	3,100
Total TCDF	9,100	400	100	ND (10)
Total PeCDF	2,200	4,600	200	ND (10)
Total HxCDF	1,000	9,300	500	100
Total HpCDF	700	1,000	300	400
Total OCDF	ND (50)	100	ND (50)	100
Total CDD/CDF	15,900	30,600	2,700	6,000

NR = Not reported.
Source: Clement et al. (1985b)

Table 4-12. CDD/CDF Concentrations in Chimney Soot (Bavaria, Germany)

Unit Type	Fuel Type	Number of Samples	CDD/CDF Concentrations in Soot (ng I-TEQ$_{DF}$/kg)		
			Minimum	Mean	Maximum
Oven	Wood	33	10.4	2,015	15,849
Tiled Stove	Wood	39	4.0	3,453	42,048
Heating System	Wood	9	16.9	1,438	20,450
Oven	Wood/coal	27	77.3	2,772	10,065
Tiled Stove	Wood/coal	5	53.1	549	4,911
Oven	Wood, wood/coal, waste	5	116.3	6,587	10,652

Source: Dumler-Gradl et al. (1995a).

Table 4-13 Fly Ash from Wood Working Industry
(Concentrations in ng/kg)

Congener	Concentration	I-TEQ_{DF}	TEQ_{DF}-WHO_{98}
2,3,7,8-TCDD	<15	<15	<15
Total TCDD	1,730	-	-
1,2,3,7,8-PeCDD	100	50	100
Total PeCDD	1,250	-	-
1,2,3,4,7,8-HxCDD	130	13	13
1,2,3,6,7,8-HxCDD	150	15	15
1,2,3,7,8,9-HxCDD	140	14	14
Total HxCDD	750	-	-
1,2,3,4,6,7,8-HpCDD	280	3	3
Total HpCDD	470	-	-
Total OCCD	300	0.3	0.03
TOTAL TCDD TEQs		**95-110**	**145-160**
2,3,7,8-TCDF	130	13	13
Total TCDF	1,300	-	-
1,2,3,7,8-PeCDF	100	5	5
2,3,4,7,8-PeCDF	120	60	60
Total PeCDF	790	-	-
1,2,3,4,7,8-HxCDF	40	4	4
1,2,3,7,8,9-HxCDF	40	4	4
1,2,3,6,7,8-HxCDF	<10	<1	<1
Total HxCDF	150	-	-
1,2,3,4,6,7,8-HpCDF	320	3	3
1,2,3,4,7,8,9-HpCDF	<10	<0.1	<0.1
Total HpCDF	570	-	-
Total OCDF	60	0.06	0.006
TOTAL CDF TEQs		**89-90**	**89-90**

Table 4-14. Electrostatic Precipitator Waste Ash from Wood-Fired Industrial Boiler

	Average[a] Concentration (ng/kg)	I-TEQ_{DF} Concentration (ng/kg)	TEQ_{DF}-WHO_{98} Concentration (ng/kg)
2,3,7,8-TCDD	17.85	17.85	17.85
Total TCDD	239.00	-	-
1,2,3,7,8-PeCDD	30.67	15.33	30.67
Total PeCDD	226.83	-	-
1,2,3,4,7,8-HxCDD	20.33	2.03	2.03
1,2,3,6,7,8-HxCDD	26.33	2.63	2.63
1,2,3,7,8,9-HxCDD	23.33	2.33	2.33
Total HxCDD	300.00	-	-
1,2,3,4,6,7,8-HpCDD	325.00	3.25	3.25
Total HpCDD	706.67	-	-
Total OCDD	786.67	0.79	0.08
Total CDD	2,439.17	44.22	58.85
2,3,7,8-TCDF	285.00	28.50	28.50
Total TCDF	2,713.33	-	-
1,2,3,7,8-PeCDF	154.50	7.73	7.73
2,3,4,7,8-PeCDF	641.67	320.83	320.83
Total PeCDF	2,666.67	-	-
1,2,3,4,7,8-HxCDF	244.83	24.48	24.48
1,2,3,6,7,8-HxCDF	179.67	17.97	17.97
2,3,4,6,7,8-HxCDF	296.67	29.67	29.67
1,2,3,7,8,9-HxCDF	7.28	0.73	0.73
Total HxCDF	1,520.00	-	-
1,2,3,4,6,7,8-HpCDF	147.67	1.48	1.48
1,2,3,4,7,8,9-HpCDF	21.33	0.21	0.21
Total HpCDF	248.33	-	-
Total OCDF	48.33	0.05	0.00
Total CDF	7,196.67	431.64	431.60
Total Dioxins/Furans		475.86	490.44

a Calculated from data in Table 30 of CARB 1990e).

Table 4-15. Estimated CDD/CDF Emission Factors for Oil-Fired Residential Furnaces

Congener/Congener Group	Mean Facility Emission Factor (pg/L oil)
2,3,7,8-TCDD	56
1,2,3,7,8-PeCDD	NR
1,2,3,4,7,8-HxCDD	NR
1,2,3,6,7,8-HxCDD	NR
1,2,3,7,8,9-HxCDD	NR
1,2,3,4,6,7,8-HpCDD	NR
OCDD	66
2,3,7,8-TCDF	53
1,2,3,7,8-PeCDF	NR
2,3,4,7,8-PeCDF	NR
1,2,3,4,7,8-HxCDF	NR
1,2,3,6,7,8-HxCDF	NR
1,2,3,7,8,9-HxCDF	NR
2,3,4,6,7,8-HxCDF	NR
1,2,3,4,6,7,8-HpCDF	NR
1,2,3,4,7,8,9-HpCDF	NR
OCDF	30
Total 2,3,7,8-CDD	NR
Total 2,3,7,8-CDF	NR
Total I-TEQ_{DF}	150
Total TCDD	139
Total PeCDD	82
Total HxCDD	66
Total HpCDD	63
Total OCDD	66
Total TCDF	663
Total PeCDF	420
Total HxCDF	170
Total HpCDF	73
Total OCDF	30
Total CDD/CDF	1,772

NR = Not reported.

Source: U.S. EPA (1997b)

Table 4-16. CDD/CDF Emission Factors for Oil-Fired Utility/Industrial Boilers

Congener/Congener Group	U.S. EPA (1997b) Median Emission Factor (pg/L oil)	EPRI (1994) Mean Emission Factor	
		ND = zero (pg/L oil)	ND = ½ DL (pg/L oil)
2,3,7,8-TCDD	117	0	26.6
1,2,3,7,8-PeCDD	104	24.7	43.1
1,2,3,4,7,8-HxCDD	215	63.3	108
1,2,3,6,7,8-HxCDD	97	65.8	79.3
1,2,3,7,8,9-HxCDD	149	79.7	102
1,2,3,4,6,7,8-HpCDD	359	477	546
OCDD	413	2055	2141
2,3,7,8-TCDF	83	0	35.7
1,2,3,7,8-PeCDF	77	64.1	73.9
2,3,4,7,8-PeCDF	86	49.3	59.6
1,2,3,4,7,8-HxCDF	109	76.5	94.9
1,2,3,6,7,8-HxCDF	68	35.4	45.2
1,2,3,7,8,9-HxCDF	104	0	37.7
2,3,4,6,7,8-HxCDF	86	23.8	42.2
1,2,3,4,6,7,8-HpCDF	169	164	218
1,2,3,4,7,8,9-HpCDF	179	0	137
OCDF	179	0	139
Total 2,3,7,8-CDD	1,453	2,766	3,047
Total 2,3,7,8-CDF	1,141	414	883
Total I-TEQ_{DF}	314	83.1	147
Total TEQ_{DF}-WHO_{98}	366	93.6	167
Total TCDD	102	NR	NR
Total PeCDD	104	NR	NR
Total HxCDD	145	NR	NR
Total HpCDD	359	NR	NR
Total OCDD	413	NR	NR
Total TCDF	90	NR	NR
Total PeCDF	131	NR	NR
Total HxCDF	172	NR	NR
Total HpCDF	27	NR	NR
Total OCDF	179	NR	NR
Total CDD/CDF	1,722	3,179	3,931

Sources:

U.S. EPA (1997b) - number of facilities not reported.
EPRI (1994) - based on two cold side ESP-equipped power plants.

Note: Assumes a density for residual fuel oil of 0.87 kg/L.

Table 4-17. CDD/CDF Concentrations in Stack Emissions from U.S. Coal-Fired Power Plants

Congener/Congener Group	Plant 1 (pg/Nm^3)	Plant 2 (pg/Nm^3)	Plant 3 (pg/Nm^3)	Plant 4 (pg/Nm^3)	Plant 5 (pg/Nm^3)	Plant 6 (pg/Nm^3)	Plant 7 (pg/Nm^3)
2,3,7,8-TCDD	ND (3.5)	ND (3.5)	1.0	ND (2.0)	ND (3.3)	ND (2.6)	ND (1.7)
1,2,3,7,8-PeCDD	ND (0.56)	ND (4.8)	ND (1.8)	ND (10)	ND (4.7)	ND (3.2)	ND (1.8)
1,2,3,4,7,8-HxCDD	ND (0.56)	ND (5.7)	ND (3.6)	ND (10)	ND (15.4)	ND (2.7)	ND (2.0)
1,2,3,6,7,8-HxCDD	ND (0.44)	5.0	ND (1.8)	ND (10)	ND (9.9)	ND (4.2)	ND (1.4)
1,2,3,7,8,9-HxCDD	ND (0.56)	4.9	ND (1.8)	ND (10)	ND (12.1)	ND (4.3)	ND (1.2)
1,2,3,4,6,7,8-HpCDD	ND (1.7)	29	ND (1.8)	ND (10)	ND (26.4)	4.3	2.4
OCDD	ND (12)	32	ND (14)	ND (20)	ND (131)	20	21.6
2,3,7,8-TCDF	ND (1.7)	8.1	7.8	ND (2.0)	ND (3.3)	13	0.7
1,2,3,7,8-PeCDF	ND (1.0)	ND (5.7)	7.2	ND (10)	ND (3.2)	ND (5.7)	ND (1.1)
2,3,4,7,8-PeCDF	2.4	ND (19)	6.6	ND (10)	ND (3.2)	ND (4.8)	ND (1.4)
1,2,3,4,7,8-HxCDF	3.3	16	8.4	ND (10)	ND (16.4)	ND (5.1)	ND (1.8)
1,2,3,6,7,8-HxCDF	1.1	ND (5.0)	2.9	ND (10)	ND (5.8)	ND (4.0)	ND (1.3)
1,2,3,7,8,9-HxCDF	ND (0.44)	11	ND (1.8)	ND (10)	ND (8.8)	ND (6.9)	ND (1.5)
2,3,4,6,7,8-HxCDF	ND (2.0)	ND (4.2)	3.0	ND (10)	ND (16.4)	ND (2.5)	ND (2.0)
1,2,3,4,6,7,8-HpCDF	2.0	29	6.0	ND (10)	ND (23)	ND (30)	ND (2.2)
1,2,3,4,7,8,9-HpCDF	ND (0.63)	ND (6.1)	ND (3.6)	ND (10)	ND (15.4)	ND (5.0)	ND (2.1)
OCDF	5.6	33	2.4	ND (20)	ND (131)	ND (19)	11.4
Total 2,3,7,8-CDD	0	71	1	0	0	24.3	24
Total 2,3,7,8-CDF	14	97	44.3	0	0	13	12.1
Total TCDD	1.8	12	12	NR	6.7	ND (2.6)	ND (55)
Total PeCDD	ND (1.0)	4.4	6.0	ND (10)	ND (4.7)	ND (3.2)	ND (32)
Total HxCDD	1.3	18	2.7	ND (10)	ND (26.3)	ND (4.0)	ND (24)
Total HpCDD	3.4	45	ND (2.4)	ND (10)	ND (26.4)	ND (14)	ND (8.1)
Total OCDD	ND (12)	32	ND (14)	ND (20)	ND (131)	20	21.6
Total TCDF	ND (5.2)	29	78	ND (2)	ND (3.3)	88	ND (37)
Total PeCDF	5.4	33	61	ND (10)	ND (6.6)	14	3.0
Total HxCDF	7.6	39	29	ND (10)	ND (16.4)	ND (5.0)	ND (27)
Total HpCDF	4.3	34	9.0	ND (10)	ND (29.5)	ND (20)	2.9
Total OCDF	5.6	33	2.4	ND (20)	ND (131)	ND (19)	11.4
Total CDD/CDF	29	279	200.1	0	6.7	122	38.9

ND = Not detected; value in parentheses is the detection limit.
NR = Not reported; suspected contamination problem.
Source: Riggs et al. (1995)

Table 4-18. Characteristics of U.S. Coal-Fired Power Plants Tested by DOE

Plant No.	Coal Type	Coal Chlorine Content (mg/kg)	Temperature (°C) at:			
			Pollution Control Device[a]			Stack
			ESP	Bag	FGD	
1	Bituminous	800	160	--	--	160
2	Bituminous	1,400	130	--	--	130
3	Subbituminous	300	--	150	--	150
4	Subbituminous	390	--	70	130	75
5	Bituminous	1,400	130	--	120	40
6	Lignite	400	170	--	170	110
7	Bituminous	1,000	150	--	--	150

[a] ESP = Electrostatic precipitator, Bag = Baghouse, FGD = Flue gas desulfurization system.

Source: Riggs et al. (1995).

Table 4-19. CDD/CDF Emission Factors for Coal-Fired Utility/Industrial Power Plants

Congener/Congener Group	Mean Emission Factor	
	ND = zero (ng/kg coal)	ND = ½ DL (ng/kg coal)
2,3,7,8-TCDD	0.005	0.018
1,2,3,7,8-PeCDD	0	0.016
1,2,3,4,7,8-HxCDD	0	0.034
1,2,3,6,7,8-HxCDD	0.004	0.028
1,2,3,7,8,9-HxCDD	0.004	0.035
1,2,3,4,6,7,8-HpCDD	0.216	0.241
OCDD	0.513	0.644
2,3,7,8-TCDF	0.109	0.117
1,2,3,7,8-PeCDF	0.007	0.021
2,3,4,7,8-PeCDF	0.074	0.084
1,2,3,4,7,8-HxCDF	0.098	0.120
1,2,3,6,7,8-HxCDF	0.014	0.030
1,2,3,7,8,9-HxCDF	0.013	0.038
2,3,4,6,7,8-HxCDF	0.043	0.060
1,2,3,4,6,7,8-HpCDF	0.354	0.385
1,2,3,4,7,8,9-HpCDF	0.087	0.112
OCDF	0.158	0.281
Total I-TEQ_{DF}	0.079	0.124
Total TEQ_{DF}-WHO_{98}	0.078	0.131
Total TCDD	0.051	0.052
Total PeCDD	0.014	0.015
Total HxCDD	0.030	0.030
Total HpCDD	0.063	0.074
Total OCDD	0.513	0.644
Total TCDF	0.154	0.158
Total PeCDF	0.180	0.180
Total HxCDF	0.104	0.104
Total HpCDF	0.064	0.064
Total OCDF	0.158	0.281
Total CDD/CDF	1.331	1.602

Source: EPRI (1994) - 11 facility data set.

Table 4-20. CDD/CDF Emission Factors from Residential Coal Combustors

Congener/Congener Group	"Salt" Lignite Ref. A (ng/kg coal)	"Normal" Lignite Ref. A (ng/kg coal)	Anthracite Ref. B (ng/kg coal)	Bituminous Ref. B (ng/kg coal)
2,3,7,8-TCDD	0.58	0.06	1.60	2.40
1,2,3,7,8-PeCDD	0.73	0.08	NR	NR
1,2,3,4,7,8-HxCDD	0.63	0.06	NR	NR
1,2,3,6,7,8-HxCDD	0.60	0.09	NR	NR
1,2,3,7,8,9-HxCDD	0.40	0.06	NR	NR
1,2,3,4,6,7,8-HpCDD	3.24	0.59	NR	NR
OCDD	16.19	2.42	77	120
2,3,7,8-TCDF	2.49	0.50	42.0	63.0
1,2,3,7,8-PeCDF	2.24	0.43	NR	NR
2,3,4,7,8-PeCDF	2.09	0.31	NR	NR
1,2,3,4,7,8-HxCDF	0.38	0.13	NR	NR
1,2,3,6,7,8-HxCDF	1.86	0.36	NR	NR
1,2,3,7,8,9-HxCDF	0.07	0.02	NR	NR
2,3,4,6,7,8-HxCDF	1.01	0.12	NR	NR
1,2,3,4,6,7,8-HpCDF	2.59	0.95	NR	NR
1,2,3,4,7,8,9-HpCDF	0.25	0.06	NR	NR
OCDF	0.63	0.30	4.2	6.3
Total 2,3,7,8-CDD*	22.37	3.38	NR	NR
Total 2,3,7,8-CDF*	13.60	3.20	NR	NR
Total I-TEQ_{DF}*	2.74	0.34	60.0	98.5
Total TCDD	14.23	9.00	61.6	92.4
Total PeCDD	14.15	2.22	31	46
Total HxCDD	11.14	1.81	60	90
Total HpCDD	7.06	0.82	57	86
Total OCDD	16.19	2.42	77	120
Total TCDF	80.34	20.33	412	613
Total PeCDF	29.21	8.98	340	550
Total HxCDF	12.72	3.78	130	190
Total HpCDF	3.87	1.27	32	47
Total OCDF	0.63	0.30	4.2	6.3
Total CDD/CDF	189.5	50.9	1,205	1,841

NR = not reported.
* Values as reported in References A and B.

Sources: Ref A: Thub et al. (1995); listed results represent means of three flue gas samples.
Ref B: U.S. EPA (1997b); based on average particulate CDD/CDF concentrations from chimney soot samples collected from seven coal ovens and particulate emission factors for anthracite and bituminous coal combustion.

Table 4-21. Coal-Fired Utility Solid Wastes

	Mean Concentration(1) (ng/kg)	Grams/Year Disposed of in Solid Waste(3) 1987	Grams/Year Disposed of in Solid Waste(2) 1995	I-TEQ_{DF}/Yr (grams) 1995	TEQ_{DF}-WHO_{98}/Yr (grams) 1995
CDDs					
2,3,7,8-TCDD (4)	0.17	10	10	9.72	9.72
1,2,3,7,8-PeCDD (4)	0.25	14	14	7.15	14.30
1,2,3,4,7,8-HxCDD (4)	0.35	20	20	2.00	2.00
1,2,3,6,7,8-HxCDD (4)	0.28	16	16	1.60	1.60
1,2,3,7,8,9-HxCDD (5)	0.30	17	17	1.72	1.72
1,2,3,4,6,7,8-HpCDD (6)	0.59	33	34	0.34	0.34
OCDD (7)	10.54	593	603	0.60	0.06
CDFs					
2,3,7,8-TCDF (8)	0.19	11	11	1.09	1.09
1,2,3,7,8-PeCDF (4)	0.17	10	10	0.49	0.49
2,3,4,7,8-PeCDF (4)	0.17	10	10	4.86	4.86
1,2,3,4,7,8-HxCDF (5)	0.25	14	14	1.43	1.43
1,2,3,6,7,8-HxCDF (4)	0.18	10	10	1.03	1.03
2,3,4,6,7,8-HxCDF (4)	0.28	16	16	1.60	1.60
1,2,3,7,8,9-HxCDF (4)	0.24	14	14	1.37	1.37
1,2,3,4,6,7,8-HpCDF (5)	0.29	16	17	0.17	0.17
1,2,3,4,7,8,9-HpCDF (4)	0.35	20	20	0.20	0.20
OCDF (9)	0.59	33	34	0.03	<0.01
Total Quantities:				**35.41**	**41.98**

(1) From Table 2-9, Data for Co-managed Wastes of U.S. EPA (1999b).
(2) Based on EPRI estimate of 63 million tons/yr of large-volume utility coal combustion solid wastes. From Section 3.3 of U.S. EPA (1999c). Assumes all waste characteristics are same as for Comanaged Wastes.
(3) Assumes that solid waste quantity for 1987 is 98.4% of 1995, based on total utility coal use in those years (see Section 4.4).
(4) All 17 analyses were non-detects.
(5) 16 of the 17 analyses were non-detects.
(6) 11 of the 17 analyses were non-detects.
(7) 5 of the 17 analyses were non-detects.
(8) 14 of the 17 analyses were non-detects.
(9) 15 of the 17 analyses were non-detects.

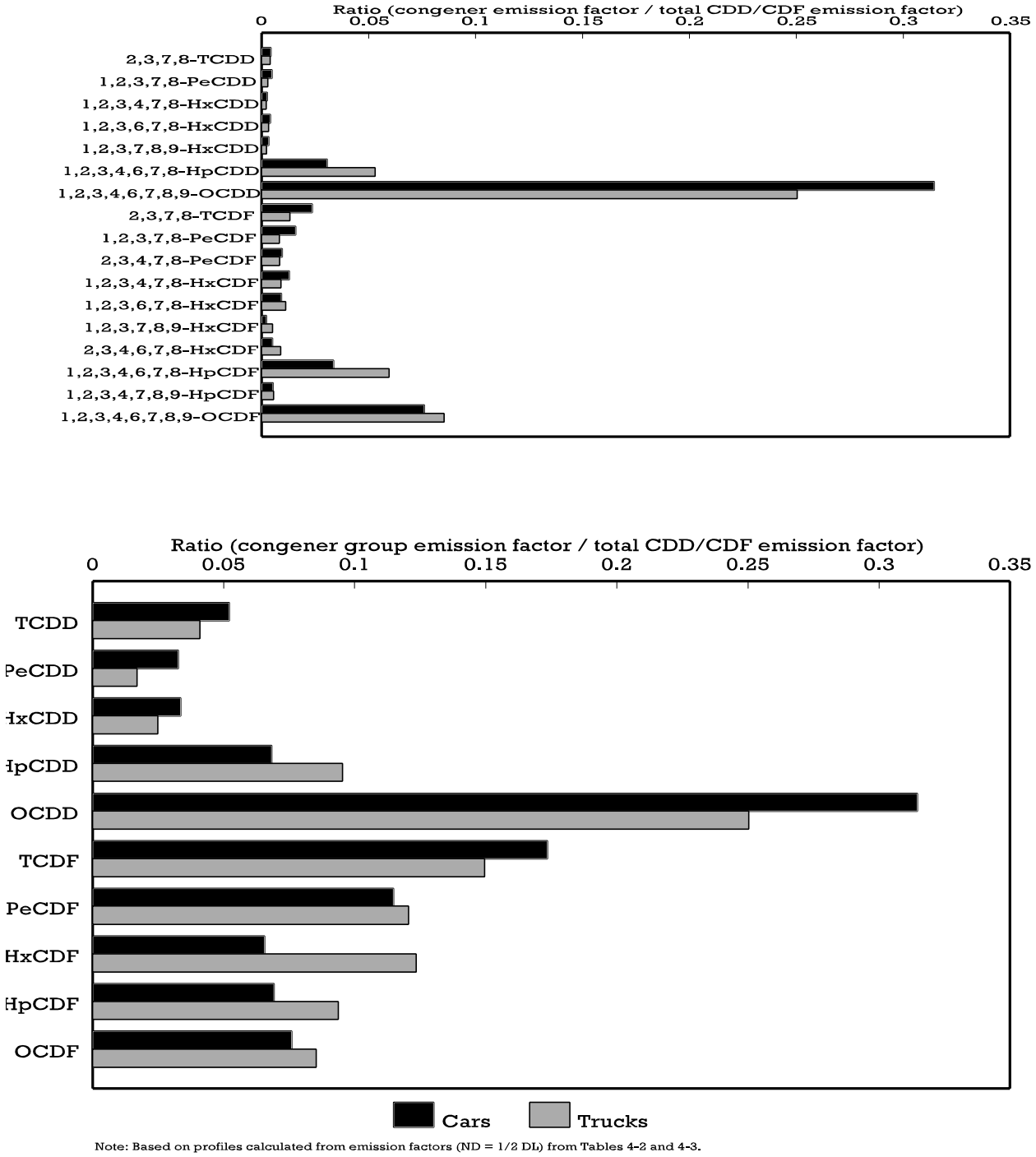
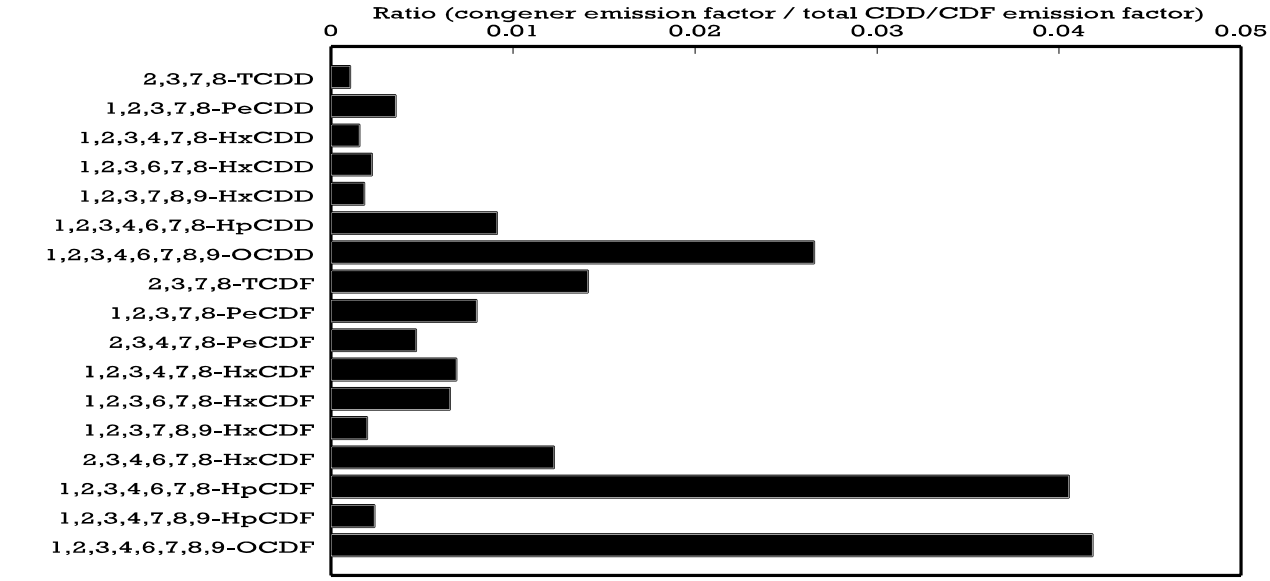
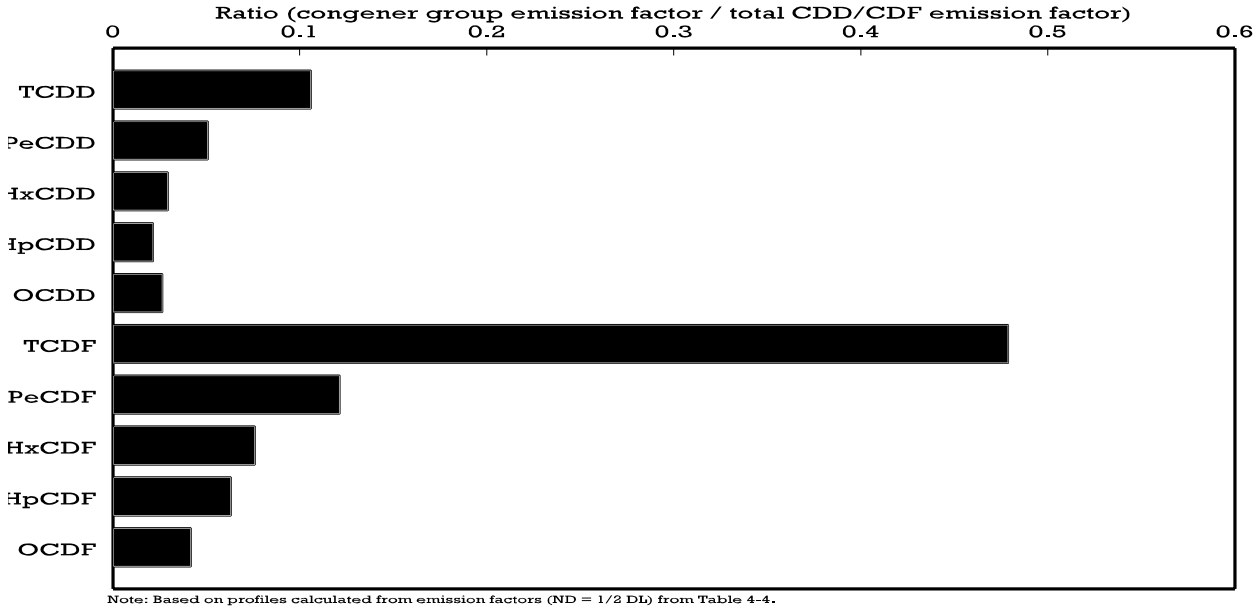


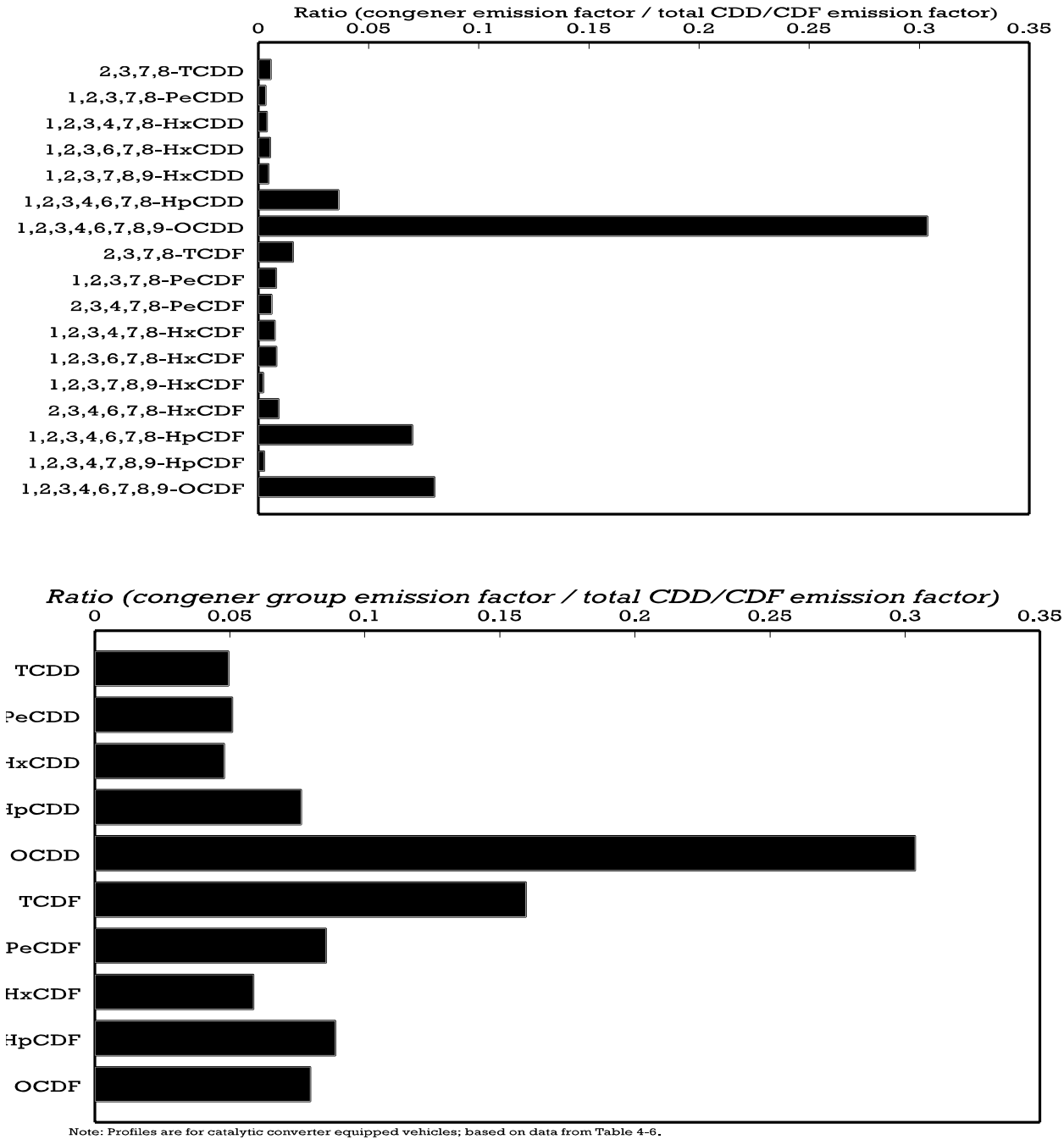
Figure 4-1. Congener and Congener Group Profiles for Air Emissions from Diesel-fueled Vehicles





Note: Based on profiles calculated from emission factors (ND = 1/2 DL) from Table 4-4.

Figure 4-2. Congener and Congener Group Profiles for Air Emissions from Leaded Gas-fueled Vehicles



Note: Profiles are for catalytic converter equipped vehicles; based on data from Table 4-6.

Figure 4-3. Congener and Congener Group Profiles for Air Emissions from Unleaded Gas-fueled Vehicles

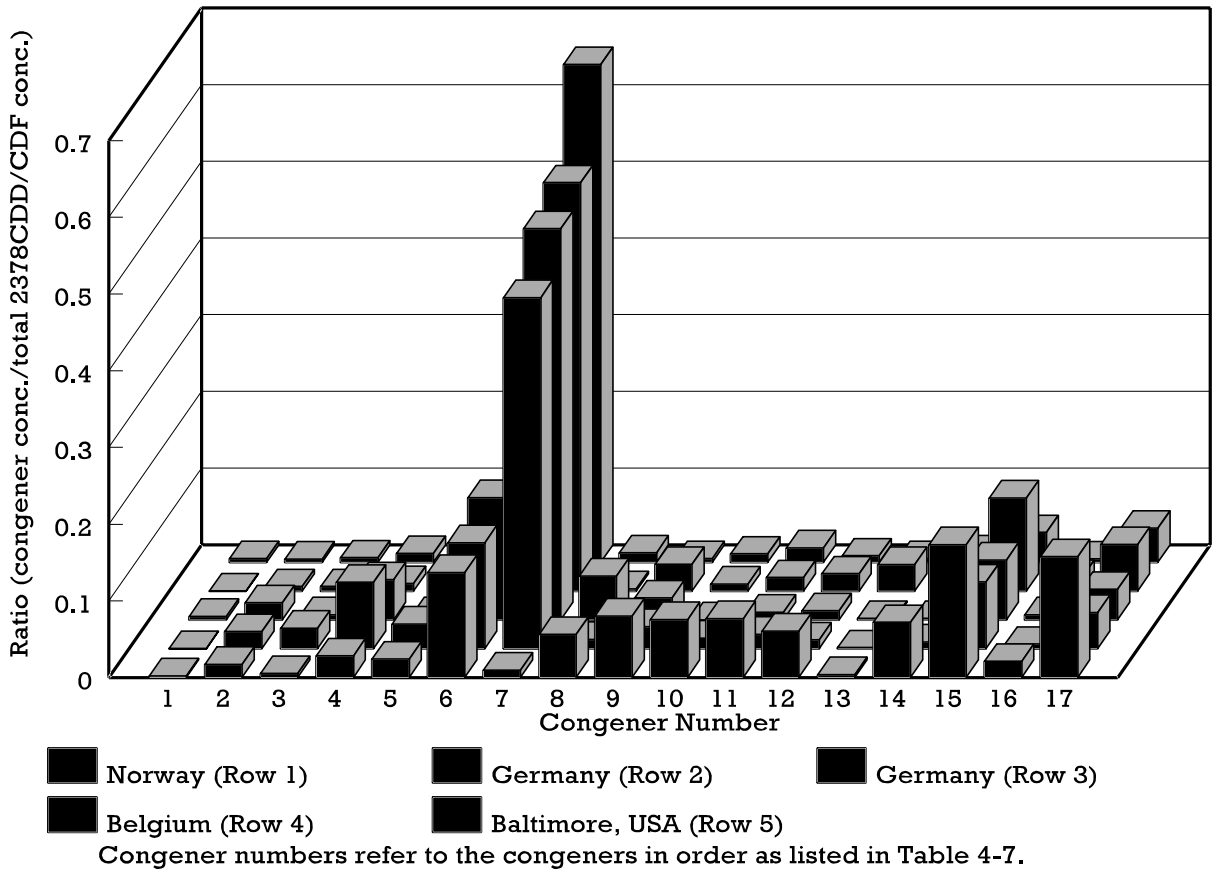
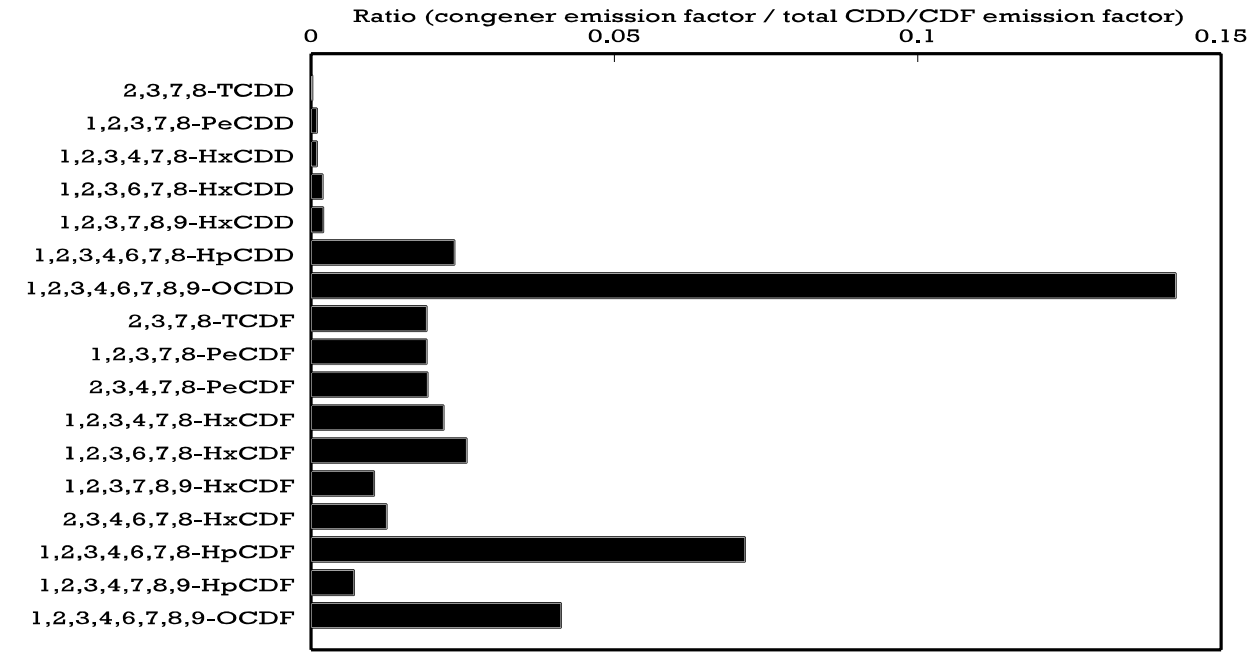


Figure 4-4. Tunnel Air Concentrations



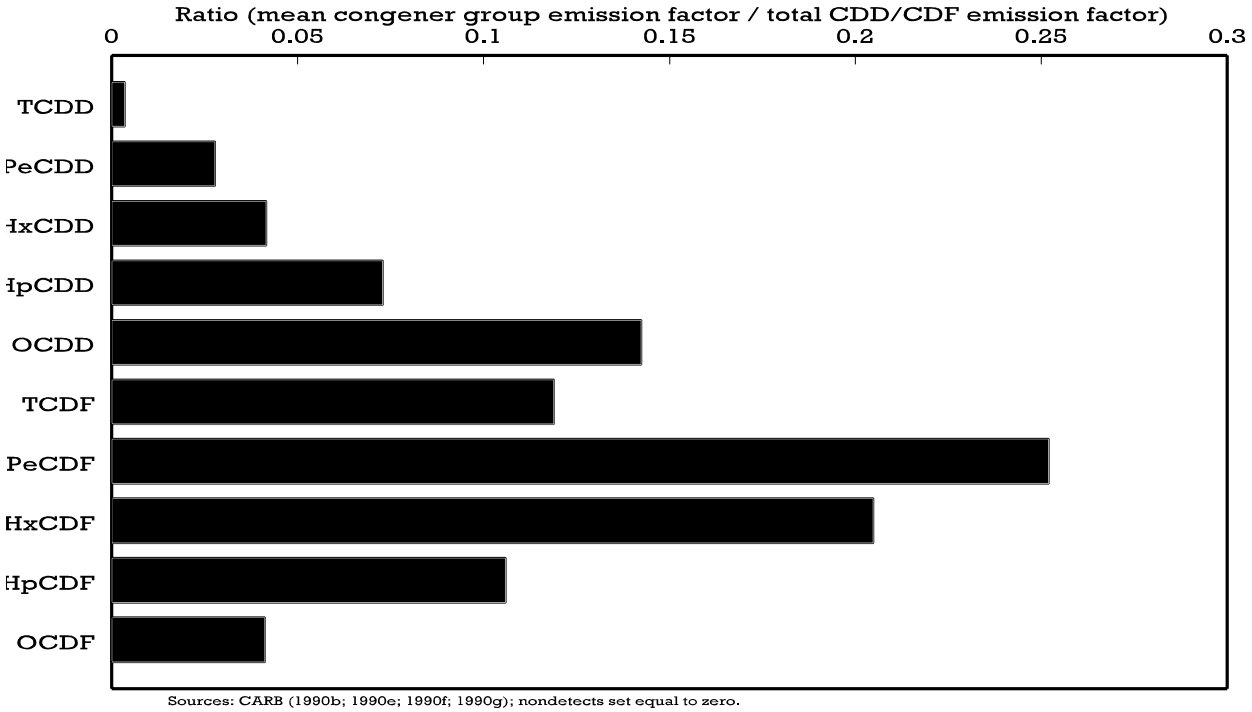
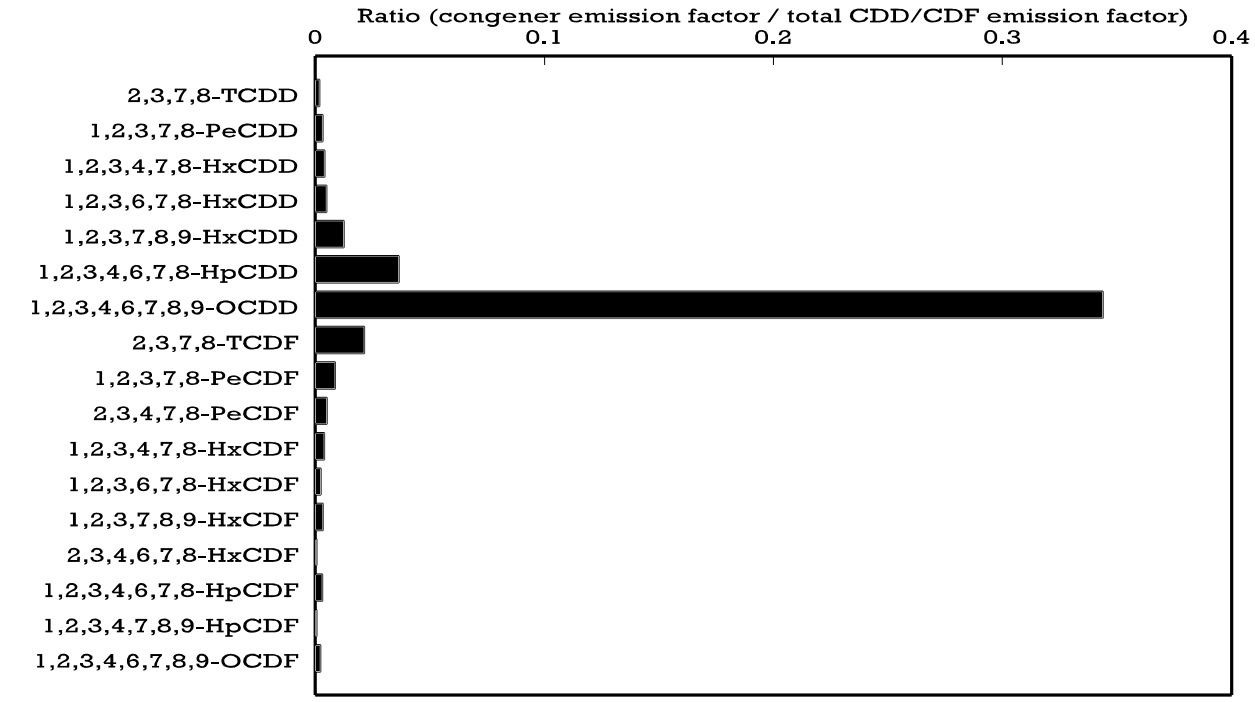
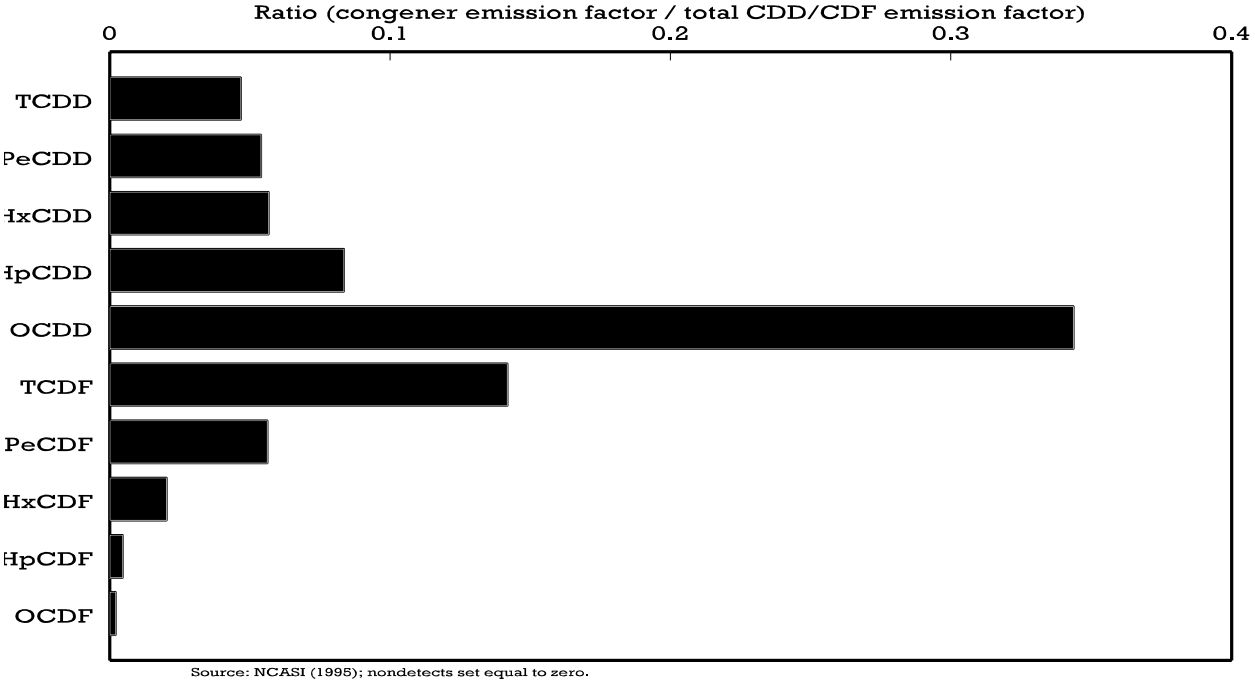


Figure 4-5a. Congener and Congener Group Profiles for Air Emissions from Industrial Wood Combustors





Source: NCASI (1995); nondetects set equal to zero.

Figure 4-5b Congener and Congener Group Profiles for Air Emissions from Bleached Kraft Mill Bark Combustors

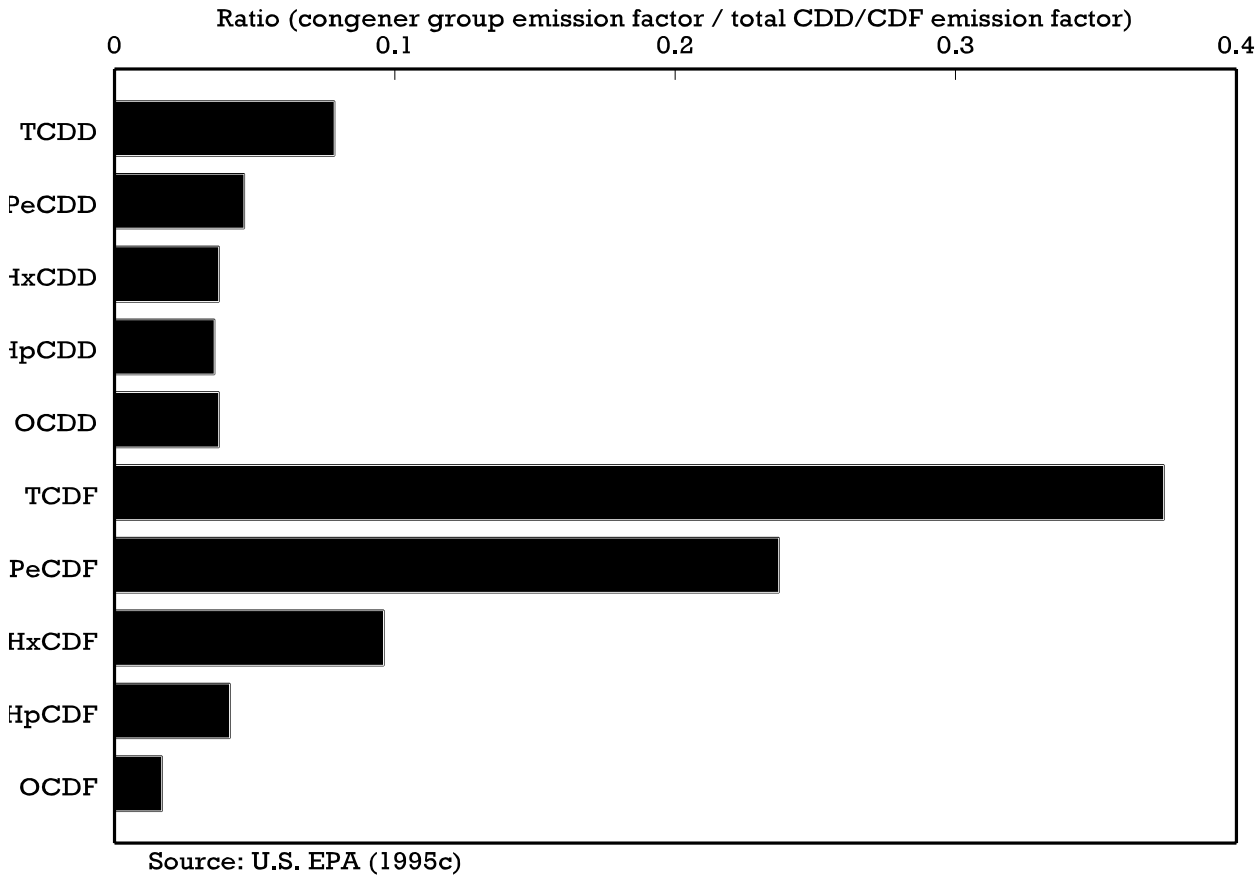


Figure 4-6. Congener Group Profile for Air Emissions from Residential Oil-fueled Furnaces

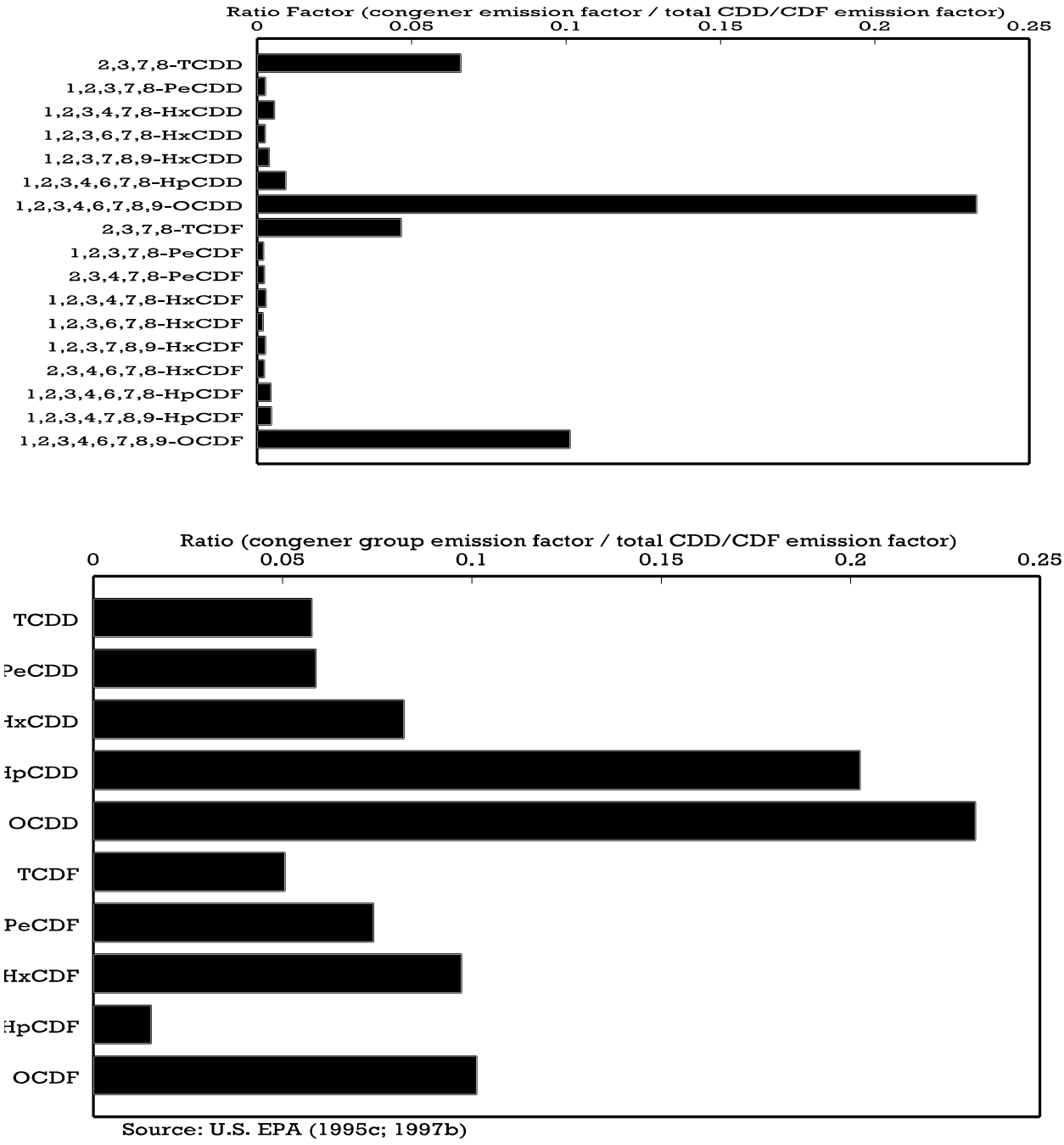


Figure 4-7. Congener and Congener Group Profiles for Air Emissions from Industrial Oil-fueled Boilers

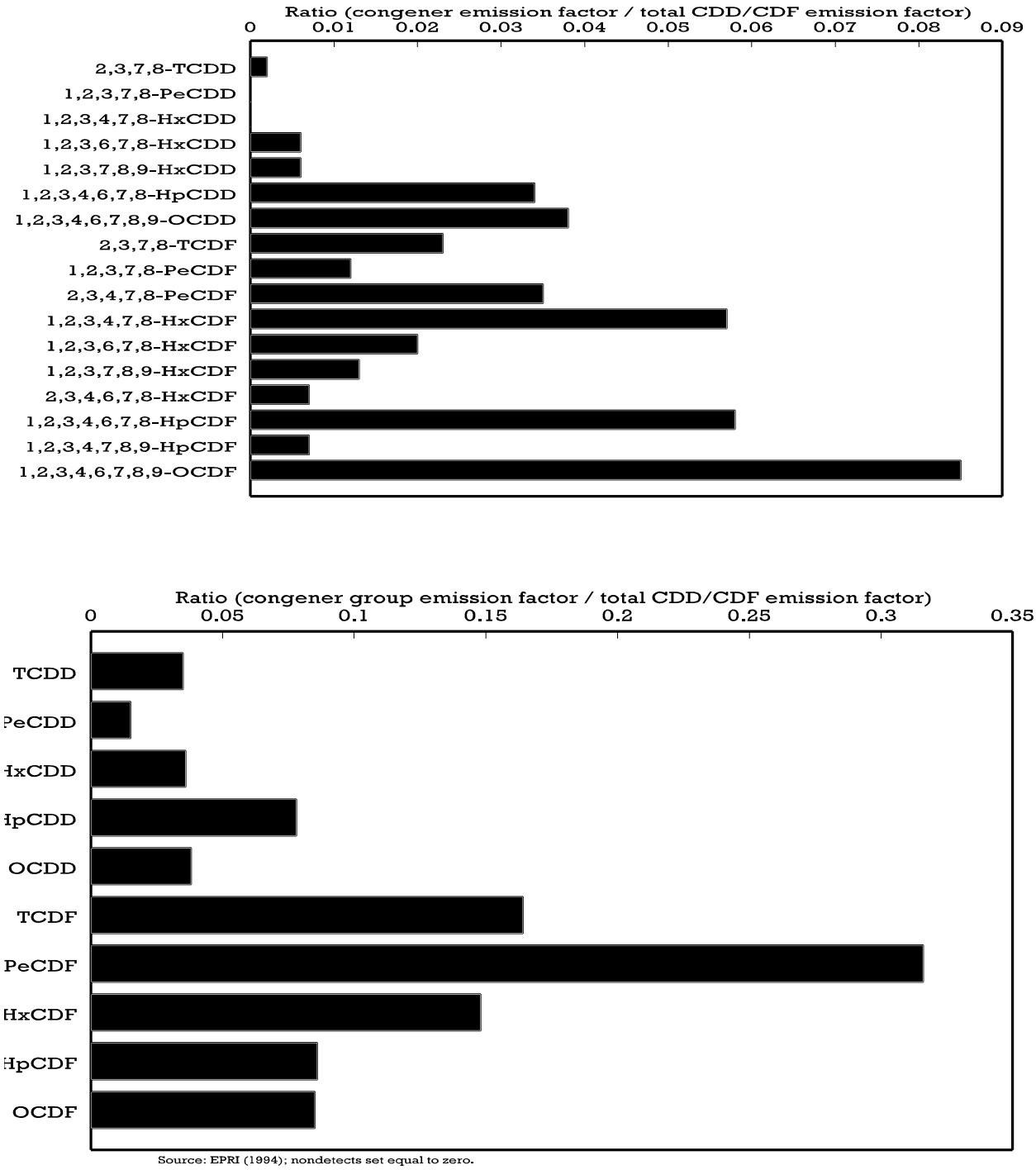


Figure 4-8. Congener and Congener Group Profiles for Air Emissions from Industrial/Utility Coal-fueled Combustors

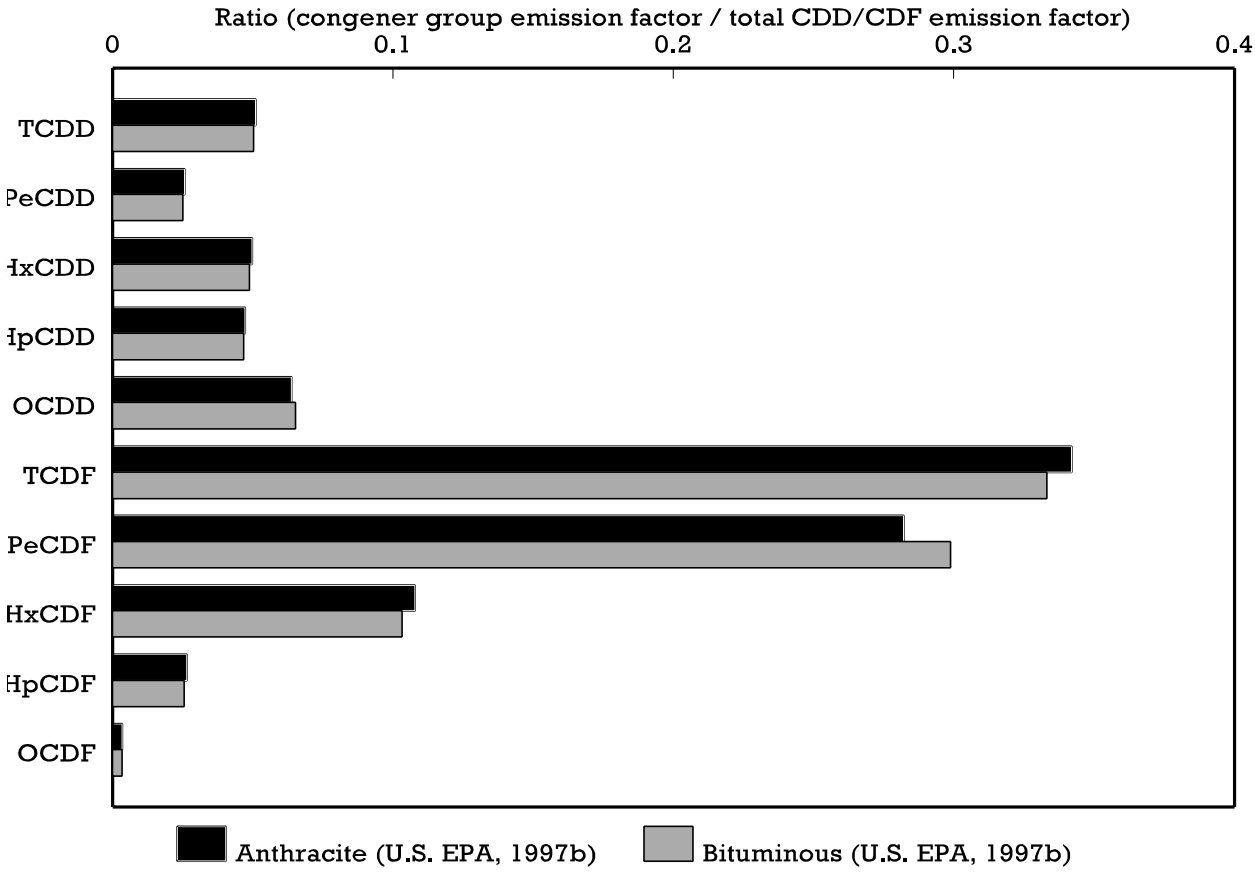


Figure 4-9. Congener Group Profile for Air Emissions from Residential Coal-fueled Combustors

5. COMBUSTION SOURCES OF CDD/CDF: OTHER HIGH TEMPERATURE SOURCES

5.1. CEMENT KILNS AND LIGHTWEIGHT AGGREGATE KILNS

This section addresses CDD/CDF emissions from portland cement kilns. These facilities use high temperatures to convert mineral feedstocks into portland cement and other types of construction materials. For purposes of this analysis, cement kilns have been subdivided into two categories, those that burn hazardous waste and those that do not, and these two subcategories are further divided into kilns with inlet APCD temperatures above and below 450°F. The following subsections describe cement kiln technology, the derivation of TEQ emission factors for cement kilns that burn hazardous waste as supplemental fuel and those that do not, and the derivation of annual TEQ air emissions (g/yr) for 1995 and 1987.

Lightweight aggregate kilns that combust liquid hazardous wastes are not addressed in detail in this report. Only 5 of the more than 36 lightweight aggregate kilns in the United States combust hazardous waste. Those facilities are estimated to have emitted 3.3 g I-TEQ$_{DF}$ to air in 1990 (Federal Register, 1998b) and 2.4 g I-TEQ$_{DF}$ in 1997 (Federal Register, 1999b). These estimates are used in this report as the estimates for reference years 1987 and 1995, respectively. Regulations issued by EPA under the Clean Air Act (CAA) and Resource Conservation and Recovery Act (RCRA) in 1999 (Federal Register, 1999b) are expected to reduce those emissions to 0.4 g I-TEQ$_{DF}$ within the next 3 to 4 years.

5.1.1. Process Description of Portland Cement Kilns

In the United States, the primary cement product is portland cement. Portland cement is a fine, grayish powder consisting of a mixture of four basic materials: lime, silica, alumina, and iron compounds. Cement production involves heating (pyroprocessing) the raw materials to a very high temperature in a rotary (rotating) kiln to induce chemical reactions that produce a fused material called clinker. The cement clinker is then ground into a fine powder and mixed with gypsum to form the portland cement. The cement kiln is a large, steel, rotating cylindrical furnace lined with refractory material. The kiln is aligned on a slight angle, usually a slope of 3 to 6°. This allows the materials to pass through the kiln by gravity. The upper end of the kiln, known as the "cold" end, is where

the raw materials, or meal, are generally fed into the kiln. Midpoint injection is practiced at some facilities. The lower end of the kiln is known as the hot end. The hot end is where the combustion of primary fuels (usually coal and petroleum coke) transpires to produce a high temperature. The cement kiln is operated in a counter-current configuration, in which the hot combustion gases are convected up through the kiln while the raw materials pass down toward the lower end. The kiln rotates about 50 to 70 revolutions per hour, and the rotation induces mixing and the forward progress of mixed materials. As the meal moves through the cement kiln and is heated by the hot combustion gases, water is vaporized and pyroprocessing of materials occurs.

When operating, the cement kiln can be viewed as consisting of three temperature zones necessary to produce cement clinker. Zone 1 is at the upper end of the kiln where the raw meal is added. Temperatures in this zone typically range from ambient up to 600°C. In this area of the kiln, moisture is evaporated from the raw meal. The second thermal zone is known as the calcining zone. Calcining occurs when the hot combustion gases from the combustion of primary fuels dissociates calcium carbonate from the limestone to form calcium oxide. In this region of the kiln, temperatures range from 600°C to 900°C. Zone 3 is known as the burning or sintering zone. The burning zone, the lowest region of the kiln, is the hottest. Here temperatures in excess of 1,500°C induce the calcium oxide to react with silicates, iron, and aluminum in the raw materials to form cement clinker. The formation of clinker actually occurs close to the combustion of primary fuel. The chemical reactions that occur in Zone 3 are referred to as pyroprocessing.

The cement clinker, which leaves the kiln at the hot end, is a gray, glass-hard material consisting of dicalcium silicate, tricalcium silicate, calcium aluminate, and tetracalcium aluminoferrite. At this point, the clinker is about 1,100°C. The hot clinker is then dumped onto a moving grate, where it cools as it passes under a series of cool air blowers. Once cooled to ambient temperature, the clinker is ground into a fine powder and mixed with gypsum to produce the portland cement product.

Cement kilns can be either wet or dry processes. In the wet process, the raw materials are ground and mixed with water to form a slurry, which is fed into the kiln through a pump. This is an older process. A greater amount of heat energy is needed in

the wet process than in other types of kilns. These kilns consume about 5 to 7 trillion BTUs per ton of clinker product to evaporate the additional water.

In the dry process, a preheater is used to dry the raw meal before it enters the kiln. A typical preheater consists of a vertical tower containing a series of cyclone-type vessels. Raw meal is added at the top of the tower, and hot exhaust gases from the kiln operation preheat the meal, thus lowering the fuel consumption of the kiln. Dry kilns are now the most popular cement kiln type. Portland cement clinker production in the United States is estimated to have been 67.6 billion kg in 1995 and 52 billion kg in 1987 (U.S. Department of Commerce, 1996).

5.1.2. Cement Kilns That Burn Hazardous Waste

The high temperatures achieved in cement kilns make the kilns an attractive technology for combusting hazardous waste as supplemental fuel. Sustaining the relatively high combustion temperatures (1,100°C to 1,500°C) that are needed to form cement clinker requires the burning of a fuel with a high energy output. Therefore, coal or petroleum coke is typically used as the primary fuel source. Because much of the cost of operating the cement kiln at high temperatures is associated with the consumption of fossil fuels, some cement kiln operators have elected to burn hazardous liquid and solid waste as supplemental fuel. Currently about 75 percent of the primary fuel is coal. Organic hazardous waste may have a similar energy output as coal (9,000 to 12,000 Btu/lb for coal). The strategy of combusting the waste as supplemental fuel is to offset the amount of coal/coke that is purchased and burned by the kiln. The operator may charge a disposal fee to the waste generator for the right to combust the hazardous waste at the kiln, which also offsets the cost of kiln operation. Much of the high-energy and ignitable wastes primarily comprise such diverse substances as waste oils, spent organic solvents, sludges from the paint and coatings industry, waste paints and coatings from auto and truck assembly plants, and sludges from the petroleum refining industry (Greer et al., 1992).

The conditions inherent in the cement kiln mimic conditions of hazardous waste incineration. For example, the gas residence time in the burning zone is typically three seconds while at temperatures in excess of 1,500°C (Greer et al., 1992). The method of introducing liquid and solid hazardous waste into the kiln is a key factor to the complete

consumption of the waste during the combustion of the primary fuel. Liquid hazardous waste is either injected separately or blended with the primary fuel (coal). Solid waste is mixed and burned along with the primary fuel. Trial burns have consistently shown that 99.99 to 99.9999 percent destruction and removal efficiencies for the very stable organic wastes can be achieved in cement kilns (Greer et al., 1992). However, although the combustion of hazardous waste as supplemental or substitute fuel does have apparent advantages, only 16 percent of the portland cement kilns (34 of 212 kilns) in the United States combusted hazardous waste in 1995 (Federal Register, 1996b). Other types of supplemental fuel used by these facilities include automobile tires, used motor oil, sawdust, and scrap wood chips.

5.1.3. Air Pollution Control Devices Used on Cement Kilns

The pyroprocessing of raw meal in a cement kiln produces fine particulates, referred to as cement kiln dust. Cement kiln dust is collected and controlled with fabric filters or electrostatic precipitators, or both. Acid gases such as SO_2 can be formed during pyroprocessing of the sulfur-laden minerals, but the minerals have high alkalinity, which neutralizes SO_2 gases. Most particulate matter (PM) control devices used at cement kilns in 1995 and 1987 were considered to be hot-side control devices. A hot-sided control device is one that operates at flue gas temperatures above 450°F (some EPA rules use different definitions for hot-sided control devices for different industries).

Reducing the flue gas temperature in the PM control device is one factor shown to have a significant impact on limiting dioxin formation and emissions at cement kilns (U.S. EPA, 1997d). Recent emissions testing at a portland cement kiln showed that CDD/CDFs were almost entirely absent at the inlet to a hot-sided ESP, but CDDs and CDFs were measured at the exit (U.S. EPA, 1997d), showing conclusively that dioxins were formed within the hot-sided ESP. Reducing the flue gas temperature in the PM control device to below 450°F has been shown to substantially limit CDD/CDF formation at cement kilns. Lower temperatures are believed to prevent the post-combustion catalytic formation of CDD/CDFs. Consequently a number of cement kilns have added flue gas quenching units upstream of the APCD to reduce the inlet APCD temperature, thereby reducing CDD/CDF stack concentrations. A quenching unit usually consists of a water spray system within the flue duct. Thus, current CDD/CDF emissions from cement kilns are believed to be

substantially lower than CDD/CDF emissions in 1987 and 1995; EPA/OAQPS estimated emissions to be 13.1 g I-TEQ_{DF} in 1997 (Federal Register, 1999b).

5.1.4. CDD/CDF Emission Factors for Cement Kilns

For purposes of deriving emission factors, the general strategy used in this document is to consider subdividing each source category on the basis of design and operation. However, cement kilns are relatively uniform in terms of kiln design, raw feed material, temperatures of operation, and APCDs. Therefore, no subdivisions were made on these bases. An important potential difference among kilns, however, is whether or not hazardous waste is burned as a supplementary fuel. The source emissions database used in this report contains CDD/CDF emissions data for 16 cement kilns burning hazardous waste and 15 cement kilns not burning hazardous waste as reported in U.S. EPA (1996c). The majority of stack emissions data from cement kilns burning hazardous waste were derived during trial burns and may overestimate the CDD/CDF emissions that most kilns achieve during normal operations. Stack emissions data from kilns not burning hazardous waste were derived from testing during normal operations. The average TEQ emission factors are 20.91 ng I-TEQ_{DF}/kg clinker produced (22.48 ng TEQ_{DF}-WHO_{98}/kg clinker) and 0.27 ng I-TEQ_{DF}/kg clinker produced (0.29 ng TEQ_{DF}-WHO_{98}/kg clinker) for cement kilns burning and not burning hazardous waste, respectively. Accordingly, the average emission factor for kilns burning hazardous waste is about 90 times greater than that for kilns not burning hazardous waste. As discussed in Section 5.1.6 (Cement Kiln Dust), a comparison of CDD/CDF concentrations in cement kiln dust samples from cement kilns burning and not burning hazardous waste shows a similar relationship (i.e., the cement kiln dust from kilns burning hazardous waste had about 100 times higher CDD/CDF TEQ concentration than dust from kilns not burning hazardous waste).

Although the average emission factors for the two groups of kilns differ substantially, the emission factors for individual kilns in the two groups overlap. Therefore, other aspects of the design and operation of the kilns are likely to be affecting CDD/CDF emissions, particularly the temperature of the APCD equipment as discussed in Section 5.1.3.

Previous attempts to understand this issue through parametric testing of cement kilns have yielded mixed results. EPA conducted a limited comparison of CDD/CDF TEQ

stack gas concentrations (ng TEQ/dscm) between cement kilns burning hazardous wastes and not burning hazardous wastes (U.S. EPA, 1997d). Those comparisons were made at 14 cement kilns. Operating conditions (e.g., APCD temperature), with the exception of the fuel being burned, were the same or similar for each set of comparisons. Baseline conditions used coal as the only primary fuel. The results of these comparisons showed the following:

- Seven kilns in which the baseline (i.e., no combustion of hazardous waste) CDD/CDF TEQ stack gas concentrations were about the same as that for the burning of hazardous wastes.
- Two kilns in which the baseline CDD/CDF I-TEQ_{DF} stack gas concentrations were about double that for the burning of hazardous wastes.
- Five kilns in which the hazardous waste CDD/CDF I-TEQ_{DF} stack gas concentrations were substantially greater (from 3 to 29 times greater) than that for the baseline operating conditions.

Subsequently, EPA/ORD conducted analyses of the available emissions data to evaluate, on a congener-specific basis, whether there were significant differences in emission factors between (a) kilns burning hazardous waste and those not burning hazardous waste; (b) kilns with APCD inlet temperatures greater than 450°F and those with temperature less than 450°F; (c) hazardous waste burning and non–hazardous waste burning facilities with APCD inlet temperatures greater than 450°F; (d) hazardous waste burning and non–hazardous waste burning facilities with APCD inlet temperatures less than 450°F; (e) hazardous waste burning facilities with APCD inlet temperatures less than or greater than 450°F; and (f) non–hazardous waste burning facilities with APCD inlet temperatures less than or greater than 450°F. The results of all analyses showed significant differences in the sample mean values ($p < 0.05$).

Currently no satisfactory explanation exists for the apparent differences in the emission factors. Given the strong empirical evidence that real differences may exist, EPA/ORD has decided to treat the kilns burning hazardous waste separately from those not burning hazardous waste for the purposes of developing a CDD/CDF emissions inventory, and to subdivide the hazardous waste burning category into subcategories by APCD inlet temperature (i.e., less than 450°F or greater than 450°F). APCD inlet

temperature data were available for 88 test runs at 14 cement kilns. The number of test runs conducted at individual kilns ranged from 1 to 26. Each test run was treated as an individual facility and each was classified according to APCD inlet temperature and whether or not hazardous waste was burned. The emission factor (EF) for each cement kiln test run was calculated using Equation 5-1.

$$EF_{ck} = \frac{C \times F_v}{I_{cl}} \qquad \text{(Eq. 5-1)}$$

Where:

EF_{ck} = Cement kiln emission factor (burning or not burning hazardous waste), (ng TEQ/kg of clinker produced)

C = TEQ or CDD/CDF concentration in flue gases (ng TEQ/dscm) (20°C, 1 atm; adjusted to 7% O_2)

F_v = Volumetric flue gas flow rate (dscm/hr) (20°C, 1 atm; adjusted to 7% O_2)

I_{cl} = Average cement kiln clinker production rate (kg/hr)

After developing the emission factor for each cement kiln test run, the overall average congener-specific emission factor was derived for all test runs in each subcategory using Equation 5-2 below.

$$EF_{avgCK} = \frac{EF_{CK_1} + EF_{CK_2} + EF_{CK_3} + \ldots\ldots + EF_{CKN}}{N} \qquad \text{(Eq. 5-2)}$$

Where:

EF_{avgCK} = Average emission factor of tested cement kilns burning hazardous waste as supplemental fuel and with APCD inlet temperatures either greater than or less than 450°F (ng TEQ/kg clinker)

N = Number of cement kiln test runs

The average emission factors representing these categories of cement kilns are summarized in Table 5-1. Because the same test reports were used, the emission factors are the same for both the 1995 and 1987 reference years. Average congener and congener group profiles for cement kilns burning hazardous waste are presented in Figure 5-1 and for cement kilns not burning hazardous wastes in Figure 5-2.

5.1.5. National Estimates of CDD/CDF Emissions from Cement Kilns

Non–hazardous waste burning cement kilns produced 61.3 billion kg of cement clinker in 1995 (Heath, 1995). Since a total of 67.6 billion kg of cement clinker were produced in the United States in 1995 (U.S. DOC, 1996), it follows that cement kilns burning hazardous waste produced 6.3 billion kg of clinker, or 9.3 percent of the clinker produced. In 1987, approximately 52 billion kg of cement clinker were produced (U.S. DOC, 1996). If it is assumed that 9.3 percent of this total clinker production was from kilns burning hazardous waste, then about 4.8 billion kg of clinker were produced in hazardous waste burning kilns in 1987. These activity level estimates are given a high confidence rating for 1995 because they are based on recent survey data, but a medium rating for 1987 because of uncertainty concerning the proportion produced by hazardous waste burning kilns (U.S. EPA, 1996c).

The TEQ emission factors are given a low confidence rating for all subcategories. The emission factor for non–hazardous waste burning kilns was given a low rating because test data were available for only 15 of 178 facilities. The tested facilities may not be representative of routine CDD/CDF emissions from all kilns not burning hazardous waste. Although a higher percentage of the kilns burning hazardous waste (with reported APCD temperature data) had been tested (10 out of 34; eight with APCD inlet temperatures greater than 450°F and two with temperatures less than 450°F), greater uncertainty exists about whether the emissions are representative of normal operations because trial burn procedures were used. Accordingly, a low confidence rating was also assigned to the estimated emissions factors for kilns burning hazardous waste.

National estimates of CDD/CDF air emissions (grams TEQ per year) from all portland cement kilns operating in 1995 and 1987 were made by multiplying the average

TEQ emission factors by an estimate of the annual activity level (cement clinker produced) for each of the three subcategories (hazardous waste burning kilns with APCD inlet temperatures greater than 450°F, hazardous waste burning kilns with APCD inlet temperatures less than 450°F, and kilns not burning hazardous waste).

Of the 10 hazardous waste burning kilns with APCD temperature data, 8 facilities (80 percent) had APCD inlet temperatures greater than 450°F; 2 (20 percent) had APCD inlet temperatures less than 450°F. If it is assumed that the percentages of hazardous waste burning kilns less than and greater than 450°F represent the actual distribution of activity level in the industry, then one can use these percentages, coupled with the TEQ emission factors presented in Table 5-1 and the activity levels established at the beginning of this section, to calculate the annual national TEQ emission estimates shown below.

Reference Year 1995

Category	TEQ Emission Factor (ng/kg clinker)		Activity Level (billion kg clinker/yr)	Annual TEQ Emission (g/yr)	
	I-TEQ_{DF}	TEQ_{DF}-WHO_{98}		I-TEQ_{DF}	TEQ_{DF}-WHO_{98}
HW >450°F	28.58	30.70	5.04	144.0	154.7
HW <450°F	1.04	1.11	1.26	1.3	1.4
NHW	0.27	0.29	61.3	16.6	17.8
TOTAL			67.6	162	174

Reference Year 1987

Category	TEQ Emission Factor (ng/kg clinker)		Activity Level (billion kg clinker/yr)	Annual TEQ Emission (g/yr)	
	I-TEQ_{DF}	TEQ_{DF}-WHO_{98}		I-TEQ_{DF}	TEQ_{DF}-WHO_{98}
HW >450°F	28.58	30.70	3.8	108.6	116.7
HW <450°F	1.04	1.11	1.0	1.0	1.1
NHW	0.27	0.29	47.2	12.7	13.7
TOTAL			52.0	122	132

5.1.6. Recent EPA Regulatory Activities

In May 1999, EPA promulgated national emission standards under the authority of the Clean Air Act for hazardous air pollutants (including CDD/CDFs) for new and existing cement kilns not burning hazardous waste (Federal Register, 1999a). EPA/OAQPS expects this rule to reduce emissions of I-TEQ_{DF} by existing and new facilities by 36 percent over the next 5 years (i.e., from an estimated 44 g I-TEQ_{DF} in 1997 to 29 g I-TEQ_{DF} per year).

In July 1999, EPA promulgated national emission standards under the joint authority of the Clean Air Act and the Resource Conservation and Recovery Act for hazardous air pollutants (including CDD/CDFs) for hazardous waste combustion facilities (including cement kilns burning hazardous waste). Within the next 3 to 4 years under the final emissions limits, emissions of I-TEQ_{DF} by hazardous waste burning facilities are projected by EPA/OAQPS to be reduced by 40 percent (i.e., from an estimated 13.1 g I-TEQ_{DF} in 1997 to 7.7 g I-TEQ_{DF} per year) (Federal Register, 1999b).

5.1.7. Solid Waste from Cement Manufacturing

The solid residual generated during the manufacturing of cement is known as Cement Kiln Dust (CKD). EPA characterized CKD in a Report to Congress (U.S. EPA, 1993g). The report was based in part on a 1991 survey of cement manufacturers conducted by the Portland Cement Association (PCA). Survey responses were received from 64 percent of the active cement kilns in the United States. On the basis of the survey responses, EPA estimated that in 1990 the U.S. cement industry generated about 12.9 million metric tons of gross CKD and 4.6 million metric tons of "net CKD," of which 4.2 million metric tons were land disposed. The material collected by the APCD system is called "gross CKD" (or "as generated" CKD). The gross CKD is either recycled back into the kiln system or is removed from the system for disposal (i.e., "net CKD" or "as managed" CKD) (U.S. EPA, 1993g).

In support of the Report to Congress, EPA also conducted sampling and analysis during 1992 and 1993 of CKD and clinker. The purposes of the sampling and analysis efforts were to: (1) characterize the CDD/CDF content of clinker and CKD; (2) determine the relationship, if any, between the CDD/CDF content of CKD and the use of hazardous

waste as fuel; and (3) determine the relationship, if any, between the CDD/CDF content of CKD and the use of wet process versus dry process cement kilns (U.S. EPA, 1993g).

Clinker samples were collected from five kilns not burning hazardous waste and six kilns burning hazardous waste (U.S. EPA, 1993g). CDD/CDFs were not detected in any cement kiln clinker samples. Tetra- through octa-chlorinated CDDs and CDFs were detected in the gross CKD samples obtained from 10 of the 11 kilns and in the net CKD samples obtained from 8 of the 11 kilns. The CDD/CDF content of gross CKD ranged from 0.008 to 247 ng I-TEQ_{DF}/kg and from 0.045 to 195 ng I-TEQ_{DF}/kg for net CKD. Analyses for seven PCB congeners were also conducted, but no congeners were detected in any clinker or CKD sample. The mean CDD/CDF concentrations in net CKD generated by the kilns burning hazardous waste are higher (35 ng I-TEQ_{DF}/kg) than in net CKD generated by the facilities not burning hazardous waste (3.0E-02 ng I-TEQ_{DF}/kg). These calculations of mean values treated nondetected values ("nondetects") as zero. If the nondetected values had been excluded from the calculation of the means, the mean value for net CKD from kilns burning hazardous waste would increase by a factor of 1.2, and the mean value for net CKD from kilns not burning hazardous waste would increase by a factor of 1.7. One sampled kiln had a net CKD TEQ concentration more than two orders of magnitude greater than the TEQ levels found in samples from any other kiln. If this kiln was considered atypical of the industry (U.S. EPA, 1993g) and was not included in the calculation, then the mean net CKD concentration for hazardous waste burning kilns decreases to 2.9 ng I-TEQ_{DF}/kg.

In a recent report (Washington, 1998), CDD/CDF congener data for CKD from Holnam, Inc., Seattle, Washington, were presented. The data were compiled and evaluated to determine total I-TEQ concentrations and loadings. Non-detect values were included as either zero, ½ DL, or at the DL. The results of three separate tests were as follows, assuming that non-detect values were at zero concentration:

Date	Location	I-TEQ (ng/kg)	I-TEQ (mg/day)
5/15/96	not stated	0.038	0.0038
10/21/97	HLMN Bin	0.67	0.0674
10/21/97	HLMN Final	0.95	0.0948

In a recently compiled database, EPA (1999d) provided data for ashes from an electric static precipitator connected to a cement kiln and a fabric filter connected to a light weight aggregate (LWA) kiln. The average congener concentrations for the ash samples are listed in Table 5-8.

The average concentrations for the cement kiln were determined from two different waste streams, each with five sample burns. The average concentrations for the LWA kiln were determined using one waste stream with three sample burns.

All CKD is normally disposed of in engineered landfills and is consequently not categorized as an environmental release as defined in this emission inventory. The amount of CDD/CDF associated with these materials is calculated for informational purposes. The estimate of land-disposed CKD from the 1991 PCA survey (4.2 million metric tons per year; basis year is 1990) was divided among kilns that burn hazardous waste (34 kilns) and those that do not (178 kilns) on the basis of the number of kilns in each category. The average TEQ concentration in the net CKD from kilns burning hazardous waste (including the high value discussed above) was 35 ng I-TEQ_{DF}/kg. For kilns that do not burn hazardous waste, the average concentration in the net CKD was 3.0E-02 ng I-TEQ_{DF}/kg. Multiplying these average concentrations by the estimated annual net CKD production yields 24 g I-TEQ_{DF}/yr for kilns burning hazardous waste and 0.1 g I-TEQ_{DF}/yr for kilns not burning hazardous waste, a total of 24.1 g I-TEQ_{DF}/yr for all kilns in 1990.

EPA is currently developing cement kiln dust storage and disposal requirements (Federal Register, 1999b).

5.2. ASPHALT MIXING PLANTS

Asphalt consists of an aggregate of gravel, sand, and filler mixed with liquid asphalt cement or bitumen. Filler typically consists of limestone, mineral stone powder, and sometimes ash from power plants and municipal waste combustors. The exact composition of an asphalt formulation depends on how it will be used. The aggregate typically constitutes over 92 percent by weight of the total asphalt mixture. The components of the aggregate are dried, heated to a temperature ranging from 275 to 325°F, and then mixed and coated with the bitumen at an asphalt mixing installation. "Old" asphalt (i.e., asphalt from dismantled bridges and roads) can be heated and

disaggregated to its original components and reused in the manufacture of new asphalt (U.S. EPA, 1996i).

No data are available on levels of CDD/CDF emissions, if any, from U.S. asphalt mixing operations. However, limited data are available for facilities in The Netherlands and Germany.

Bremmer et al. (1994) reported the CDD/CDF emissions factor for an asphalt mixing plant in The Netherlands at 47 ng I-TEQ_{DF} per metric ton of produced asphalt. No congener-specific emission factors were reported. The facility they tested heated old asphalt to about 150°C in an individual recycling drum with flue gases that were mixed with ambient air and heated to a temperature of 300–400°C. Parallel to this recycling drum, the main drum dried and heated the aggregate (sand and gravel/granite chippings) to a temperature of about 220°C. The flue gases leaving the recycling drum were led along the main burner of the main drum for incineration. The old asphalt, the minerals from the main drum, and new bitumen from a hot storage tank (about 180°C) were mixed in a mixer to form new asphalt. Natural gas fueled the tested facility during the sample collection period and used old asphalt as 46 percent of the feed. The facility's APCD system consisted of cyclones and a fabric filter.

Umweltbundesamt (1996) reported lower emission factors for three tested facilities in Germany that were also equipped with fabric filters. These three facilities were fueled by oil or butane gas and used old asphalt at rates ranging from 30 to 60 percent of the feed. The emission factors calculated from the stack gas concentrations, gas flow rates, and hourly throughputs for these three facilities were 0.2, 3.5, and 3.8 ng I-TEQ_{DF}/metric ton of asphalt produced.

Approximately 25 million metric tons of asphalt bitumen were produced in the United States in 1992. An identical quantity was produced in 1990 (U.S. DOC, 1995a). Bitumen constitutes approximately 5 percent by weight of finished paving asphalt (Bremmer et al., 1994). Thus, an estimated 500 million metric tons of paving asphalt are produced in the United States annually.

Because there are no direct measurements of CDD/CDF emissions from U.S. asphalt plants and because of uncertainties regarding the comparability of U.S. and Dutch asphalt plant technologies and feed materials, no national emission estimate for this category is proposed at this time. However, a preliminary estimate of the potential

magnitude of annual TEQ emissions for U.S. production of asphalt can be obtained by averaging the emission factors for the four facilities reported by Bremmer et al. (1994) and Umweltbundesamt (1996). Applying this average emission factor (i.e., 14 ng I-TEQ_{DF}/metric ton of asphalt produced) to the activity level of 500 million metric tons of paving asphalt produced annually yields an annual emission of 7 g I-TEQ_{DF}/yr. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions. Congener-specific results were not reported in either report. Therefore, TEQ_{DF}-WHO_{98} estimates could not be calculated.

5.3. PETROLEUM REFINING CATALYST REGENERATION

Regeneration of spent catalyst from the reforming process at petroleum refineries is a potential source of CDDs and CDFs according to limited testing conducted in the United States (Amendola and Barna, 1989; Kirby, 1994), Canada (Maniff and Lewis, 1988; Thompson et al., 1990), and The Netherlands (Bremmer et al., 1994). This section summarizes the catalyst regeneration process, relevant studies performed to date, and the status of EPA regulatory investigations of this source.

Catalytic reforming is the process used to produce high-octane reformates from lower octane reformates for blending of high-octane gasolines and aviation fuels. The reforming process occurs at high temperature and pressure and requires the use of a platinum or platinum/rhenium catalyst. During the reforming process, a complex mixture of aromatic compounds, known as coke, is formed and deposited onto the catalyst. As coke deposits onto the catalyst, its activity is decreased. The high cost of the catalyst necessitates its regeneration. Catalyst regeneration is achieved by removing the coke deposits via burning at temperatures of 750 to 850°F and then reactivating the catalyst at elevated temperatures (850 to 1,000°F) using chlorine or chlorinated compounds (e.g., methylene chloride, 1,1,1-trichloroethane, and ethylene dichloride). Burning of the coke produces flue gases that can contain CDDs and CDFs along with other combustion products. Because flue gases, if not vented directly to the atmosphere, may be scrubbed with caustic or water, internal effluents may become contaminated with CDD/CDFs (Kirby, 1994; SAIC, 1994).

There are three basic catalyst regeneration processes used: semi-regenerative, cyclic, and continuous. During the semi-regenerative process, the entire catalytic reformer is taken off-line. In the cyclic process, one of two (or more) reforming reactors is taken off-line for catalyst regeneration; the remaining reactor(s) remains on-line so that reforming operations continue. In the continuous process, aged catalyst is continuously removed from one or more on-line stacked or side-by-side reactors, regenerated in an external regenerator, and then returned to the system; the reforming system, consequently, never shuts down (SAIC, 1994).

In 1988, the Canadian Ministry of the Environment detected concentrations of CDDs in an internal waste stream of spent caustic in a petroleum refinery that ranged from 1.8 to 22.2 μgL, and CDFs ranging from 4.4 to 27.6 μg/L (Maniff and Lewis, 1988). The highest concentration of 2,3,7,8-TCDD was 0.0054 μg/L. CDDs were also observed in the refinery's biological sludge at a maximum concentration of 74.5 μg/kg, and CDFs were observed at a maximum concentration of 125 μg/kg. The concentration of CDD/CDFs in the final combined refinery plant effluent was below the detection limits.

Amendola and Barna (1989) reported detecting trace levels of hexa- to octa-CDDs and CDFs in untreated wastewaters (up to 2.9 pg I-TEQ_{DF}/L) and wastewater sludges (0.26 to 2.4 ng I-TEQ_{DF}/kg) at a refinery in Ohio. The levels of detected total CDD/CDFs in the wastewater and sludge were much lower ($<$3 ng/L and $<$1 μg/kg, respectively) than the levels reported by Maniff and Lewis (1988). No CDD/CDFs were detected in the final treated effluent (i.e., less than 0.2 ng I-TEQ_{DF}/L). The data collected in the study were acknowledged to be too limited to enable identifying the source(s) of the CDD/CDFs within the refinery. Amendola and Barna (1989) also present in an appendix to their report the results of analyses of wastewater from the catalyst regeneration processes at two other U.S. refineries. In both cases, untreated wastewaters contained CDDs and CDFs at levels ranging from high pg/L to low ng/L (results were reported for congener group totals, not specific congeners). However, CDD/CDFs were not detected in the only treated effluent sample collected at one refinery.

Thompson et al. (1990) reported total CDD and CDF concentrations of 8.9 ng/m^3 and 210 ng/m^3, respectively, in stack gas samples from a Canadian petroleum refinery's reforming operation. They also observed CDDs and CDFs in the internal wash water from a scrubber of a periodic/cyclic regenerator in the pg/L to ng/L range.

Beard et al. (1993) conducted a series of benchtop experiments to investigate the mechanism(s) of CDD/CDF formation in the catalytic reforming process. A possible pathway for the formation of CDFs was found, but the results could not explain the formation of CDDs. Analyses of the flue gas from burning coked catalysts revealed the presence of unchlorinated dibenzofuran (DBF) in quantities up to 220 μg/kg of catalyst. Chlorination experiments indicated that DBF and possibly biphenyl and similar hydrocarbons act as CDF precursors and can become chlorinated in the catalyst regeneration process. Corrosion products on the steel piping of the process plant seem to be the most likely chlorinating agent.

In May 1994, EPA's Office of Water conducted a sampling and analytical study of catalyst regeneration wastewater for CDD/CDFs at three petroleum refining plants (Kirby, 1994). The study objectives were to determine the analytical method best suited for determining CDD/CDFs in refinery wastewater and to screen and characterize wastewater discharges from several types of reforming operations for CDD/CDFs. The report for this study (Kirby, 1994) also presented results submitted voluntarily to EPA by two other facilities. The sampled internal untreated wastewaters and spent caustics were found to contain a wide range of CDD/CDF concentrations, 0.1 pg I-TEQ_{DF}/L to 57.2 ng I-TEQ_{DF}/L. The study results also showed that 90 percent of the TEQ was contained in the wastewater treatment sludges generated during the treatment of wastewater and caustic from the regeneration process.

In 1995, EPA issued a notice of its proposed intent not to designate spent reformer catalysts as a listed hazardous waste under RCRA (Federal Register, 1995b). The final rule was issued in August 1998 (Federal Register, 1998a). The Agency's assessment of current management practices associated with recycling of reforming catalyst found no significant risks to human health or the environment. The Agency estimated that 94 percent of the approximately 3,600 metric tons of spent reformer catalyst sent off-site by refineries are currently recycled for their precious-metal content. However, EPA made no determination of the "listability" of spent caustic residuals formed during regeneration of spent reforming catalyst. The Agency did identify as being possibly of concern potential air releases from the combustion of the reforming catalyst prior to reclamation. The Agency requested comments on (a) opportunities for removing dioxin prior to discharge of scrubber water into the wastewater treatment system; (b) opportunities to segregate this

wastestream; and (c) potential health risks associated with insertion of dioxin-contaminated media back into the refinery process (such as the coker). In this proposed rulemaking, EPA also noted the possibility of dioxin releases to air during regeneration operations.

As part of its regulatory investigation under RCRA, EPA's OSW commissioned a study to analyze and discuss existing data and information concerning CDD/CDF formation in the treatment of catalytic reformer wastes. This report (SAIC, 1994) also identified potential process modifications that may prevent the formation of CDD/CDFs. SAIC (1994) concluded that, although the available data indicate that CDD/CDFs can be generated during the catalyst regeneration process, the available data indicate that CDD/CDF concentrations in treated wastewater and in solid waste are minimal. Releases to air could result from vented flue gases at some facilities. In addition, the CDD/CDFs formed could possibly be reintroduced into other refining operations (e.g., the coker) and resulting products.

In 1998, emissions from the caustic scrubber used to treat gases from the external regeneration unit of a refinery in California were tested (CARB, 1999). This facility uses a continuous regeneration process. The reactor is not taken off-line during regeneration; rather, small amounts of catalyst are continuously withdrawn from the reactor and are regenerated. The emissions from the regeneration unit are neutralized by a caustic scrubber before being vented to the atmosphere. The catalyst recirculation rate during the three tests ranged from 733 to 1,000 lbs/hr.

All 2,3,7,8-substituted CDD/CDFs were detected in each of the three samples collected. The average emission factors in units of ng/barrel of reformer feed are presented in Table 5-2. The congener profile is presented in Figure 5-3. The samples showed a wide range in concentrations of the CDD/CDF congeners (up to fivefold difference); however, the congener profile was consistent in all samples. The concentrations of the individual furan congener groups were always higher than the concentrations of the corresponding dioxin congener group. The average I-TEQ_{DF} emission factor for these three tests is 3.04 ng TEQ/barrel and the average TEQ_{DF}-WHO_{98} is 3.18 ng TEQ/barrel.

In 1991, stack testing was performed on the exhaust from one of three semi-regenerative catalytic reforming units of a refinery in California (Radian, 1991b). A caustic

solution is introduced to the exhaust to neutralize hydrochloric acid emissions from the catalyst beds prior to release to the atmosphere. The tested unit was considered to be representative of the other units. Each unit is periodically (approximately once per year) taken off-line so the catalyst beds can be regenerated. The tested unit has a feed capacity of 7,000 barrels per day. Approximately 59,500 pounds of catalyst were regenerated during the tested regeneration cycle, which tested for 62 hours.

The average emission factors for this facility (in units of ng/barrel of reformer feed) are presented in Table 5-2 and the congener profile is presented in Figure 5-3. The majority of the 2,3,7,8-substituted CDD congeners were not detected during testing. In contrast, the majority of the 2,3,7,8-substituted CDF congeners were detected. The average I-TEQ_{DF} emission factor (assuming not detected values are zero) is 1.01E-03 ng TEQ/barrel and the average TEQ_{DF}-WHO_{98} emission factor is 1.04E-03 ng TEQ/barrel. These values are three orders of magnitude less than the emission factor reported in CARB (1999). The calculation of these emission factors involved several assumptions: the unit is regenerated once per year; the unit operates at capacity (i.e., 7,000 barrels/day); and the facility operates 362 days per year.

The average of the two facility emission factors, 1.52 ng I-TEQ_{DF}/barrel of reformer feed (1.59 ng TEQ_{DF}-WHO_{98}/barrel), is assigned a low confidence rating. Only one continuous and only one semi-regenerative unit in the United States have been tested. Combined, these two facilities represent less than 1 percent of the catalytic reforming capacity in U.S. petroleum refineries in 1987 (3.805 million barrels per day) and in 1995 (3.867 million barrels per day) (EIA, 1997c). The average emission factor developed above assumes that emissions are proportional to reforming capacity; however, emission factors may be more related to the amount of coke burned, the APCD equipment present, or other process parameters.

The 1987 and 1995 national daily average catalytic reforming capacities in the United States were 3.805 and 3.867 million barrels per day (EIA, 1997c). If it is conservatively assumed that all units operated at full capacity in 1987 and 1995, then applying the average emission factors of TEQ/barrel yields annual emissions of 2.11 g I-TEQ_{DF} in 1987 (2.21 g TEQ_{DF}-WHO_{98}) and 2.14 g I-TEQ_{DF} in 1995 (2.24 g TEQ_{DF}-WHO_{98}).

5.4. CIGARETTE SMOKING

Bumb et al. (1980) were the first to report that cigarette smoking is a source of CDD emissions. Subsequent studies by Muto and Takizawa (1989), Ball et al. (1990), and Löfroth and Zebühr (1992) also reported the presence of CDDs as well as CDFs in cigarette smoke. A recent study by Matsueda et al. (1994) reported the CDD/CDF content of the tobacco from 20 brands of cigarettes from seven countries. Although a wide range in the concentrations of total CDD/CDFs and total TEQs were reported in these studies, similar congener profiles and patterns were reported. The findings of each of these studies are described in this section.

No studies published to date have demonstrated a mass balance, and it is not known whether the CDD/CDFs measured in cigarette smoke are the result of formation during tobacco combustion, volatilization of CDD/CDFs present in the unburned tobacco, or a combination of these two source mechanisms. The combustion processes operating during cigarette smoking are complex and could be used to justify both source mechanisms. As reported by Guerin et al. (1992), during a puff, gas phase temperatures reach 850°C at the core of the firecone, and solid phase temperatures reach 800°C at the core and 900°C or greater at the char line. Thus, temperatures are sufficient to cause at least some destruction of CDD/CDFs initially present in the tobacco. Both solid and gas phase temperatures rapidly decline to 200 to 400°C within 2 mm of the char line. Formation of CDD/CDFs has been reported in combustion studies with other media in this temperature range of 200 to 900°C. However, it is known that a process likened by Guerin et al. (1992) to steam distillation takes place in the region behind the char line because of high, localized concentrations of water and temperatures of 200 to 400°C. At least 1,200 tobacco constituents (e.g., nicotine, n-paraffin, some terpenes) are transferred intact from the tobacco into the smoke stream by distillation in this region, and it is plausible that CDD/CDFs present in the unburned tobacco would be subject to similar distillation.

Bumb et al. (1980), using low-resolution mass spectrometry, analyzed the CDD content of mainstream smoke from the burning of a U.S. brand of unfiltered cigarette. A package of 20 cigarettes was combusted in each of two experiments. Approximately 20 to 30 puffs of 2 to 3 seconds duration were collected from each cigarette on a silica

column. Hexa-, hepta-, and octa-CDD were detected at levels of 0.004–0.008, 0.009, and 0.02–0.05 ng/g, respectively.

Muto and Takizawa (1989) employed a continuous smoking apparatus to measure CDD congener concentrations in the mainstream smoke generated from the combustion of one kind of filtered cigarette (brand not reported). The apparatus pulled air at a constant continuous rate (rather than a pulsed rate) through a burning cigarette and collected the smoke on a series of traps (glass fiber filter, polyurethane foam, and XAD-II resin). The CDD content of the smoke, as well as the CDD content of the unburned cigarette and the ash from the burned cigarettes, were also analyzed using low-resolution mass spectrometry. The results are presented in Table 5-3, and the congener group profiles are presented in Figure 5-4. Table 5-3 and Figure 5-4 present the mainstream smoke results on a mass per cigarette basis to enable comparison with the results of other studies. The major CDD congener group that was found was HpCDD, which accounted for 84 percent of total CDDs found in the cigarette, 94 percent of total CDDs found in smoke, and 99 percent of total CDDs found in the ash. The 2,3,7,8-HpCDDs also accounted for the majority of the measured TEQ in the cigarettes and smoke; however, none were measured in the ash. Although no PeCDDs were detected in the cigarette, PeCDDs were detected at low levels in the smoke, indicating probable formation during combustion. On the basis of the similarities in the congener group profiles for the three media, Muto and Takizawa (1989) concluded that most of the CDDs found in the cigarette smoke are the result of volatilization of CDD/CDFs present in the unburned cigarette rather than formation during combustion.

Ball et al. (1990) measured the CDD/CDF content of mainstream smoke for the 10 best-selling German cigarette brands. The international test approach (i.e., 1 puff/min; puff flow rate of 35 mL/2 sec) was employed with an apparatus that smoked 20 cigarettes at a time in three successive batches with a large collection device. The average TEQ content (on both an I-TEQ_{DF} and TEQ_{DF}-WHO_{98} basis) in mainstream smoke for the 10 brands tested, normalized to a mass per cigarette basis, was 0.09 pg/cigarette (i.e., 16.5 times less than the value reported by Muto and Takizawa (1989) for a Japanese cigarette brand). However, the congener group profiles were similar to those reported by Muto and Takizawa (1989) with HpCDD and OCDD the dominant congener groups found.

Löfroth and Zebühr (1992) measured the CDD/CDF content of mainstream and sidestream smoke from one common Swedish cigarette brand. The cigarette brand was labeled as giving 17 mg carbon monoxide, 21 mg tar, and 1.6 mg nicotine. The international test approach (i.e., 1 puff/min; puff flow rate of 35 mL/2 sec) was used, and the smoke was collected on glass fiber filters followed by two polyurethane plugs. The analytical results for mainstream and sidestream smoke are presented in Table 5-4. The TEQ content in mainstream smoke, normalized to a mass per cigarette basis, was 0.90 pg I-TEQ_{DF}/cigarette or 0.96 pg TEQ_{DF}-WHO_{98}/cigarette (i.e., about 2 times less than the value reported by Muto and Takizawa (1989) and 10 times greater than the average value reported by Ball et al. 1990). As was reported by Muto and Takizawa (1989) and Ball et al. (1990), the dominant congener groups were HpCDDs and OCDD; however, HpCDFs were also relatively high compared to the other congener group totals. The sidestream smoke contained 1.96 pg I-TEQ_{DF} per cigarette (2.08 pg TEQ_{DF}-WHO_{98} per cigarette), or twice that of mainstream smoke.

Using high-resolution mass spectrometry, Matsueda et al. (1994) analyzed the CDD/CDF content of tobacco from 20 brands of commercially available cigarettes collected in 1992 from Japan, the United States, Taiwan, China, the United Kingdom, Germany, and Denmark. Table 5-5 presents the study results. The total CDD/CDF content and total I-TEQ_{DF} content ranged from 109 to 1,136 pg/pack and from 1.4 to 12.6 pg/pack (1.9 to 14.0 pg/pack on a TEQ_{DF}-WHO_{98} basis), respectively. The Chinese cigarette brand contained significantly lower CDD/CDFs and TEQs than any other brand of cigarette. Figure 5-6 depicts the congener group profiles for the average results for each country. A high degree of similarity is shown in the CDF congener group profiles between the tested cigarette brands. The Japanese and Taiwanese cigarettes show CDD congener group profiles different from the other countries' cigarettes.

In 1995, approximately 487 billion cigarettes were consumed in the United States and by U.S. overseas armed forces personnel. In 1987, approximately 575 billion cigarettes were consumed. Per capita U.S. cigarette consumption, based on total U.S. population aged 16 and over, declined to 2,415 in 1995; the record high was 4,345 in 1963 (The Tobacco Institute, 1995; USDA, 1997). These activity level estimates are assigned a high confidence rating.

The available emission factor data presented above provide the basis for two methods of estimating the amount of TEQs that may have been released to the air in the United States in 1995 and in 1987 from the combustion of cigarettes. The confidence rating assigned to the emission factor is low because of the very limited amount of testing performed to date. First, an annual emission estimate for 1995 of 0.21 g TEQ (on an I-TEQ_{DF} or TEQ_{DF}-WHO_{98} basis) is obtained if it is assumed that (a) the average TEQ content of seven brands of U.S. cigarettes reported by Matsueda et al. (1994), 8.6 pg I-TEQ_{DF}/pack or 8.8 pg TEQ_{DF}-WHO_{98}/pack, are representative of cigarettes smoked in the United States; (b) CDD/CDFs are not formed, and the congener profile reported by Matsueda et al. (1994) is not altered during combustion of cigarettes; and (c) all CDD/CDFs contributing to the TEQ are released from the tobacco during smoking. The second method of estimating is based on the assumption that the TEQ emission rates for a common Swedish brand of cigarette reported by Löfroth and Zebühr (1992) for mainstream smoke (0.90 pg I-TEQ_{DF}/cigarette or 0.96 pg TEQ_{DF}-WHO_{98}/cigarette) and sidestream smoke (1.96 pg I-TEQ_{DF}/cigarette or 2.08 pg TEQ_{DF}-WHO_{98}/cigarette) are representative of the emission rates for U.S. cigarettes. This second method yields an annual emission estimate of 1.41 g I-TEQ_{DF} or 1.48 g TEQ_{DF}-WHO_{98}. For 1987, the two methods yield estimates of 0.25 g TEQ (I-TEQ_{DF} or TEQ_{DF}-WHO_{98} basis) and 1.67 g I-TEQ_{DF} (or 1.75 g TEQ_{DF}-WHO_{98}).

For purposes of this report, the best estimates of annual emissions are assumed to be the average of the annual emissions estimated by the two methods for 1995 and 1987 (0.8 g TEQ and 1.0 g TEQ), respectively (I-TEQ_{DF} or TEQ_{DF}-WHO_{98} basis). Although these emission quantities are relatively small when compared to the emission quantities estimated for various industrial combustion source categories, the emissions are significant because humans are directly exposed to cigarette smoke.

5.5. PYROLYSIS OF BROMINATED FLAME RETARDANTS

The pyrolysis and photolysis of brominated phenolic derivatives and polybrominated biphenyl ethers used as flame retardants in plastics (especially those used in electronic devices), textiles, and paints can generate considerable amounts of polybrominated dibenzo-p-dioxins (BDDs) and dibenzofurans (BDFs) (Watanabe and Tatsukawa, 1987; Thoma and Hutzinger, 1989; Luijk et al., 1992). Watanabe and Tatsukawa (1987)

observed the formation of BDFs from the photolysis of decabromobiphenyl ether. Approximately 20 percent of the decabromobiphenyl ether was converted to BDFs in samples that were irradiated with ultraviolet light for 16 hours.

Thoma and Hutzinger (1989) observed the formation of BDFs during combustion experiments with polybutylene-terephthalate polymers containing 9 to 11 percent decabromodiphenyl ether. Maximum formation of BDFs occurred at 400 to 600°C, with a BDF yield of 16 percent. Although Thoma and Hutzinger (1989) did not provide specific quantitative results for similar experiments conducted with octabromodiphenyl ether and 1,2-bis(tri-bromophenoxy)ethane, they did report that BDDs and BDFs were formed.

Luijk et al. (1992) studied the formation of BDD/BDFs during the compounding and extrusion of decabromodiphenyl ether into high-impact polystyrene polymer at 275°C. HpBDF and OBDF were formed during repeated extrusion cycles, and the yield of BDFs increased as a function of the number of extrusion cycles. HpBDF increased from 1.5 to 9 ppm (in the polymer matrix), and OBDF increased from 4.5 to 45 ppm after four extrusion cycles.

Insufficient data are available at this time from which to derive annual BDD/BDF emission estimates for this source.

5.6. CARBON REACTIVATION FURNACES

Granular activated carbon (GAC) is an adsorbent that is widely used to remove organic pollutants from wastewater and to treat finished drinking water at water treatment plants. Activated carbon is manufactured from the pyrolytic treatment of nut shells and coal (Buonicore, 1992a). The properties of GAC make it ideal for adsorbing and controlling vaporous organic and inorganic chemicals entrained in combustion plasmas, as well as soluble organic contaminants in industrial effluents and drinking water. The high ratio of surface area to particle weight (600 to 1,600 m^2/g), combined with the extremely small pore diameter of the particles (15–25 angstroms), increases the adsorption characteristics (Buonicore, 1992a). GAC eventually becomes saturated, and the adsorption properties significantly degrade. When saturation occurs, GAC usually must be replaced and discarded, which significantly increases the costs of pollution control. The introduction of carbon reactivation furnace technology in the mid-1980s created a method involving the thermal treatment of used GAC to thermolytically desorb the synthetic

compounds and restore the adsorption properties for reuse (Lykins et al., 1987). Large-scale regeneration operations, such as those used in industrial water treatment operations, typically use multiple-hearth furnaces. For smaller-scale operations, such as those used in municipal water treatment operations, fluidized-bed and infrared furnaces are used. Emissions are typically controlled by afterburners followed by water scrubbers (U.S. EPA, 1997b).

The used GAC can contain compounds that are precursors to the formation of CDD/CDFs during the thermal treatment process. EPA measured precursor compounds in spent GAC that was used as a feed material to a carbon reactivation furnace tested during the National Dioxin Study (U.S. EPA, 1987a). The total chlorobenzene content of the GAC ranged from 150 to 6,630 ppb. Trichlorobenzene was the most prevalent species present, with smaller quantities of di- and tetra-chlorobenzenes detected. Total halogenated organics were measured to be about 150 ppm.

EPA has stack-tested two GAC reactivation furnaces for the emission of dioxin (U.S. EPA, 1987a; Lykins et al., 1987). One facility was an industrial carbon reactivation plant, and the second facility was used to restore GAC at a municipal drinking water plant. EPA (1997b) also reported results of other testing performed at a county water facility in California during 1990.

The industrial carbon reactivation plant processed 36,000 kg/day of spent GAC used in the treatment of industrial wastewater effluents. This facility was chosen for testing because it was considered to be representative of other facilities in the source category (U.S. EPA, 1987a). Spent carbon was reactivated in a multiple-hearth furnace, cooled in a water quench, and shipped back to primary chemical manufacturing facilities for reuse. The furnace was fired by natural gas and consisted of seven hearths arranged vertically in series. The hearth temperatures ranged from 480 to 1,000°C. Air pollutant emissions were controlled by an afterburner, a sodium spray cooler, and a fabric filter. Temperatures in the afterburner were about 930°C. The estimated I-TEQ_{DF} emission factor (treating not-detected values as zero) was 0.64 ng I-TEQ_{DF}/kg carbon processed (0.76 ng TEQ_{DF}-WHO_{98}). The emission factor for total CDD/CDF was 58.6 ng/kg. Because analyses were performed only for 2,3,7,8-TCDD, 2,3,7,8-TCDF, OCDD, and OCDF and the congener groups, equivalent concentrations were assumed for all toxic and nontoxic congeners in each of the penta-, hexa-, and hepta-congener groups.

The second GAC reactivation facility tested by EPA consisted of a fluidized-bed furnace located at a municipal drinking water treatment plant (Lykins et al., 1987). The furnace was divided into three sections: a combustion chamber, a reactivation section, and a dryer section. The combustion section was fired by natural gas and consisted of a stoichiometrically balanced stream of fuel and oxygen. Combustion temperatures were about 1,038°C. Gases from the reactivation and combustion section were directed through an acid gas scrubber and high-temperature afterburner prior to discharge from a stack. Although measurable concentrations of dioxin-like compounds were detected in the stack emissions, measurements of the individual CDD/CDF congeners were not performed; therefore, it was not possible to derive TEQ emission factors for this facility. With the afterburner operating, no CDD congeners below HpCDD were detected in the stack emissions. Concentrations of HpCDDs and OCDD ranged from 0.001 to 0.05 ppt/v and 0.006 to 0.28 ppt/v, respectively. All CDF congener groups were detected in the stack emissions even with the afterburner operating. Total CDFs emitted from the stack averaged 0.023 ppt/v.

From the results of a test of the reactivation unit at a county water facility in California in 1990, EPA reported a TEQ emission factor of 1.73 ng I-TEQ_{DF}/kg of carbon processed (U.S. EPA, 1997b). The emission factor for total CDD/CDF was reported to be 47 ng/kg (i.e., similar to the total CDD/CDF emission factor of 58.6 ng/kg at the industrial GAC facility). Because congener-specific results were not reported, it was not possible to calculate the TEQ_{DF}-WHO_{98} emission factor. The report also did not provide the configuration and type of furnace tested; however, it did state that the emissions from the furnace were controlled by an afterburner and a scrubber.

The industrial GAC reaction furnace test data indicate that an average of 0.64 ng I-TEQ_{DF}/kg of GAC may be released. The I-TEQ_{DF} emission rate for the reactivation unit at the county water treatment facility was 1.73 ng I-TEQ_{DF}/kg carbon. Low confidence ratings are given to these emission factors because only two GAC reactivation furnaces were stack-tested and not all congeners were analyzed at the industrial GAC facility.

The mass of GAC that is reactivated annually in carbon reactivation furnaces is not known. However, a rough estimate, to which a low confidence rating is assigned, is the mass of virgin GAC shipped each year by GAC manufacturers. According to the Department of Commerce (1990c), 48,000 metric tons of GAC were shipped in 1987.

EPA (1995c; 1997b) reported that in 1990, water and wastewater treatment operations consumed 65,000 metric tons of GAC. The 1990 activity level is used in this document as a surrogate for the 1995 activity level.

Applying the average TEQ emission factor of 1.2 ng I-TEQ_{DF} (or TEQ_{DF}-WHO_{98}) per kg of reactivated carbon for the two tested facilities to the estimates of potential GAC reactivation volumes, yields annual release estimates of 0.06 g I-TEQ_{DF} (or TEQ_{DF}-WHO_{98}) in 1987 and 0.08 g I-TEQ_{DF} (or TEQ_{DF}-WHO_{98}) in 1995 (assuming that the activity level for 1990 is representative of the 1995 activity level).

5.7. KRAFT BLACK LIQUOR RECOVERY BOILERS

Kraft black liquor recovery boilers are associated with the production of pulp in the making of paper using the Kraft process. In this process, wood chips are cooked in large vertical vessels called digesters at elevated temperatures and pressures in an aqueous solution of sodium hydroxide and sodium sulfide. Wood is broken down into two phases: a soluble phase containing primarily lignin, and an insoluble phase containing the pulp. The spent liquor (called black liquor) from the digester contains sodium sulfate and sodium sulfide, which the industry recovers for reuse in the Kraft process. In the recovery of black liquor chemicals, weak black liquor is first concentrated in multiple-effect evaporators to about 65 percent solids. The concentrated black liquor also contains 0.5 to 4 percent chlorides by weight, which are recovered through combustion. The concentrated black liquor is sprayed into a Kraft black liquor recovery furnace equipped with a heat recovery boiler. The bulk of the inorganic molten smelt that forms in the bottom of the furnace contains sodium carbonate and sodium sulfide in a ratio of about 3:1. The combustion gas is usually passed through an electrostatic precipitator (ESP) that collects particulate matter prior to being vented out the stack. The particulate matter can be processed to further recover and recycle sodium sulfate (Someshwar and Pinkerton, 1992).

In 1987, EPA stack-tested three Kraft black liquor recovery boilers for the emission of dioxin in conjunction with the National Dioxin Study (U.S. EPA, 1987a). The three sites tested by EPA were judged to be typical of Kraft black liquor recovery boilers at that time. During pretest surveys, two facilities were judged to have average potential and one was judged to have high potential for CDD/CDF emissions based on the amount of

chlorine found in the feed to these units. Dry-bottom ESPs controlled emissions from two of the boilers; a wet-bottom ESP controlled emissions from the third. The results of these tests include congener group concentrations but lack measurement results for specific congeners other than 2,3,7,8-TCDD and 2,3,7,8-TCDF. NCASI (1995) provided congener-specific emission test results for six additional boilers tested during 1990 to 1993. Three boilers were of the direct contact type, and three were noncontact type. All were equipped with ESPs. The average congener and congener group emission factors are presented in Table 5-6 for the three facilities from U.S. EPA (1987a) and the six facilities from NCASI (1995). Figure 5-7 presents the average congener and congener group profiles based on the test results presented in NCASI (1995).

The average TEQ emission factor based on the data for the six NCASI facilities with complete congener data is 0.029 ng I-TEQ_{DF}/kg of black liquor solids, assuming nondetected values are zero (0.028 ng TEQ_{DF}-WHO_{98}/kg), and 0.068 ng I-TEQ_{DF}/kg assuming nondetected values are present at one-half the detection limit (0.078 ng TEQ_{DF}-WHO_{98}/kg). The results for the three facilities reported in U.S. EPA (1987a) were not used in the derivation of the TEQ emission factor because congener-specific measurements for most 2,3,7,8-substituted congeners were not made in the study. A medium confidence rating is assigned to those emission factors because the emission factors were derived from the stack-testing of six Kraft black liquor recovery boilers that were judged to be fairly representative of technologies used at Kraft pulp mills in the United States. A 1995 survey of the industry indicated that 215 black liquor recovery boilers were in operation at U.S. pulp and paper mills. All but one of these boilers used ESPs for control of particulate emissions; the one unique facility used dual scrubbers. In addition, ESPs were reported to have been the predominant means of particulate control at recovery boilers for the past 20 years (Gillespie, 1998).

The amounts of black liquor solids burned in Kraft black liquor recovery boilers in the United States during 1987 and 1995 were 69.8 million metric tons and 80.8 million metric tons, respectively (American Paper Institute, 1992; American Forest & Paper Association, 1997). These activity level estimates are assigned a high confidence rating because they are based on recent industry survey data. Combining the emission factors derived above with the activity level estimates of 69.8 and 80.8 million metric tons in 1987 and 1995, respectively, yields estimated annual emissions from this source of

approximately 2.0 g I-TEQ_{DF} (2.0 g TEQ_{DF}-WHO_{98}) in 1987 and 2.3 g I-TEQ_{DF} (2.3 g TEQ_{DF}-WHO_{98}) in 1995.

5.8. OTHER IDENTIFIED SOURCES

Several manufacturing processes are identified as potential sources of CDD/CDF formation because the processes use chlorine-containing components or involve application of high temperatures. However, no testing of emissions from these processes has been performed in the United States, and only minimal emission rate information has been reported for these processes in other countries.

Burning of Candles. Schwind et al. (1995) analyzed the wicks and waxes of uncolored candles, as well as the fumes of burning candles, for CDD/CDF, total chlorophenol, and total chlorobenzene content. The results presented in Table 5-7 show that beeswax contained the highest levels of CDD/CDF and total chlorophenols. In contrast, the concentration of total chlorobenzenes in stearin wax was higher by a factor of 2 to 3 times than that in paraffin or beeswax. The concentrations of the three analyte groups were significantly lower in the wicks than in the waxes. Emissions of CDD/CDF from all three types of candles were very low during burning. In fact, comparison of the emission factor to the original CDD/CDF concentration in the wax indicates a net destruction of the CDD/CDF originally present in the wax.

Information is not readily available on the volume of candles consumed annually in the United States. However, in 1992, the value of wholesale shipments of candles in the United States was nearly $360 million (U.S. DOC, 1996). Assuming that the average wholesale cost per kg of candle is $1, then the volume of candles shipped was 360 million kg. If it is further assumed that 75 percent of the candle volume is actually burned and that the CDD/CDF emissions rate is 0.015 ng/kg, then a rough preliminary estimate of the potential annual emission from combustion of candles is 4 mg I-TEQ_{DF}/yr.

Glass Manufacturing. Bremmer et al. (1994) and Douben et al. (1995) estimated annual emissions of less than 1 g I-TEQ_{DF}/yr from glass manufacturing facilities in The Netherlands and the United Kingdom, respectively. Glass is manufactured by heating a mixture of sand and, depending on the type of glass, lime, sodium carbonate, dolomite, clay, or feldspar to a temperature of 1,400 to 1,650°C. In addition, various coloring and clarifying agents may be added. Chlorine enters the process as a contaminant (i.e., NaCl)

in sodium carbonate (Bremmer et al. 1994). However, the emission factors used by Bremmer et al. (1994) and Douben et al. (1995) were not reported. Umweltbundesamt (1996) reported relatively low emission factors (approximately 0.002 and 0.007 ng I-TEQ_{DF}/kg) for two glass manufacturing facilities in Germany.

Lime Kilns. Annual emissions from lime kilns in Belgium and the United Kingdom have been reported by Wevers and De Fre (1995) and Douben et al. (1995), respectively. However, the emission factors used to generate those estimates were not provided. Umweltbundesamt (1996) reported low emissions (0.016 to 0.028 ng I-TEQ_{DF}/kg) during tests at two lime kilns in Germany.

Ceramics and Rubber Manufacturers. Douben et al. (1995) estimated annual emissions from ceramic manufacturers and rubber manufacturers in the United Kingdom. Lexen et al. (1993) had previously detected high concentrations of CDD/CDF in emissions from a ceramic manufacturer in Sweden, which occasionally glazed ceramics by volatilization of sodium chloride in a coal-fired oven. Lexen et al. (1993) also detected high pg/L levels of I-TEQ_{DF} in the scrubber water from the vulcanization process at a Swedish rubber manufacturer.

Table 5-1. CDD/CDF Emission Factors for Cement Kilns

Congener/Congener Group	Kilns Burning Hazardous Waste—Mean Emission Factor (ND values set equal to zero) (ng/kg clinker produced)		Kilns Not Burning Hazardous Waste—Mean Emission Factor (ND values set equal to zero) (ng/kg clinker produced)
	APCD Inlet Temperature >450°F	APCD Inlet Temperature <450°F	
2,3,7,8-TCDD	3.38	0.02	0.012
1,2,3,7,8-PeCDD	4.28	0.13	0.034
1,2,3,4,7,8-HxCDD	4.85	0.29	0.028
1,2,3,6,7,8-HxCDD	6.93	0.42	0.042
1,2,3,7,8,9-HxCDD	9.55	0.40	0.048
1,2,3,4,6,7,8-HpCDD	27.05	3.16	0.426
OCDD	18.61	1.08	0.692
2,3,7,8-TCDF	36.26	3.24	0.729
1,2,3,7,8-PeCDF	13.36	0.23	0.102
2,3,4,7,8-PeCDF	23.48	0.65	0.224
1,2,3,4,7,8-HxCDF	22.24	0.55	0.185
1,2,3,6,7,8-HxCDF	8.46	0.27	0.054
1,2,3,7,8,9-HxCDF	0.96	0.06	0.007
2,3,4,6,7,8-HxCDF	13.33	0.52	0.082
1,2,3,4,6,7,8-HpCDF	7.73	0.34	0.146
1,2,3,4,7,8,9-HpCDF	2.16	0.16	0.005
OCDF	2.51	0.37	0.234
Total I-TEQ_{DF}	28.58	1.04	0.27
Total TEQ_{DF}-WHO_{98}	30.70	1.11	0.29
Total TCDD	406.76	1.78	1.97
Total PeCDD	608.65	0.89	2.07
Total HxCDD	845.99	0.69	5.96
Total HpCDD	192.99	0.42	0.84
Total OCDD	18.61	1.08	0.69
Total TCDF	295.72	11.52	6.82
Total PeCDF	127.99	3.83	2.00
Total HxCDF	50.75	1.88	0.60
Total HpCDF	8.36	0.47	0.24
Total OCDF	2.51	0.37	0.23
Total CDD/CDF	2558.33	22.92	21.44

NR = Not reported.

Source: U.S. EPA (1996c)

Table 5-2. CDD/CDF Emission Factors for Petroleum Catalytic Reforming Units

Congener/Congener Group	Semi-regenerative Unit (ng/barrel)		Continuous Regeneration Unit (ng/barrel)	
	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit
2,3,7,8-TCDD	ND	2.35e-05	1.61e-02	1.61e-02
1,2,3,7,8-PeCDD	5.69e-05	9.58e-05	2.87e-01	2.87e-01
1,2,3,4,7,8-HxCDD	4.22e-05	8.09e-05	3.47e-01	3.47e-01
1,2,3,6,7,8-HxCDD	ND	5.52e-05	8.45e-01	8.45e-01
1,2,3,7,8,9-HxCDD	ND	5.10e-05	5.56e-01	5.56e-01
1,2,3,4,6,7,8-HpCDD	7.02e-04	7.02e-04	3.02e+00	3.02e+00
OCDD	2.55e-03	2.55e-03	1.71e+00	1.71e+00
2,3,7,8-TCDF	2.32e-04	2.32e-04	6.10e-01	6.10e-01
1,2,3,7,8-PeCDF	4.68e-04	4.68e-04	1.72e+00	1.72e+00
2,3,4,7,8-PeCDF	1.09e-03	1.09e-03	2.33e+00	2.33e+00
1,2,3,4,7,8-HxCDF	1.06e-03	1.06e-03	4.70e+00	4.70e+00
1,2,3,6,7,8-HxCDF	1.07e-03	1.07e-03	3.58e+00	3.58e+00
1,2,3,7,8,9-HxCDF	ND	6.82e-05	4.34e-01	4.34e-01
2,3,4,6,7,8-HxCDF	1.24e-03	1.24e-03	3.10e+00	3.10e+00
1,2,3,4,6,7,8-HpCDF	2.94e-03	2.94e-03	1.59e+01	1.59e+01
1,2,3,4,7,8,9-HpCDF	8.32e-04	8.32e-04	1.45e+00	1.45e+00
OCDF	1.01e-03	1.01e-03	3.75e+00	3.75e+00
Total 2,3,7,8-CDD	3.35e-03	3.56e-03	6.77e+00	6.77e+00
Total 2,3,7,8-CDF	9.94e-03	1.00e-02	3.76e+01	3.76e+01
Total I-TEQ_{DF}	1.01e-03	1.08e-03	3.04e+00	3.04e+00
Total TEQ_{DF}-WHO_{98}	1.04e-03	1.12e-03	3.18e+00	3.18e+00
Total TCDD	ND	2.35e-05	6.84e+00	6.84e+00
Total PeCDD	3.56e-04	3.56e-04	5.61e+00	5.61e+00
Total HxCDD	1.28e-03	1.28e-03	8.18e+00	8.18e+00
Total HpCDD	1.39e-03	1.39e-03	6.58e+00	6.58e+00
Total OCDD	2.55e-03	2.55e-03	1.71e+00	1.71e+00
Total TCDF	2.70e-03	2.70e-03	4.68e+01	4.68e+01
Total PeCDF	5.12e-03	5.12e-03	3.30e+01	3.30e+01
Total HxCDF	7.85e-03	7.85e-03	2.96e+01	2.96e+01
Total HpCDF	4.88e-03	4.88e-03	2.11e+01	2.11e+01
Total OCDF	1.01e-03	1.01e-03	3.75e+00	3.75e+00
Total CDD/CDF	2.71e-02	2.72e-02	1.63e+02	1.63e+02

ND = Not detected.

Note: 1 barrel assumed to be equivalent to 139 kg.

Sources: Radian (1991b) and CARB (1999)

Table 5-3. CDD Concentrations in Japanese Cigarettes, Smoke, and Ash

Congener/Congener Group	Cigarette (pg/g)	Concentrations	
		Mainstream Smoke (ng/m^3)	Ash (pg/g)
2,3,7,8-TCDD	ND (0.5)	ND (0.22)	ND (0.5)
1,2,3,7,8-PeCDD	ND (0.5)	0.43	ND (0.5)
1,2,3,4,7,8-HxCDD	2.01[a]	2.15[a]	0.56[a]
1,2,3,6,7,8-HxCDD	a	a	a
1,2,3,7,8,9-HxCDD	a	a	a
1,2,3,4,6,7,8-HpCDD	1,343	783	ND (0.5)
OCDD	257	240	ND (0.5)
2,3,7,8-TCDF	—	—	—
1,2,3,7,8-PeCDF	—	—	—
2,3,4,7,8-PeCDF	—	—	—
1,2,3,4,7,8-HxCDF	—	—	—
1,2,3,6,7,8-HxCDF	—	—	—
1,2,3,7,8,9-HxCDF	—	—	—
2,3,4,6,7,8-HxCDF	—	—	—
1,2,3,4,6,7,8-HpCDF	—	—	—
1,2,3,4,7,8,9-HpCDF	—	—	—
OCDF	—	—	—
Total 2,3,7,8-CDD	1,602	1,026	0.56
Total 2,3,7,8-CDF	--	--	--
Total I-TEQ_{DF}	13.9	8.5	0.06
Total TEQ_{DF}-WHO_{98}	13.7	8.3	0.06
Total TCDD	44.9	68.0	4.63
Total PeCDD	ND (0.5)	1.51	ND (0.5)
Total HxCDD	13.41	7.51	5.01
Total HpCDD	1,629	4,939	3,211
Total OCDD	257	240	ND (0.5)
Total TCDF	—	—	—
Total PeCDF	—	—	—
Total HxCDF	—	—	—
Total HpCDF	—	—	—
Total OCDF	—	—	—
Total CDD/CDF	1,944	5,256	3,221

ND = Not detected (detection limit is in parentheses).
— = Not reported.

a Value reported only for total 2,3,7,8-substituted HxCDDs.

Source: Muto and Takizawa (1989)

Table 5-4. CDD/CDF Emissions in Cigarette Smoke

Congener/Congener Group	Concentrations — Normalized to a per Cigarette Basis (pg/cig)			
	Ref. A (1 Japanese brand) (mainstream smoke)	Ref. B (Avg of 10 German brands) (mainstream smoke)	Ref. C (1 Swedish brand) (mainstream smoke)	Ref. C (1 Swedish brand) (sidestream smoke)
2,3,7,8-TCDD	ND (0.04)	ND (0.03)	0.028	0.07
1,2,3,7,8-PeCDD	0.075	ND (0.03)	0.15	0.32
1,2,3,4,7,8-HxCDD	0.376	0.06	0.10	0.19
1,2,3,6,7,8-HxCDD	b	0.05	0.34	0.60
1,2,3,7,8,9-HxCDD	b	0.04	0.25	0.55
1,2,3,4,6,7,8-HpCDD	137	1.3	6.05	12.2
OCDD	42	3.4	22.1	38.8
2,3,7,8-TCDF	—	0.19	1.2[c]	2.1[c]
1,2,3,7,8-PeCDF	—	0.13	0.34[c]	0.80[c]
2,3,4,7,8-PeCDF	—	0.04	0.34	0.60
1,2,3,4,7,8-HxCDF	—	ND (0.03)	1.3[c]	3.8[c]
1,2,3,6,7,8-HxCDF	—	0.03	0.48	1.2
1,2,3,7,8,9-HxCDF	—	0.03	0.14	0.39
2,3,4,6,7,8-HxCDF	—	0.05	0.21	0.50
1,2,3,4,6,7,8-HpCDF	—	0.16	10.0	23.5
1,2,3,4,7,8,9-HpCDF	—	0.03	2.6	5.0
OCDF	—	0.11	3.2	10.7
Total 2,3,7,8-CDD	179	4.85	29.0	52.7
Total 2,3,7,8-CDF	--	0.77	19.8	48.6
Total I-TEQ_{DF}	1.49	0.09	0.90	1.96
Total TEQ_{DF}-WHO_{98}	1.49	0.09	0.96	2.08
Total TCDD	11.9	0.51	0.61	0.67
Total PeCDD	0.264	0.14	1.07	2.14
Total HxCDD	1.31	0.53	2.52	5.2
Total HpCDD	864	2.9	12.3	21.3
Total OCDD	42	3.4	22.1	38.8
Total TCDF	—	1.41	4.5	5.75
Total PeCDF	—	0.83	3.23	6.35
Total HxCDF	—	0.35	5.30	12.9
Total HpCDF	—	0.27	19.8	47.8
Total OCDF	—	0.11	3.2	10.7
Total CDD/CDF	919	10.5	74.5	152

Ref. A: Muto and Takizawa (1989)
Ref. B: Ball et al. (1990)
Ref. C: Löfroth and Zebühr (1992)

ND = Not detected (detection limit is in parentheses).
— = Not reported.
a Emissions calculated assuming 0.0035 m^3 of smoke are inhaled per 20 cigarettes smoked (Muto and Takizawa, 1992).
b Ref. A reported a value only for total 2,3,7,8-HxCDDs (0.38 pg/cig).
c Concentrations listed include the contribution of a coeluting non-2,3,7,8-substituted congener.

Table 5-5. CDD/CDF Concentrations in Cigarette Tobacco

Congener/Congener Group	Concentrations in Brands from Various Countries (pg/pack)						
	U.S. Brands (Avg of 7 brands)	Japan (Avg of 6 brands)	United Kingdom (Avg of 3 brands)	Taiwan (1 brand)	China (1 brand)	Denmark (1 brand)	Germany (1 brand)
2,3,7,8-TCDD	1.2	0.5	1.7	1.0	ND	0.5	1.1
1,2,3,7,8-PeCDD	1.6	1.4	3.1	3.3	1.1	0.8	3.3
1,2,3,4,7,8-HxCDD	6.9	4.8	6.1	12.2	1.1	6.2	5.7
1,2,3,6,7,8-HxCDD	a	a	a	a	a	a	a
1,2,3,7,8,9-HxCDD	a	a	a	a	a	a	a
1,2,3,4,6,7,8-HpCDD	52.7	17.8	23.9	26.4	2.2	53.3	32.7
OCDD	589.3	244.0	189.5	272.7	28.2	354.3	288.6
2,3,7,8-TCDF	18.2	4.8	15.6	11.0	1.2	2.2	7.9
1,2,3,7,8-PeCDF	8.7	5.3	21.2	16.0	1.5	4.3	14.4
2,3,4,7,8-PeCDF	b	b	b	b	b	b	b
1,2,3,4,7,8-HxCDF	8.1	8.1	17.0	12.9	2.2	4.3	13.2
1,2,3,6,7,8-HxCDF	c	c	c	c	c	c	c
1,2,3,7,8,9-HxCDF	c	c	c	c	c	c	c
2,3,4,6,7,8-HxCDF	c	c	c	c	c	c	c
1,2,3,4,6,7,8-HpCDF	17.6	11.1	13.6	13.2	1.5	7.0	12.9
1,2,3,4,7,8,9-HpCDF	d	d	d	d	d	d	d
OCDF	24.6	10.5	8.3	13.9	0.5	10.5	13.9
Total 2,3,7,8-CDD	652	268.5	224.3	315.6	32.6	415.1	331.4
Total 2,3,7,8-CDF	77.2	39.8	75.7	67	6.9	28.3	62.3
Total I-TEQ_{DF}	8.6	4.6	12.6	9.3	1.4	3.8	9.1
Total TEQ_{DF}-WHO_{98}	8.8	5.1	14.0	10.7	1.9	3.9	10.5
Total TCDD	47.1	296.3	85.1	329	9.7	17.0	49.5
Total PeCDD	27.6	33.6	62.9	150.5	5.2	9.8	40.8
Total HxCDD	40.6	29.2	49.2	99.4	5.4	26.7	40.6
Total HpCDD	108.7	40.0	47.7	62.0	3.8	93.1	60.2
Total OCDD	589.3	244.0	189.5	272.7	28.2	354.3	288.6
Total TCDF	183.8	102.1	348.9	372.1	35.4	97.8	233.4
Total PeCDF	57.7	45.9	134.5	149.1	11.2	35.5	97.5
Total HxCDF	29.1	26.4	51.3	45.8	7.8	18.1	40.8
Total HpCDF	27.3	16.6	19.0	18.5	1.7	11.1	21.2
Total OCDF	24.6	10.5	8.3	13.9	0.5	10.5	13.9
Total CDD/CDF	1136	845	996	1513	109	674	887

Source: Matsueda et al. (1994)

a Value reported only for total 2,3,7,8-substituted HxCDDs.
b Value reported only for total 2,3,7,8-substituted PeCDFs.
c Value reported only for total 2,3,7,8-substituted HxCDFs.
d Value reported only for total 2,3,7,8-substituted HpCDFs.

Table 5-6. CDD/CDF Emission Factors for Black Liquor Recovery Boilers

Congener	U.S. EPA (1987) — 3 Facilities Mean Emission Factors (ng/kg feed)		NCASI (1995) — 6 Facilities Mean Emission Factors (ng/kg feed)	
	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit	Nondetects Set to Zero	Nondetects Set to ½ Det. Limit
2,3,7,8-TCDD	0	0.04	0	0.016
1,2,3,7,8-PeCDD	NR	NR	0	0.016
1,2,3,4,7,8-HxCDD	NR	NR	0.001	0.018
1,2,3,6,7,8-HxCDD	NR	NR	0.003	0.015
1,2,3,7,8,9-HxCDD	NR	NR	0.006	0.019
1,2,3,4,6,7,8-HpCDD	NR	NR	0.108	0.135
OCDD	4.24	4.24	1.033	1.054
2,3,7,8-TCDF	0.04	0.06	0.040	0.049
1,2,3,7,8-PeCDF	NR	NR	0.030	0.036
2,3,4,7,8-PeCDF	NR	NR	0.033	0.037
1,2,3,4,7,8-HxCDF	NR	NR	0.007	0.022
1,2,3,6,7,8-HxCDF	NR	NR	0.012	0.021
1,2,3,7,8,9-HxCDF	NR	NR	0.005	0.016
2,3,4,6,7,8-HxCDF	NR	NR	0.010	0.021
1,2,3,4,6,7,8-HpCDF	NR	NR	0.024	0.035
1,2,3,4,7,8,9-HpCDF	NR	NR	0	0.014
OCDF	0.35	0.35	0.113	0.130
Total TCDD	0.21	0.36	0.106	0.123
Total PeCDD	0.27	0.35	0.013	0.059
Total HxCDD	0.80	1.02	0.104	0.122
Total HpCDD	2.05	2.05	0.252	0.279
Total OCDD	4.24	4.24	1.033	1.054
Total TCDF	0.95	1.00	1.270	1.275
Total PeCDF	0.64	0.77	0.370	0.376
Total HxCDF	1.16	1.20	0.102	0.109
Total HpCDF	1.05	1.05	0.024	0.038
Total OCDF	0.35	0.35	0.113	0.130
Total I-TEQ_{DF}	0.10*	0.15*	0.029	0.065
Total TEQ_{DF}-WHO_{98}	0.10*	0.16*	0.028	0.072
Total CDD/CDF	11.71	12.17	3.386	3.566

NR = Not reported.

* Estimated based on the measured data for 2,3,7,8-TCDD, 2,3,7,8-TCDF, OCDD, and OCDF and congener group emissions (i.e., for the penta-, hexa-, and hepta-CDD and CDFs, it was assumed that the measured emission factor within a congener group was the sum of equal emission factors for all congeners in that group, including non-2,3,7,8-substituted congeners).

Sources: U.S. EPA (1987a); NCASI (1995)

Table 5-7. Concentrations of CDD/CDF in Candle Materials and Emissions

Wax Material	Candle Component	Concentration			Emission Factor
		CDD/CDF (ng I-TEQ$_{DF}$/kg)	Total Chlorophenols (μg/kg)	Total Chlorobenzenes (μg/kg)	CDD/CDF (ng I-TEQ$_{DF}$/kg burnt wax)
Paraffin	Wax	0.59	14.8	130	0.015
Stearin	Wax	1.62	32.3	330	0.027
Beeswax	Wax	10.99	256	120	0.004
Paraffin	Wick	0.18	1.23	0.67	—
Stearin	Wick	0.12	0.94	0.34	—
Beeswax	Wick	0.08	0.74	0.35	—

Source: Schwind et al. (1995)

Table 5-8. CDD/CDF Concentrations in Ash Samples from Cement Kiln Electric Static Precipitator and LWA Kiln Fabric Filter
(concentrations in ng/kg)

Congener	Cement Kiln	LWA Kiln	Cement Kiln		LWA Kiln	
	Avg. Conc.	Avg. Conc.	I-TEQ	WHO-TEQ	I-TEQ	WHO-TEQ
2,3,7,8-TCDD	0.429	3.97	0.429	0.429	3.97	3.97
Total TCDD	36.1	333	–	–	–	–
1,2,3,7,8-PeCDD	0.886	17.3	0.443	0.886	8.65	17.3
Total PeCDD	54.9	467	–	–	–	–
1,2,3,4,7,8-HxCDD	1.03	15.4	0.103	0.103	1.54	1.54
1,2,3,6,7,8-HxCDD	2.36	35.6	0.236	0.236	3.56	3.56
1,2,3,7,8,9-HxCDD	2.47	56.6	0.247	0.247	5.66	5.66
Total HxCDD	173	500	–	–	–	–
12,2,3,4,6,7,8-HpCDD	17.7	133	0.177	0.177	1.33	1.33
Total HpCDD	55.2	300	–	–	–	–
OCDD	21.0	133	0.021	0.0021	0.133	0.133
Total TCDD TEQs			**1.66**	**2.08**	**2.48**	**33.4**
2,3,7,8-TCDF	4.65	833	0.465	0.465	83.3	83.3
Total TCDF	18.1	4,630	–	–	–	–
1,2,3,7,8-PeCDF	1.04	100	0.0518	0.0518	5.00	5.00
2,3,4,7,8-PeCDF	2.59	267	1.30	1.30	133	133
Total PeCDF	31.8	2,930	–	–	–	–
1,2,3,4,7,8-HxCDF	2.13	267	0.213	0.213	26.7	26.7
1,2,3,6,7,8-HxCDF	0.869	100	0.0869	0.869	10.0	10.0
1,2,3,7,8,9-HxCDF	0.523	7.80	0.0523	0.0523	0.780	0.780
2,3,4,6,7,8-HxCDF	2.14	133	0.214	0.214	13.3	13.3
Total HxCDF	9.26	1,230	–	–	–	–
1,2,3,4,6,7,8-HpCDF	1.84	167	0.0184	0.0184	1.67	1.67
1,2,3,4,7,8,9-HpCDF	0.739	22.6	0.00739	0.00739	0.226	0.226
Total HpCDF	3.06	2,670	–	–	–	–
OCDF	1.43	39.2	0.00143	0.000143	0.0392	0.00392
Total TCDF TEQs			**2.41**	**2.40**	**274**	**274**

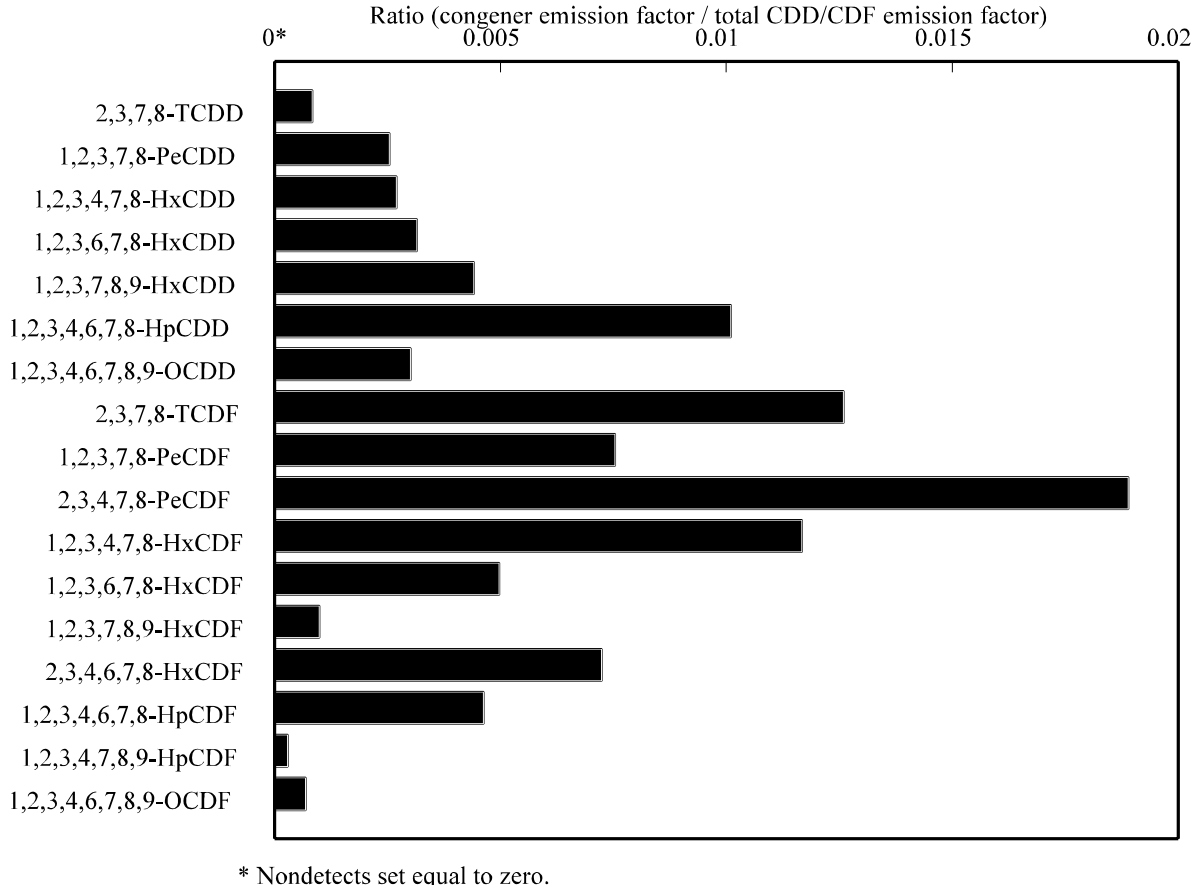
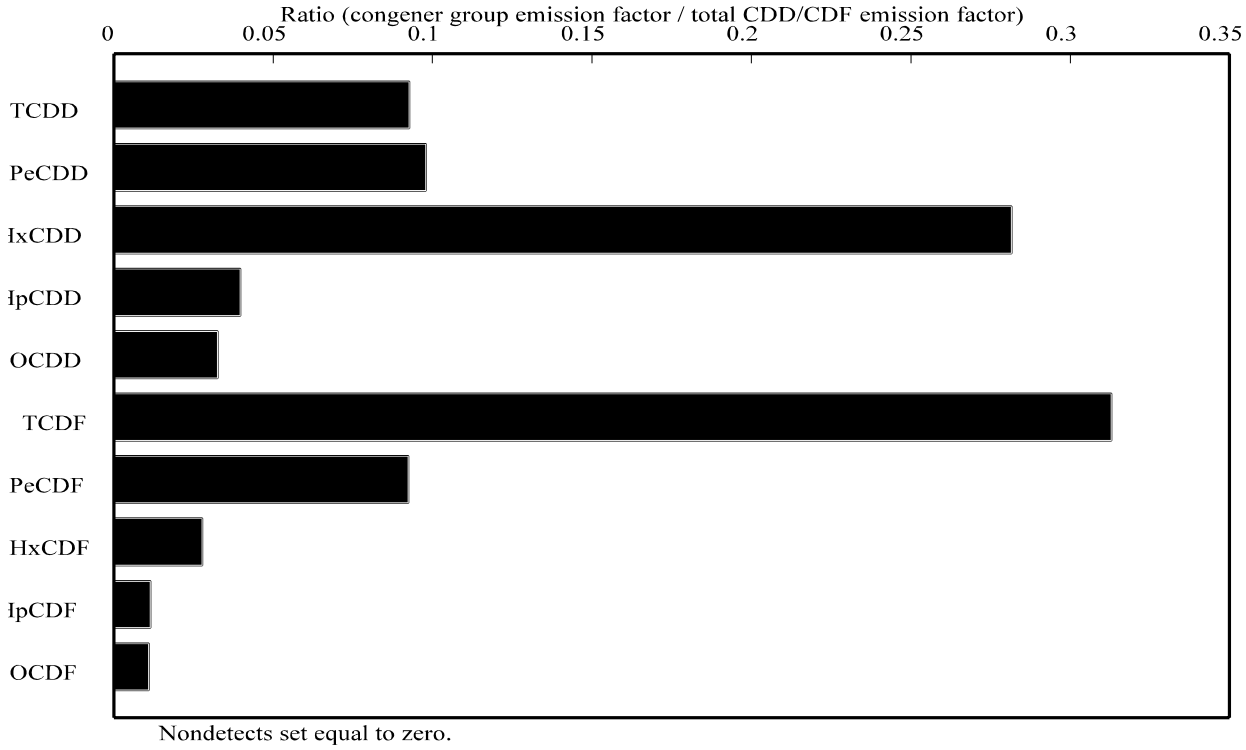


Figure 5-1. Congener Profile for Air Emissions from Cement Kilns Burning Hazardous Waste



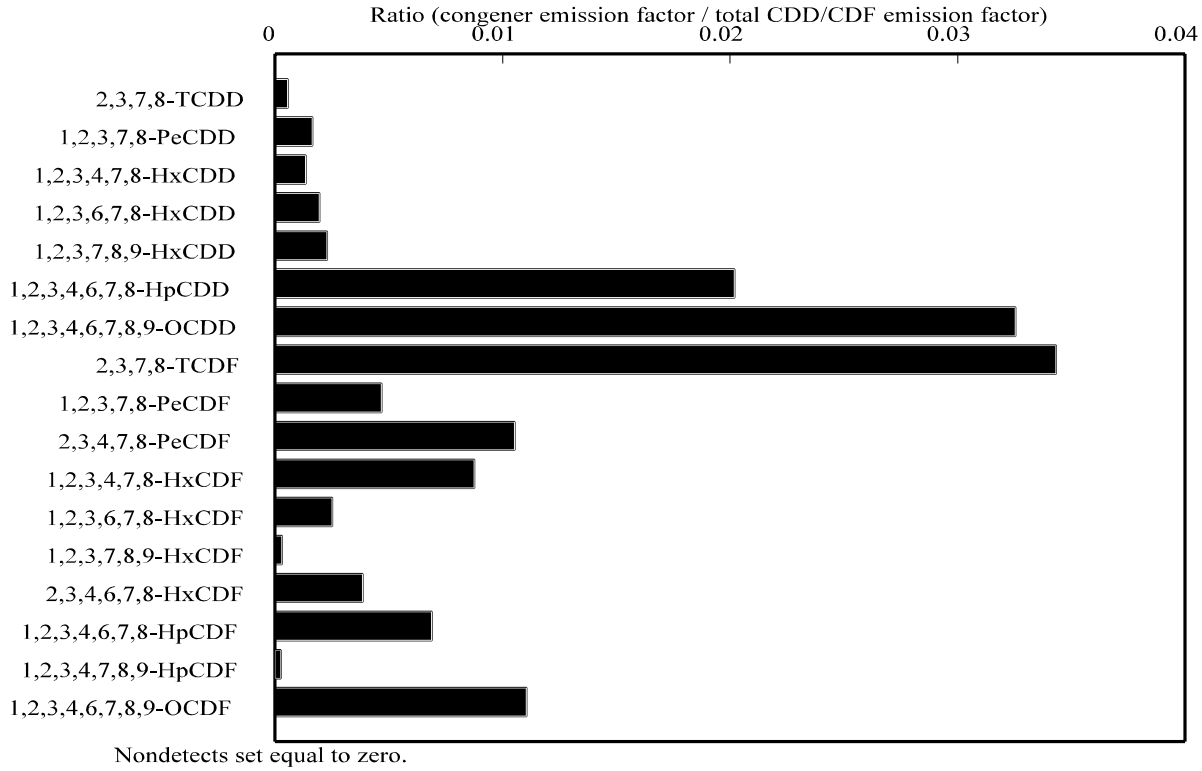


Figure 5-2. Congener and Congener Group Profiles for Air Emissions from Cement Kilns Not Burning Hazardous Waste

Figure 5-3. Congener and Congener Group Profiles for Air Emissions from Petroleum Catalytic Reforming Units

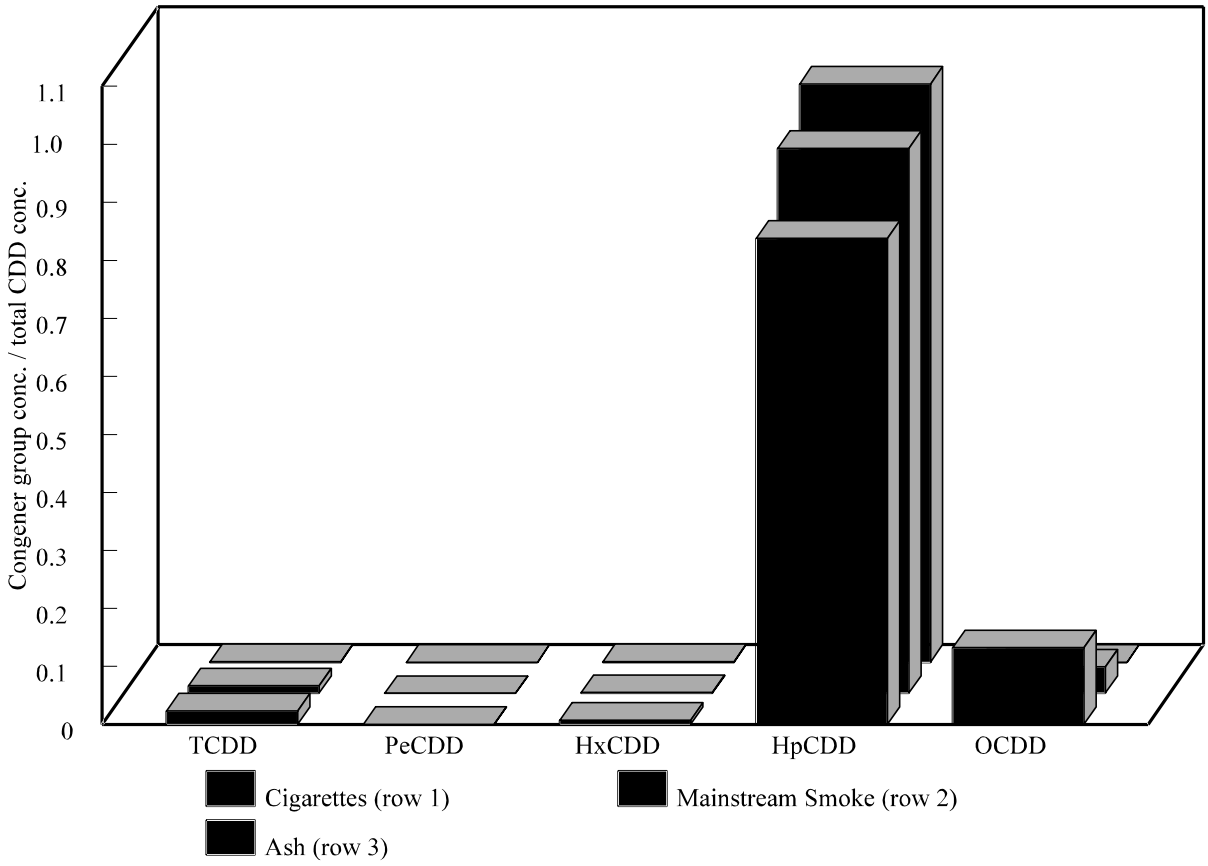


Figure 5-4. CDD Profiles for Japanese Cigarettes, Smoke, and Ash

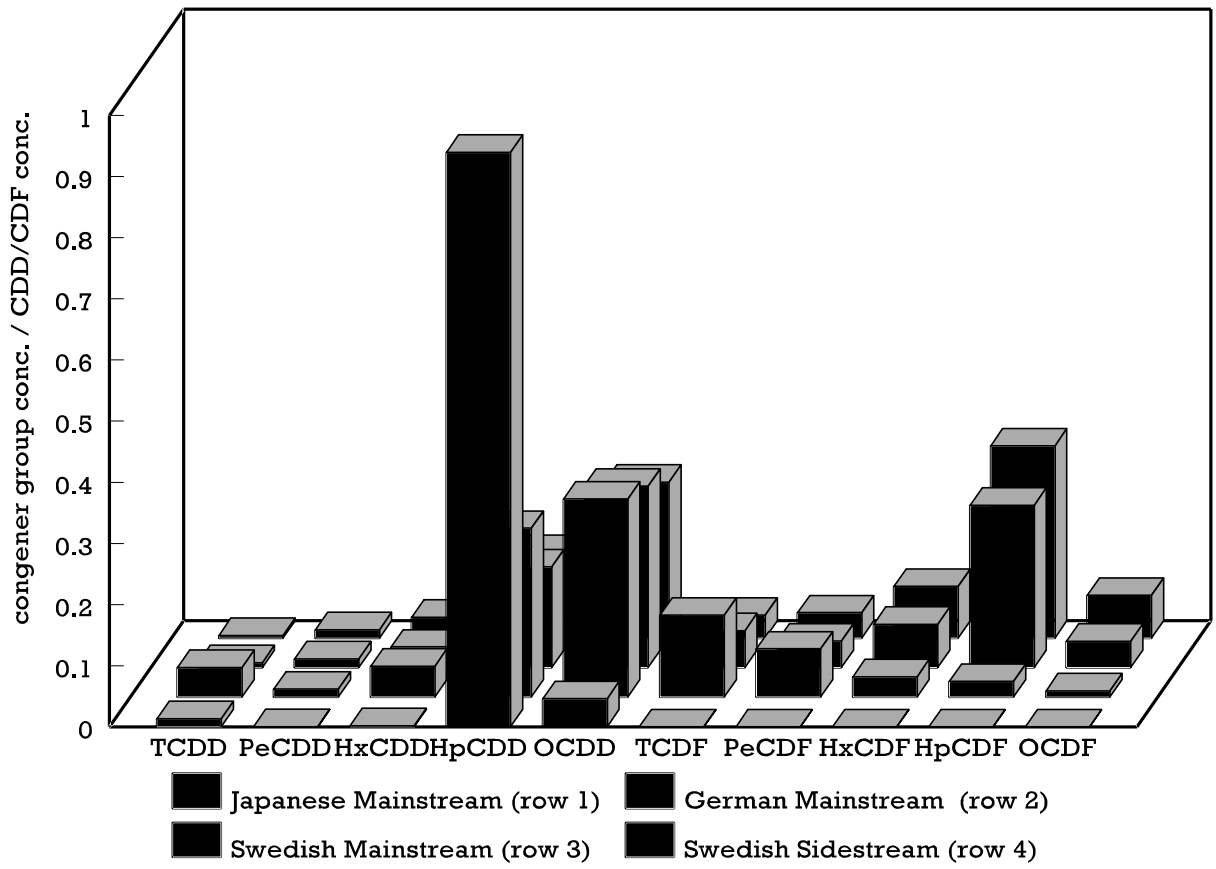
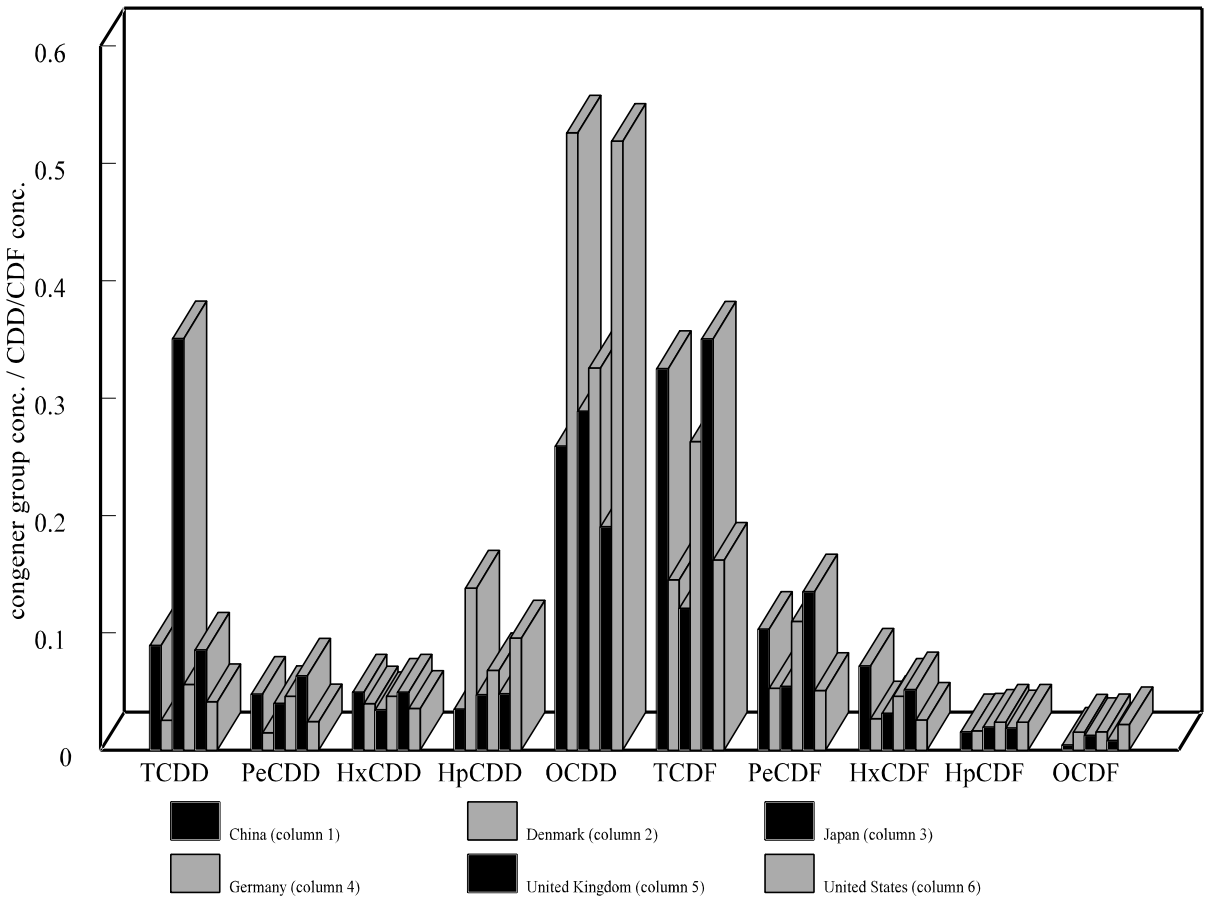
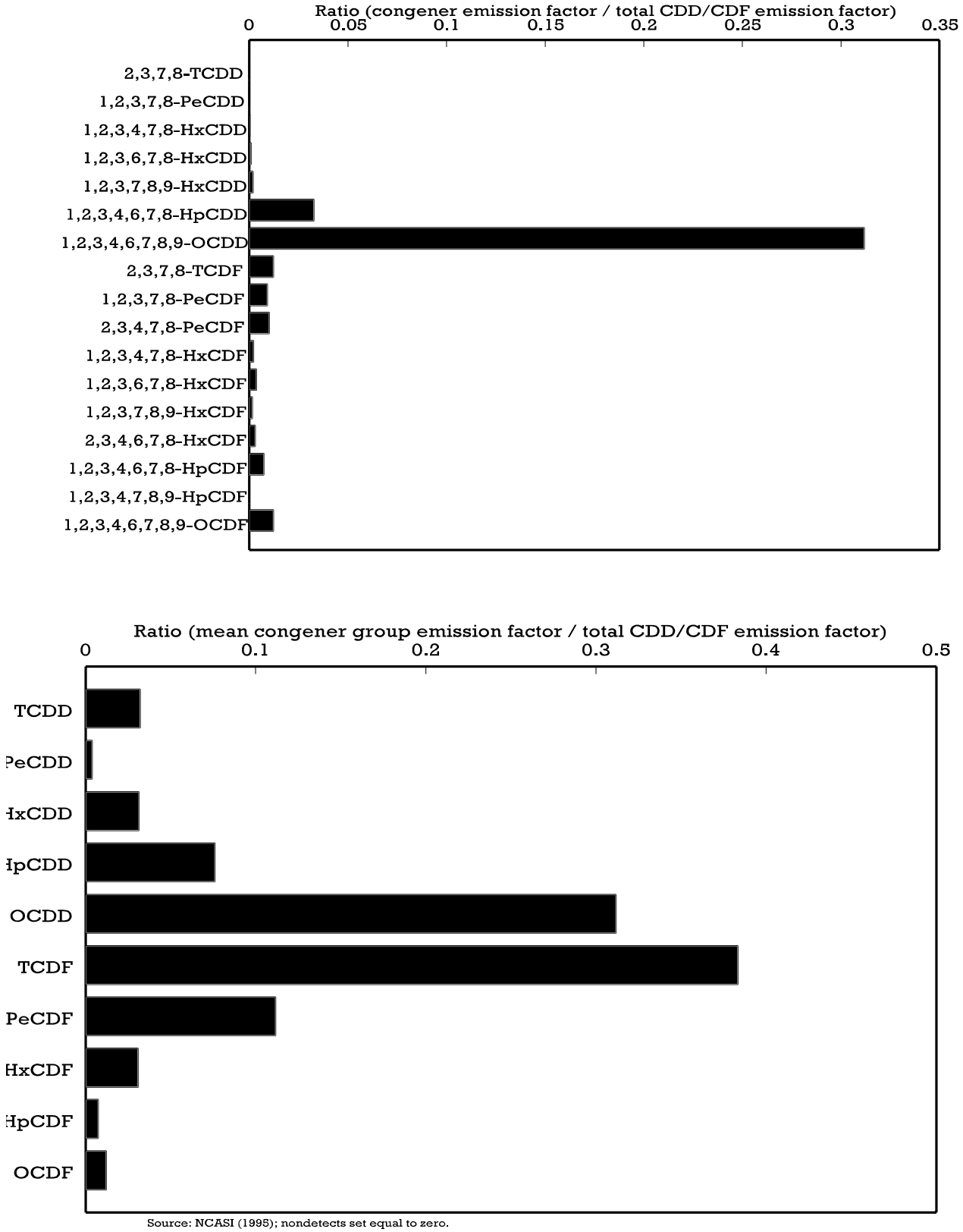


Figure 5-5. Congener Group Profiles for Mainstream and Sidestream Cigarette Smoke



Source: Matsueda et al. (1994)

Figure 5-6. Congener Group Profiles for Cigarette Tobacco from Various Countries



Source: NCASI (1995); nondetects set equal to zero.

Figure 5-7. Congener and Congener Group Profiles for Air Emissions from Kraft Black Liquor Recovery Boilers

6. COMBUSTION SOURCES OF CDD/CDF: MINIMALLY CONTROLLED AND UNCONTROLLED COMBUSTION SOURCES*

6.1. COMBUSTION OF LANDFILL GAS

The U.S. EPA promulgated emission standards and guidelines in 1996 to control emissions of landfill gas from existing and future landfills under the Clean Air Act (Federal Register, 1996a). Those regulations require the largest landfills in the United States (approximately 312) (i.e., largest on the basis of design capacity) to periodically measure and determine their annual emissions of landfill gas. Landfills that emit annually more than 50 metric tons of nonmethane organic compounds (NMOC) must collect landfill gas and reduce its NMOC content by 98 percent weight through use of a control device. EPA estimates that, when implemented, these controls will reduce NMOC annual emissions from existing landfills by 77,600 metric tons. The cost analysis supporting this rulemaking based control device costs on open flares, because flares are applicable to all the regulated facilities. Assuming that this mass reduction is achieved by use of flares, the corresponding volume of landfill gas that will be burned is approximately 14 billion m^3/yr. The calculation is based on an assumed default NMOC concentration in landfill gas of 1,532 ppmv and a conversion factor of 3.545 mg/m^3 of NMOC per 1 ppmv of NMOC (Federal Register, 1993d). EPA estimated that more than 100 of the approximately 312 landfills had some form of collection or control system, or both, in place in 1991 (Federal Register, 1991b). Thus, a rough approximation of the volume of landfill gas that is currently combusted is 4.7 billion m^3/yr (or 33 percent of the future expected 14 billion m^3/yr reduction). This estimate is similar to the 2.0 to 4.0 billion m^3 of landfill gas that were estimated in EIA (1994) as collected and consumed for energy recovery purposes in 1992. The Energy Information Administration (EIA, 1992) estimated that between 0.9 and 1.8 billion m^3 of landfill gas were collected and burned in 1990 for energy recovery purposes.

Although no data could be located on the levels of CDD/CDFs in untreated landfill gas, several studies have reported detecting CDD/CDFs in the emissions resulting from the

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* This chapter discusses combustion sources of CDD/CDF that have some (in the case of combustion of landfill gas) or no post-combustion pollution control equipment for conventional pollutant emissions. Note that very few of the CDD/CDF sources listed in this report control specifically for CDD/CDF emissions.

combustion of landfill gas. Only one study of CDD/CDF emissions from a landfill flare has been reported for a U.S. landfill (CARB, 1990d). The I-TEQ_{DF} and TEQ_{DF}-WHO_{98} emission factor calculated from the results of this study is approximately 2.4 ng TEQ/m^3 of landfill gas combusted. The congener-specific results of this study are presented in Table 6-1. Figure 6-1 presents the CDD/CDF congener emission profile based on these emission factors. Bremmer et al. (1994) reported a lower emission factor, 0.4 ng I-TEQ_{DF}/m^3, from the incineration of untreated landfill gas in a flare at a facility located in The Netherlands. No congener-specific emission factors were provided in Bremmer et al. (1994). The average TEQ emission factor for the CARB (1990d) and Bremmer et al. (1994) studies is 1.4 ng I-TEQ_{DF}/m^3 of landfill gas combusted. Umweltbundesamt (1996) reported even lower TEQ emission factors for landfill gas burned in engines or boiler mufflers rather than in a flare. The reported results for 30 engines and mufflers tested in Germany ranged from 0.001 to 0.28 ng I-TEQ_{DF}/m^3 with most values below 0.1 ng I-TEQ_{DF}/m^3. However, Bremmer et al. (1994) also reported an emission factor of 0.5 ng I-TEQ_{DF}/m^3 from a landfill gas–fired engine in The Netherlands.

The limited emission factor data that are available were judged inadequate for developing national emission estimates that could be included in the national inventory. However, a preliminary estimate of the potential annual TEQ release from landfills can be obtained using the estimated volume of combusted gas and the available emission factors. Combining the estimate of current landfill gas volume that is combusted (4.7 billion m^3/yr) with the emission factor of 1.4 ng I-TEQ_{DF}/m^3 of flare-combusted gas yields an annual emission estimate of 6.6 g I-TEQ_{DF}. This estimate should be regarded as a preliminary indication of possible emissions from this source; further testing is needed to confirm the true magnitude of those emissions.

6.2. ACCIDENTAL FIRES

Accidental fires in buildings and vehicles are uncontrolled combustion processes that, because of poor combustion conditions, typically result in relatively high emissions of incomplete combustion products (Bremmer et al., 1994). The incomplete combustion products can include CDDs and CDFs. Polyvinyl chloride (PVC) building materials and furnishings, chloroparaffin-containing textiles and paints, and other chlorinated organic compound–containing materials appear to be the primary sources of the chlorine (Rotard,

1993). Although the results of several studies demonstrate the presence of CDD/CDF concentrations in soot deposits and residual ash from such fires, few direct measurements of CDD/CDFs in the fumes or smoke of fires have been reported. The results of some of those studies are described below, followed by an evaluation of the available data.

6.2.1. Soot and Ash Studies

Christmann et al. (1989b) analyzed the soot formed during combustion and pyrolysis of pure PVC and PVC cable sheathings in simple laboratory experiments designed to mimic the conditions of fires. For the combustion experiments, 2 grams of a PVC sample were incinerated with a laboratory gas burner. The combustion products were collected on the inner walls of a cooled gas funnel placed above the sample. For the pyrolysis experiments, about 50 mg of the sample were placed in a quartz tube and heated to about 950°C for 10 minutes in either an air atmosphere or a nitrogen atmosphere. The combustion experiments yielded CDD/CDF concentrations in soot of 110 μg I-TEQ$_{DF}$/kg for a low-molecular-weight PVC, 450 μg I-TEQ$_{DF}$/kg for a high molecular weight PVC, and 270 μg I-TEQ$_{DF}$/kg for PVC cable. The pyrolysis experiments in the air atmosphere yielded lower CDD/CDF concentrations in soot: 24.4 μg I-TEQ$_{DF}$/kg for a low-molecular-weight PVC, 18.7 μg I-TEQ$_{DF}$/kg for a high-molecular-weight PVC, and up to 41 μg I-TEQ$_{DF}$/kg for PVC cable. In general, CDFs were predominantly formed over CDDs. The lower chlorinated CDF congeners were dominant in the combustion experiments; however, the HpCDF and OCDF congeners were dominant in the pyrolysis experiments. No CDD/CDFs were detected in pyrolysis experiments under a nitrogen atmosphere. Also, no CDD/CDFs were detected when chlorine-free polyethylene samples were subjected to the same combustion and pyrolysis conditions.

Deutsch and Goldfarb (1988) reported finding CDD/CDF concentrations ranging from 0.04 to 6.6 μg/kg in soot samples collected after a 1986 fire in a State University of New York lecture hall. The fire consumed or melted plastic furnishings, cleaning products containing chlorine, wood, and paper.

Funcke et al. (1988; as reported in Bremmer et al., 1994, and Rotard, 1993) analyzed 200 ash and soot samples from sites of accidental fires in which PVC was involved. CDD/CDFs were detected in more than 90 percent of the samples at concentrations in the ng I-TEQ$_{DF}$/kg to μg I-TEQ$_{DF}$/kg range. Fires involving the

combustion of materials containing relatively large amounts of PVC and other chlorinated organic substances resulted in the highest levels of CDD/CDFs, with CDD/CDF concentrations ranging from 0.2 to 110 μg I-TEQ$_{DF}$/kg of residue.

Thiesen et al. (1989) analyzed residues from surfaces of PVC-containing materials that were partially burned during accidental fires at sites in Germany that manufactured or stored plastics. CDD/CDF concentrations in residues were reported as 0.5 μg I-TEQ$_{DF}$/kg for soft PVC, 4.6 μg I-TEQ$_{DF}$/kg for PVC fibers, and 28.3 μg I-TEQ$_{DF}$/kg for a hard PVC. The ratio of total CDFs to total CDDs in the three samples ranged from 4:1 to 7:1. The dominant 2,3,7,8-substituted CDF and CDD congeners in all three samples were 1,2,3,4,6,7,8-HpCDF and 1,2,3,4,6,7,8-HpCDD.

Following an accidental fire at a Swedish carpet factory in 1987, 200 metric tons of PVC and 500 metric tons of PVC-containing carpet burned. Marklund et al. (1989) analyzed snow samples within 1,500 meters downwind from the fire site and found CDD/CDF concentrations in the top 2 cm ranging from 0.32 μg I-TEQ$_{DF}$/m^2 at 10 meters of the site to 0.01 μg I-TEQ$_{DF}$/m^2 at 1,500 meters downwind of the site. Because of an atmospheric inversion and very light wind at the time of the fire, the smoke from the fire remained close to the ground. The soot deposited onto the snow was thus assumed to be representative of the soot generated and released from the fire. Wipe samples of soot from interior posts of the plant (5 and 20 meters from the fire) contained EADON TEQ concentrations of 0.18 and 0.05 μg/m^2, respectively. On the basis of these deposition measurements, Marklund et al. (1989) estimated the total CDD/CDF emission from the fire to be less than 3 mg I-TEQ$_{DF}$.

Carroll (1996) estimated a soot-associated CDD/CDF emission factor (i.e., not including volatile emissions) of 28 to 138 ng I-TEQ$_{DF}$/kg of PVC burned for the Swedish carpet factory fire using the following assumptions: (1) the PVC carpet backing was one-half the weight of the carpet, (2) the carpet backing contained 30 percent by weight PVC resin, and (3) 20 to 100 percent of the PVC and PVC carpet backing present in the warehouse actually burned. Carroll (1996) also estimated a similar soot-associated emission factor (48 to 240 ng I-TEQ$_{DF}$/kg of PVC burned) for a fire at a plastics recycling facility in Lengerich, Germany. Carroll (1996) used the results of wipe samples collected at downwind distances of up to 6,300 meters from the fire to estimate the emission factor.

Fiedler et al. (1993) presented a case study of CDD/CDF contamination and associated remedial actions taken at a kindergarten in Germany following a fire, that destroyed parts of the roof, windows, and furnishings. Soot collected from the building contained CDD/CDFs at a concentration of 45 μg I-TEQ$_{DF}$/kg (or 15 μg I-TEQ$_{DF}$/m^2). Fiedler et al. (1993) attributed the CDD/CDFs detected to the combustion of plastic and wooden toys, floors, and furnishings; however, no information was provided on the quantities of those materials.

Fiedler and Lindert (1998) presented results of soot sampling following a serious fire at Düsseldorf Airport in Germany. Polystyrene sheets and PVC-coated cables were involved in the fire, together with PCB-containing condensers (bulbs). Surface wipe samples contained up to 0.33 μg I-TEQ$_{DF}$/m^2. Concentrations in soot ranged from 7 to 130 μg I-TEQ$_{DF}$/kg. Concentrations of BDD/BDFs were detected in soot at concentrations as high as 0.9 mg/kg soot.

Wichmann et al. (1993, 1995) measured the CDD/CDF content of ash and debris and deposited surface residues that resulted from experimental test burns of two cars (a 1974 Ford Taurus and a 1988 Renault Espace), one subway car, and one railway coach in a tunnel in Germany. On the basis of measurements obtained from sampled ash and debris and from soot collectors placed at regular intervals up to 420 meters downwind of the burn site, the total amounts of CDD/CDF in the ash/debris and tunnel surface residues from each vehicle burn experiment were estimated as follows: 1974 model car—0.044 mg I-TEQ$_{DF}$; 1988 model car—0.052 mg I-TEQ$_{DF}$; subway car—2.6 mg I-TEQ$_{DF}$; and railway coach—10.3 mg I-TEQ$_{DF}$. For each vehicle burn experiment, the mass of TEQ in tunnel surface residue exceeded the mass in ash and debris; 73 to 89 percent were accounted for by the tunnel surface residues and 11 to 27 percent by ash and debris. The average CDD/CDF content of the ash and debris from each experimental burn was as follows: new car—0.14 μg I-TEQ$_{DF}$/kg; old car—0.30 μg I-TEQ$_{DF}$/kg; subway car—3.1 μg I-TEQ$_{DF}$/kg; and railway coach—5.1 μg I-TEQ$_{DF}$/kg.

6.2.2. Fume and Smoke Studies

Merk et al. (1995) collected fume and smoke generated during the burning of 400 kg of wood and 40 kg of PVC in a building (4,500 m^3 volume) over a 45-minute period. The sampling device consisted of dual glass fiber filters to collect particles greater than

0.5 μm, followed by a polyurethane foam filter to collect vapor phase CDD/CDFs. The particulate phase and gas phase showed the same congener pattern, decreasing concentration with increasing degree of chlorination, thus indicating no preferential sorption of higher chlorinated congeners to smoke particulates. However, the CDD/CDF found in the gas phase (about 5 ng I-TEQ_{DF}/m^3) accounted for more than 90 percent of the detected CDD/CDFs. Merk et al. (1995) also reported that the soot deposited from this fire onto a 1 m^2 aluminum sheet resulted in surface contamination of 0.050 μg I-TEQ_{DF}/m^2. Although it was stated in Merk et al. (1995) that the building was 'closed,' subsequent communication with one of the coauthors (Schramm, 1998) clarified that a 'gas cleaning' system was in operation during the testing. Because a ventilation system was in operation during the testing, there was likely some loss of vapor phase CDD/CDFs from the hall. Therefore, the deposits (from particulate deposition and vapor phase condensation) on the test aluminum plate may not reflect total CDD/CDF formation during the fire.

Dyke and Coleman (1995) reported a fourfold increase in CDD/CDF TEQ concentrations in the ambient air during "bonfire" night in Oxford, England. Bonfire night (November 5) is an annual event in England during which it is customary to set off fireworks and have bonfires to commemorate a failed plot to overthrow the king in 1605. Air concentrations before and after bonfire night ranged from 0.15 to 0.17 pg I-TEQ_{DF}/m^3. The air concentration during the bonfire night was 0.65 pg I-TEQ_{DF}/m^3. The dominant congeners in all samples were the hepta- and octa-CDDs. The study was not designed to collect data that would enable calculation of an emission rate nor to differentiate the relative importance of the various materials combusted. However, the results do indicate that open burning of materials likely to be combusted in accidental fires (with the exception of fireworks) results in the release of CDDs and CDFs.

6.2.3. Data Evaluation

Structural Fires — The limited data available on structural fires were judged inadequate for developing national emission estimates that could be included in the national inventory. This conclusion was also reached in national emission inventories developed for The Netherlands (Bremmer et al., 1994) and the United Kingdom (UK Department of the Environment, 1995). Most cited studies involved situations (i.e., field

and laboratory) where relatively high loadings of PVC or plastics were combusted. The effects of different mixes of combusted materials, oxygen supplies, building configurations, durations of burn, and so forth, likely to be found in accidental fires cannot be accounted for by the factors that can be derived from these studies. Also, most of the studies addressed only soot or ash residues and did not address potential volatile emissions of CDD/CDFs which, according to Merk et al. (1995), may represent 90 percent of the CDD/CDFs generated during burning of PVC.

Two recent reports (Carroll, 1996; Thomas and Spiro, 1995) attempted to quantify CDD/CDF emissions from U.S. structural fires, and Lorenz et al. (1996) estimated emissions from structural fires in the Federal Republic of Germany. The estimates derived in these three studies are presented below, following a brief summary of the number and types of accidental fires reported annually in the United States.

In 1995, approximately 574,000 structural fires were reported in the United States. Of these, 426,000 were reported for residential structures, including 320,000 fires in 1–2 family units, 94,000 fires in apartments, and 12,000 fires in other residential settings. The remaining 148,000 structural fires were broken down as follows: 15,000—public assembly; 9,000—educational; 9,000—institutional; 29,000—stores and offices; 29,000—special structures; 39,000—storage; and 18,000—industry, utility, and defense. The latter two categories may be underreported as some incidents were handled by private fire brigades or fixed suppression systems, which do not report (U.S. DOC, 1997).

Carroll (1996) estimated the total CDD/CDF content of soot and ash generated from the 358,000 fires reported in U.S. DOC (1995a) for 1993 in 1–2 family unit residential structural fires. Carroll (1996) developed detailed estimates of the PVC content of typical homes, including plumbing, wiring, siding and windows, wallpaper, blinds and shades, and upholstery. Using statistical data on fire loss (i.e., dollar value) provided the typical loss per recorded fire (9.5 percent of value) which Carroll assumed also represented the typical percentage of PVC burned. Extrapolating to all 358,000 1–2 family unit fires yielded an annual mass of 2,470 metric tons of PVC burned. Carroll (1996) then developed TEQ emission factors from the results of Thiesen et al. (1989) and Marklund et al. (1989). The estimated CDD/CDF content ranged from 0.47 to 22.8 g I-TEQ_{DF} with 0.07 to 8.6 g I-TEQ_{DF} in soot and 0.4 to 14.2 g I-TEQ_{DF} in ash. Carroll derived

a soot emission factor (i.e., grams of soot produced per gram of PVC combusted) from his assumptions regarding the surface area of the soot collection funnel used by Christmann et al. (1989a) and the soot deposition rate on that funnel. Carroll then applied these I-TEQ_{DF} emission factors to the estimated 2,470 metric tons of PVC burned annually in 1–2 family unit residential fires to obtain estimates of the annual mass of TEQ that would be found in the soot and ash of residential fires (i.e., 0.48 to 22.8 g I-TEQ_{DF}/yr). The average emission per fire is thus 1.3 to 64 μg I-TEQ_{DF}.

Thomas and Spiro (1995) estimated that 20 g of I-TEQ_{DF} may be released annually to air from structural fires. This estimate assumed an emission factor of 4 ng I-TEQ_{DF}/kg of material combusted (i.e., the emission rate for "poorly controlled" wood combustion), an assumed material combustion factor of 6,800 kg/fire, and 688,000 structural fires per year. The average emission per fire is thus 29 μg I-TEQ_{DF}.

Lorenz et al. (1996) estimated annual generation of CDD/CDF TEQs in the Federal Republic of Germany using data on the number of residential and industrial/commercial structural fires coupled with data on CDD/CDF content in soot and ash residues remaining after fires. The potential annual I-TEQ_{DF} generation was estimated to be 78 to 212 grams.

Although, as stated above, the available data were judged to be inadequate to support development of an emission estimate for the national inventory, a preliminary estimate of the potential magnitude of TEQ emissions can be obtained using the estimates of Carroll (1996) and Thomas and Spiro (1995), that annual releases are about 20 g I-TEQ_{DF}.

There is very low confidence in these estimated emissions because of the numerous assumptions employed in their derivation. If the conclusion of Merk et al. (1995) is assumed to be correct, that 90 percent of the CDD/CDFs formed in fires are in the gaseous phase rather than particulate phase (i.e., greater than 0.5 μm diameter), and it is also assumed that the estimates of Carroll (1996) and of Thomas and Spiro (1995) do not totally account for volatile emissions, then the total CDD/CDF emissions estimated by Carroll (1996) and by Thomas and Spiro (1995) may be underestimates. Further testing is needed to confirm the true magnitude of these releases.

Vehicle Fires—The limited data available on vehicle fires were judged inadequate for developing national emission estimates that could be included in the national inventory. However, a preliminary estimate of the range of potential CDD/CDF emissions that may

result from vehicle fires can be calculated using the results reported by Wichmann et al. (1993, 1995) for controlled vehicle fires in a tunnel (0.044 mg I-TEQ_{DF} for an old car to 2.6 mg I-TEQ_{DF} for a subway car). Although Wichmann et al. (1993; 1995) did not measure volatile CDD/CDFs (which were reported by Merk et al. (1995) to account for the majority of CDD/CDFs formed during a fire), the study was conducted in a tunnel, and it is likely that a significant fraction of the volatile CDD/CDFs sorbed to tunnel and collector surfaces and were thus measured as surface residues. In 1995, approximately 406,000 vehicle fires were reported in the United States (U.S. DOC, 1997). If it is assumed that 99 percent of those involved cars and trucks (i.e., the approximate percentage of all U.S. motor vehicles that are in-service cars and trucks; U.S. DOC, 1995a), and that the applicable emission rate is 0.044 mg I-TEQ_{DF} per incident, then the annual TEQ formation is 17.7 g I-TEQ_{DF}. The emission factor of 2.6 mg I-TEQ_{DF}/fire is assumed to be applicable to the remaining 1 percent of vehicle fires, thus yielding an emission of 10.6 g I-TEQ_{DF}/yr. The total TEQ annual emission is roughly estimated to be 28.3 g I-TEQ_{DF}/yr. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions.

6.3. LANDFILL FIRES

In the late 1980s, two serious fires occurred in landfills near Stockholm, Sweden. The first involved a fire in a large pile of refuse-derived fuel. Using measurements of chlorobenzenes in the air emissions, it was estimated that 50 to 100 kg of chlorobenzenes were released. CDD/CDF emissions were estimated to be several tens of grams, on the assumption that the ratio of CDD/CDFs to chlorobenzenes in landfill fire emissions is similar to the ratio observed in stack gases of municipal waste incinerators. In connection with the second fire, which occurred at a large conventional landfill, birch leaves were collected from trees close to the fire and at distances up to 2 km downwind of the fire, as well as from nearby areas not affected by smoke from the fire. The discharge of CDD/CDF necessary to cause the CDD/CDF concentrations measured on the leaves was estimated to be several tens of grams (Persson and Bergström, 1991).

In response to these incidents, Persson and Bergström (1991) measured CDD/CDF emissions from experimental fires designed to simulate surface landfill fires and deep landfill fires. The experiments used 9-month-old domestic waste. The tests showed no

significant difference in CDD/CDF content of the fire gas produced by the simulated surface and deep fires. The average CDD/CDF emission rate was reported to be 1 μg Nordic TEQ/kg of waste burned. Persson and Bergström (1991) and Bergström and Björner (1992) estimated annual CDD/CDF Nordic TEQ emissions in Sweden from landfill fires to be 35 grams. The estimate was based on the emission rate of 1 μg Nordic TEQ/kg waste burned, an assumed average density of landfill waste of 700 kg/m^3, an assumed waste burn of 150 m^3 for each surface landfill fire (167 fires in Sweden per year), and an assumed waste burn of 500 m^3 for each deep landfill fire (50 fires in Sweden per year). The estimates of waste burn mass for each type of fire were the average values obtained from a survey of 62 surface fires and 25 deep fires. The estimated number of fires per year was based on the results of a survey of all Swedish municipalities for fires reported during the years 1988 and 1989. In 1991, Sweden had an estimated 400 municipal landfills (Persson and Bergström, 1991).

Ruokojärvi et al. (1995) measured the ambient air concentrations of CDD/CDF in the vicinity of real and experimental landfill fires in Finland. The most abundant toxic congeners were the hepta- and octa-CDDs and the penta-, hepta-, and octa-CDFs. The highest contributions to the measured TEQ were made by 1,2,3,7,8-PeCDD and 2,3,4,7,8-PeCDF. In Finland, annual CDD/CDF emissions from landfill fires are estimated to be 50–70 g Nordic TEQ (Aittola, 1993, as reported by Ruokojärvi et al., 1995).

Although no U.S. monitoring studies are available, an emission factor similar to the Swedish emission factor would be expected in the United States, because the contents of the municipal waste are expected to be similar between the United States and Sweden. However, because no data could be located on characterization of landfill fires in the United States (i.e., number, type, mass of waste involved), the limited data available were judged inadequate for developing national emission estimates that could be included in the national inventory. However, a preliminary estimate of the potential magnitude of TEQ emissions associated with landfill fires in the United States can be obtained by assuming a direct correlation of emissions to population size for the United States and Sweden or by assuming a direct correlation between emissions and the number of landfills in each country. Both countries are Western, industrialized countries. Although the per capita waste generation rate in the United States is nearly 1.5 times that of Sweden, the composition of municipal waste and the fraction of municipal waste disposed of in landfills

in the two countries are nearly identical (U.S. EPA, 1996b). The 1995 population of Sweden is 8,822,000 (U.S. DOC, 1995a). Thus, the per capita landfill fire–associated Nordic TEQ emission factor is 4.0 μg TEQ/person/year (i.e., 35 grams/8,822,000 people). Because congener-specific results were not provided in Persson and Bergström (1991) and Bergström and Björner (1992), it was not possible to derive emission factors in units of I-TEQ_{DF} or TEQ_{DF}-WHO_{98}. Applying this factor to the U.S. population (263,814,000) (U.S. DOC, 1995a) results in an estimated annual emission of 1,050 g of TEQ. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions. An annual emission of similar size is obtained if it is assumed that the ratio of annual TEQ emissions to number of landfills in Sweden, 87.5 mg TEQ/landfill (i.e., 35 grams/400 landfills), is applicable to the United States, which has 3,558 landfills (U.S. EPA, 1996b). The resulting annual emission estimate is 311 g TEQ/yr.

6.4. FOREST AND BRUSH FIRES

Because CDD/CDFs have been detected both in the soot from residential wood burning (Bumb et al., 1980; Nestrick and Lamparski, 1982, 1983; Bacher et al., 1992), and in the flue gases from residential wood burning (Schatowitz et al., 1993; Vickelsoe et al., 1993), it is reasonable to presume that wood burned in forest and brush fires may also be a source of CDD/CDFs (Section 4.2 contains details on these studies).

Only one study could be found that reported direct measurements of CDD/CDFs in the emissions from forest fires. This study, by Tashiro et al. (1990), reported detection of total CDD/CDFs in air at levels ranging from about 15 to 400 pg/m^3. The samples were collected from fixed collectors located 10 meters above the ground and from aircraft flying through the smoke. Background samples collected before and after the tests indicated negligible levels in the atmosphere. These results were presented in a preliminary report; however, no firm conclusions were drawn about whether forest fires are a CDD/CDF source. The final report on this study, Clement and Tashiro (1991), reported total CDD/CDF levels in the smoke of about 20 pg/m^3. The authors concluded that CDD/CDFs are emitted during forest fires but recognized that some portion of these emissions could represent resuspension from residues deposited on leaves rather than newly formed CDD/CDFs.

Although not designed to directly assess whether CDD/CDFs are formed during brush fires, Buckland et al. (1994) measured the CDD/CDF levels in soil samples from both burnt and unburnt areas in national parks in New Zealand 6 weeks after large-scale brush fires. Four surface soil cores (2 cm depth) were collected and composited from each of three burnt and three unburnt areas. Survey results indicated that brush fires did not have a major impact on the CDD/CDF levels in soil. The I-TEQ_{DF} contents in soil sample composites of the three unburnt areas were 3.0 ng/kg, 8.7 ng/kg, and 10.0 ng/kg. The I-TEQ_{DF} contents in the soil sample composites of three burnt areas were 2.2 ng/kg, 3.1 ng/kg, and 36.8 ng/kg. Total CDD/CDF contents ranged from 1,050 to 7,700 ng/kg in the unburnt area soil samples and from 1,310 to 27,800 ng/kg in the burnt area soil samples. OCDD accounted for 94 to 97 percent of the total CDD/CDF content in all samples.

Similarly, a survey of controlled straw-field burning in the United Kingdom (Walsh et al., 1994) indicated that the straw burning did not increase CDD/CDF burden in the soil; however, a change in congener distribution was observed. Soils from three fields were sampled immediately before and after burning, along with ash from the fire. The mean I-TEQ_{DF} concentrations in the preburn soil, postburn soil, and ash were 1.79 ng/kg, 1.72 ng/kg, and 1.81 ng/kg, respectively. Concentrations of 2,3,7,8-TCDF were lower in the postburn soils than in the preburn soils. Conversely, the concentrations of OCDD were higher in the postburn soils indicating possible formation of OCDD during the combustion process.

Van Oostdam and Ward (1995) reported finding no detectable levels of 2,3,7,8-substituted CDD/CDFs in three soil samples and four ash samples following a forest fire in British Columbia. The detection limits on a congener-specific basis (unweighted for TEQ) ranged from 1 to 2 ng/kg. Nondetected values were also reported by Van Oostdam and Ward (1995) for ashes at a slash and burn site; the soil contained about 0.05 ng I-TEQ_{DF}/kg, whereas background soil contained about 0.02 ng I-TEQ_{DF}/kg.

The concentrations presented by Clement and Tashiro (1991) cannot accurately be converted to an emission factor, because the corresponding rates of combustion gas production and wood consumption are not known. As a result, three alternative approaches were considered to develop an emission factor.

Soot-Based Approach—This approach assumes that the levels of CDD/CDFs in chimney soot are representative of the CDD/CDFs in emissions. The CDD/CDF emission factor is calculated as the product of the CDD/CDF concentration in soot and the total particulate emission factor. This calculation involves first assuming that the CDD/CDF levels measured in chimney soot (720 ng I-TEQ_{DF}/kg) by Bacher et al. (1992) are representative of the CDD/CDF concentrations of particles emitted during forest fires. Second, the total particulate generation factor must be estimated. Ward et al. (1976) estimated the national average particulate emission factor for wildfires as 150 lb/ton biomass dry weight using primarily data for head fires. Ward et al. (1993) estimated the national average particulate emission factor for prescribed burning as 50 lb/ton biomass dry weight. Combining the total particulate generation rates with the I-TEQ_{DF} level in soot results in emission factor estimates of 54 ng of I-TEQ_{DF} and 18 ng of I-TEQ_{DF}/kg of biomass burned in wildfires and prescribed burns, respectively. These estimated factors are likely to be overestimates, because the levels of CDD/CDF measured in chimney soot by Bacher et al. (1992) may represent the accumulation and enrichment of CDD/CDFs measured in chimney soot over time, leading to much higher assumed levels than what is actually on emitted particles.

Carbon Monoxide (CO) Approach—Carbon monoxide is a general indicator of the efficiency of combustion, and the emission factors of many emission products can be correlated to the CO emission factor. The Schatowitz et al. (1993) data for emissions during natural wood burning in open stoves suggest an emission factor of 10 μg I-TEQ_{DF}/kg of CO. Combining this factor with the CO emission factor during forest fires (roughly 0.1 kg CO/kg of biomass, Ward et al., 1993) yields an emission factor of 1,000 ng I-TEQ_{DF}/kg biomass. This factor is higher than the soot-based factor discussed above, which is itself considered to be an overestimate. In addition, although the formation kinetics of CDD/CDF during combustion are not well understood, CDD/CDF emissions have not been shown to correlate well with CO emissions from other combustion sources. (See Chapter 2.)

Wood Stove Approach—This approach assumes that the emission factor for residential wood burning (using natural wood and open door, i.e., uncontrolled draft)

applies to forest fires. As discussed in Section 4.2.1, this approach suggests an emission factor of about 2 ng I-TEQ_{DF}/kg of wood burned. This value appears more reasonable than the factors suggested by the soot and CO approaches because it is based on direct measurement of CDD/CDFs from combustion of wood rather than indirect techniques. However, forest fire conditions differ significantly from combustion conditions in wood stoves. For example, forest fire combustion does not occur in an enclosed chamber, and the biomass consumed in forest fires is usually green and includes underbrush, leaves, and grass. Given these differences and the uncertainties about the formation kinetics of CDD/CDF during combustion, it is difficult to determine whether CDD/CDF emissions would be higher or lower from forest fires than from wood stoves. Thus, although an emission factor of 2 ng I-TEQ_{DF}/kg appears to be the best estimate that can be made currently, it must be considered highly uncertain.

The limited emission factor data available and the degree of confidence in the three approaches evaluated to derive an emission factor were judged inadequate for developing national emission estimates that could be included in the national inventory. However, a preliminary estimate of the potential annual TEQ release associated with forest and brush fires can be obtained using estimates of the biomass burned annually in wildfire and prescribed burns and the emission factor used for wood stoves (2 ng I-TEQ_{DF}/kg of biomass). According to the Council on Environmental Quality's 25th Annual Report (CEQ, 1997), 5 million acres of forest were lost to wildfires in 1987 and 7 million acres were lost in 1995. Estimates of the acreage consumed annually during prescribed burns are not readily available for the reference years 1995 and 1997. An estimated 5.1 million acres of biomass were burned in 1989 during prescribed burns (Ward et al., 1993). Prescribed burning, also known as managed or controlled burning, is used as a forest, range, and wetland management tool conducted under prescribed weather and fuel conditions. This value of 5.1 million acres is assumed to be an appropriate value to use for reference years 1987 and 1995.

Combining these acreage estimates with biomass consumption rates of 9.43 metric tons/acre in areas consumed by wildfires (Ward et al., 1976) and 7.44 metric tons/acre in areas consumed in prescribed burns (Ward et al., 1993) indicates that 47 million metric tons of biomass were consumed by wildfires in 1987, 66 million metric tons were

consumed by wildfires in 1995, and 38 million metric tons were consumed by prescribed burns in 1987 and 1995.

Combining the emission factor developed using the wood stove approach (2 ng I-TEQ_{DF}/kg biomass) with the amount of biomass consumed annually in wildfires and prescribed fires (total of 85 million metric tons in 1987 and 104 million metric tons in 1995) yields I-TEQ_{DF} annual emission estimates of 170 g in 1987 and 208 g in 1995. These estimates should be regarded as preliminary indications of possible emissions from this source; further testing is needed to confirm the true magnitude of emissions.

6.5 BACKYARD BARREL BURNING

In many rural areas of the United States, disposal of residential solid waste may take place via open backyard burning in barrels or similar homemade devices. Although no national statistics on the prevalence of this practice have been reported, the results of a telephone survey conducted in the early 1990s of residents in five central Illinois counties indicate that about 40 percent of the residents in a typical rural Illinois county burn household waste. The survey also found that, on average, those households that burn waste dispose of approximately 63 percent of their household waste by burning it in barrels (Two Rivers Region Council of Public Officials and Patrick Engineering, 1994).

Similar results were recently obtained in a survey conducted by Zenith Research Group, Inc. for the Western Lake Superior Sanitary District of Minnesota (Zenith, 2000). This survey of 760 residents of selected portions of Northwest Wisconsin and Northeast Minnesota addressed, in part, use of burn barrels or other devices to burn household garbage or other materials. The survey found that 71 percent of the respondents indicated their residence currently had garbage hauling service. Of those respondents lacking a garbage hauling service, 92 percent said they currently used a nearby garbage disposal site. However, among all respondents, 27.5 percent admitted they currently use a burn barrel or other device to burn household garbage or other materials. Of these respondents who admitted burning, 39 percent indicated they burn at least weekly and 30 percent indicated they burned once or twice monthly.

6.5.1. Emission Estimates from Backyard Barrel Burning

The low combustion temperatures and oxygen-starved conditions associated with barrel burning may result in incomplete combustion and increased pollutant emissions. In 1997, EPA's Control Technology Center, in cooperation with the New York State Departments of Health (NYSDOH) and Environmental Conservation (NYSDEC), conducted an initial study to examine, characterize, and quantify emissions from the simulated open burning of household waste materials in barrels (Lemieux, 1997). A representative waste to be burned was prepared based on the typical percentages of various waste materials disposed of by New York State residents (i.e., nonavid recyclers); hazardous wastes (i.e., chemicals, paints, oils, etc.) were not included in the test waste. A variety of compounds, including CDD/CDFs, were measured in the emissions from two simulated open burnings of this "baseline" waste.

Combustion studies were subsequently performed by EPA to provide additional "baseline" waste tests and to provide an initial indication of the impact of limited variation in waste composition and combustion conditions on CDD/CDF emissions from a simulated domestic backyard barrel burn of 6.8 kg of unshredded household waste (Gullet et al., 1999; 2000a; 2000b; Lemieux et al., 2000; Lemieux, 2000).

The results of seven "baseline" waste tests were reported in these EPA studies. These tests exhibited variation in the emissions of CDD/CDFs with a 1-2 order of magnitude spread between the lowest and highest values for individual congeners, congener groups, total CDD/CDFs, and TEQ values. The average TEQ emission factor for the seven wastes was 72.8 ng I-TEQ_{DF}/kg of waste burned (setting not detected values equal to zero) and 73.7 ng I-TEQ_{DF}/kg (setting not detected values equal to one-half the detection limit). The corresponding TEQ_{DF}-WHO_{98} values were 76.8 and 77.7 ng TEQ_{DF}-WHO_{98}/kg. Table 6-2 presents the average congener and congener group results for these tests.

Variation from the baseline waste chlorine content (0.2 percent by weight PVC) included testing at three different PVC levels (0, 1.0, and 7.5 percent by weight PVC). The average emissions from the 0, 1.0, and 7.5 percent PVC were, respectively, 14, 201, and 4,916 ng I-TEQ_{DF}/kg. Two tests using waste impregnated with inorganic chloride (i.e., $CaCl_2$) at a 7.5 percent by weight level (and no PVC) averaged 734 ng I-TEQ_{DF}/kg.

Qualitative comparisons suggest that the tests with higher Cl, via PVC or $CaCl_2$, resulted in substantial increase in TEQ emissions.

Other variations in baseline waste composition included conducting one test with compressed waste, one test with a double load of waste, and one test in which some of the waste paper was wetted to simulate high moisture burns. These tests resulted in a higher mean TEQ emission factor (534 ng I-TEQ_{DF}) than that of the baseline runs.

Several waste combustion variables were studied such as average temperatures at prescribed barrel heights, duration that temperatures were within the favorable temperature range for CDD/CDF formation, and measurement of CO, CO_2, O_2, PM, and HCl. Statistical analyses of the results indicated that an interactive term, the product of the CO emissions and the temperature in the uppermost portion of the barrel, and CO emissions were the best predictors of TEQ variation. However, the wide variability in test results (i.e., from less than 10 to more than 6,000 ng I-TEQ_{DF}/kg) also indicates that a high degree of CDD/CDF emission variation can be expected due to factors, such as waste orientation, that are not wholly related to waste composition or burning practice.

The limited emission factor and activity level data available for developing national emission estimates that could be included in the national inventory were assigned low confidence ratings. The number of households nationwide burning waste in barrels and the total amount and variability of burned waste can only be roughly estimated, and the representativeness of the trash and burning conditions used in the baseline experiments to conditions nationwide is uncertain. Combining the emission factors of 72.8 ng I-TEQ_{DF}/kg of waste burned and 76.8 ng TEQ_{DF}-WHO_{98}/kg with the following information and assumptions allows estimates to be made of the potential magnitude of national CDD/CDF TEQ emissions from backyard household trash burning.

- Of the rural population in the United States, 40 percent are assumed to burn their household waste in a barrel (Two Rivers Region Council of Public Officials and Patrick Engineering, 1994).

- On average, each U.S. citizen generates 3.72 pounds of solid waste (excluding yard waste) per day (or 616 kg/person-yr) (U.S. EPA, 1996b).

- On average, in households that dispose of household waste by burning, approximately 63 percent of waste generated is burned (i.e., 63 percent of 616 kg/person-yr = 388 kg/person-year) (Two Rivers Region Council of Public Officials and Patrick Engineering, 1994).

- In 1994 (used for 1995 reference year), 52.7 million people lived in nonmetropolitan areas. In 1990 (used for 1987 reference year), 50.7 million people lived in nonmetropolitan areas (U.S. DOC, 1997).

Annual nationwide TEQ emissions were calculated using Equation 6-1.

$$E_{TEQ} = EF_{TEQ} \times P \times F \times W \qquad \text{(Eqn. 6-1)}$$

where:

E_{TEQ}	=	Annual TEQ_{DF} emissions (g/yr)
EF_{TEQ}	=	TEQ_{DF} emission factor (g TEQ_{DF}/kg of waste)
P	=	Nonmetropolitan population of U.S. in reference year
F	=	Fraction of nonmetropolitan population assumedto burn household waste (0.4)
W	=	Mass of household waste burned per year on a per capita basis (388 kg/person-year)

Therefore, estimated nationwide emissions in 1995 and 1987 were 595 g I-TEQ_{DF} (628 g TEQ_{DF}-WHO_{98}) and 573 g I-TEQ_{DF} (604 g TEQ_{DF}-WHO_{98}), respectively.

6.5.2. Barrel Burning Ash Composition

Ash samples were also collected from the open barrel burning (Lemieux, 1997) and analyzed for PCDD/PCDFs and PCBs. Ash samples from the experiments were combined resulting in two composite samples, one for "avid" recyclers and one for non-recyclers. The results for PCBs depict only the data for specific PCB congeners. Remaining PCB data reported in Lemieux (1997) could not be related to a particular congener. The results are depicted in Tables 6-3 and 6-4.

6.6. UNCONTROLLED COMBUSTION OF POLYCHLORINATED BIPHENYLS (PCBs)

The accidental combustion of PCB-containing electrical equipment or intentional combustion of PCBs in incinerators and boilers not approved for PCB burning (40 CFR 761) may produce CDDs and CDFs. At elevated temperatures, such as in transformer fires, PCBs can undergo reactions to form CDF and other by-products. More than 30 accidental fires and explosions involving PCB transformers and capacitors in the United States and Scandinavia, which involved the combustion of PCBs and the generation of CDDs and CDFs, have been documented (Hutzinger and Fiedler, 1991b; O'Keefe and Smith, 1989; Williams et al., 1985). For example, analyses of soot samples from a

Binghamton, New York, office building fire detected 20 μg/g of total CDDs (0.6 to 2.8 μg/g of 2,3,7,8-TCDD) and 765 to 2,160 μg/g of total CDFs with 12 to 270 μg/g of 2,3,7,8-TCDF. At that site, the fire involved the combustion of a mixture containing PCBs (65 percent) and chlorobenzene (35 percent). Laboratory analyses of soot samples from a PCB transformer fire, which occurred in Reims, France, indicated total CDD and CDF levels in the range of 4 to 58,000 ng/g and 45 to 81,000 ng/g, respectively.

Using a bench-scale thermal destruction system, Erickson et al. (1984) determined the optimum conditions for CDF formation to be 675°C, an excess oxygen concentration of 8 percent, and a residence time of 0.8 seconds or longer. Combusting mineral oil and silicone oil containing 5, 50, and 500 ppm of Aroclor 1254 at these conditions for 0.8 seconds yielded PCB to CDF conversion efficiencies as high as 4 percent. Up to 3 percent conversion efficiency was observed when an askarel (70 percent Aroclor 1260) was combusted under the same conditions.

The use of PCBs in new transformers in the United States is banned, and their use in existing transformers and capacitors is being phased out under regulations promulgated under the Toxic Substances Control Act (TSCA).

Because of the accidental nature of these incidents, the variation in duration and intensity of elevated temperatures, the variation in CDD/CDF content of residues, and uncertainty regarding the amount of PCBs still in service in electrical equipment, EPA judged the available data inadequate for developing national emission estimates that could be included in the national inventory. However, Thomas and Spiro (1995) conservatively estimated that about 15 g of TEQ may be generated annually from fires in commercial and residential buildings each year. This estimate is based on the following assumptions: (1) the I-TEQ_{DF} emission rate is 20 μg/kg of PCB burned; (2) 74,000 metric tons of PCB are still in use in various electrical equipment; and (3) 1 percent of the in-use PCBs is burned during the course of structural fires annually.

6.7. VOLCANOES

To date, no studies demonstrating formation of CDD/CDFs by volcanoes have been published. Given the available information from the studies discussed below, volcanoes do not appear to be sources of CDD/CDF release to the environment.

Gribble (1994) summarized some of the existing information on the formation of chlorinated compounds by natural sources, including volcanoes. Gribble (1994) reported that several studies had demonstrated the presence of chlorofluorocarbons and simple halogenated aliphatic compounds (one and two carbon chain length) in volcanic gases. In addition, several chlorinated monoaromatic compounds as well as three PeCB congeners were reported as having been detected in the ash from the 1980 eruption of Mount St. Helens. Gribble hypothesized that the formation of these PCB compounds was the result of rapid, incomplete high-temperature combustion of chloride-containing plant material in the eruption zone. However, he presented no information indicating formation of CDD/CDFs by volcanoes.

Lamparski et al. (1990) analyzed groundfall ash samples collected at various distances and locations from Mount St. Helens following the eruption in 1980. The findings of this study indicate that volcanic particulate emissions were free of detectable PCBs and nearly free of detectable CDDs (0.8 ng/kg HpCDD detected) upon exiting the volcano and remained so throughout their period of deposition in the blast zone. However, upon transport through the atmosphere, measurable and increasing levels of CDDs and PCBs were detected in deposited ash as the ash passed from rural to urban environments. The authors hypothesized that CDDs and PCBs in the atmosphere became associated with the volcanic ash particulates through gas-phase sorption or particulate agglomeration.

Takizawa et al. (1994) sampled the dust fall from the active volcano, Fugendake, as well as the volcanic ash from the active volcano, Sakurajima, for CDD and CDF congener group concentrations. The study was not designed to determine whether the CDD/CDFs observed were formed by the volcanoes or were scavenged from the atmosphere by the falling dust and ash. The dust fall was collected for 1-month periods during July and October 1992; two samples of the volcanic ash were collected in 1992. The results of the sample analyses for 2,3,7,8-substituted CDDs and CDFs, presented in Table 6-5, show that no 2,3,7,8-substituted congeners with less than 7 chlorines were detected; however, Takizawa et al. (1994) reported that non-2,3,7,8-substituted congeners in the lower chlorinated congener groups were detected.

Table 6-1. CDD/CDF Emission Factors for a Landfill Flare

Congener/Congener Group	Mean Facility Emission Factor* (ng/m^3 gas combusted)
2,3,7,8-TCDD	0.018
1,2,3,7,8-PeCDD	0.092
1,2,3,4,7,8-HxCDD	0.074
1,2,3,6,7,8-HxCDD	0.074
1,2,3,7,8,9-HxCDD	0.259
1,2,3,4,6,7,8-HpCDD	0.755
OCDD	4.414
2,3,7,8-TCDF	14.074
1,2,3,7,8-PeCDF	0.385
2,3,4,7,8-PeCDF	1.136
1,2,3,4,7,8-HxCDF	1.455
1,2,3,6,7,8-HxCDF	0.422
1,2,3,7,8,9-HxCDF	0.110
2,3,4,6,7,8-HxCDF	0.681
1,2,3,4,6,7,8-HpCDF	1.215
1,2,3,4,7,8,9-HpCDF	0.073
OCDF	0.639
Total 2,3,7,8-CDD	5.686
Total 2,3,7,8-CDF	20.192
Total I-TEQ_{DF}	2.392
Total TEQ_{DF}-WHO_{98}	2.433
Total TCDD	NR
Total PeCDD	NR
Total HxCDD	NR
Total HpCDD	NR
Total OCDD	NR
Total TCDF	NR
Total PeCDF	NR
Total HxCDF	NR
Total HpCDF	NR
Total OCDF	NR
Total CDD/CDF	NR

* Assumes heat content of 1.86E+07 J/m^3 for landfill gas (Federal Register, 1996a).
NR = not reported.

Source: CARB (1990d)

Table 6-2. CDD/CDF Air Emission Factors from Barrel Burning of Household Waste

Congener/Congener Group	Average Air Emission Factors [a] (ng/kg waste burned)	
	Nondetects Set to 1/2 Det. Limit	Nondetects Set to Zero
2,3,7,8-TCDD	3.4	2.7
1,2,3,7,8-PeCDD	8.2	8.1
1,2,3,4,7,8-HxCDD	6.6	6.4
1,2,3,6,7,8-HxCDD	9.9	9.7
1,2,3,7,8,9-HxCDD	19.1	19.0
1,2,3,4,6,7,8-HpCDD	39.8	39.8
OCDD	49.7	49.7
2,3,7,8-TCDF	45.6	45.6
1,2,3,7,8-PeCDF	37.2	37.2
2,3,4,7,8-PeCDF	65.2	65.2
1,2,3,4,7,8-HxCDF	113.8	113.8
1,2,3,6,7,8-HxCDF	38.5	38.5
2,3,4,6,7,8-HxCDF	61.9	61.9
1,2,3,7,8,9-HxCDF	3.0	2.5
1,2,3,4,6,7,8-HpCDF	128.6	124.4
1,2,3,4,7,8,9-HpCDF	14.6	15.0
OCDF	37.5	36.4
Total 2,3,7,8-CDD	136.6	135.4
Total 2,3,7,8-CDF	545.8	540.4
Total I-TEQ_{DF}	73.7	72.8
Total TEQ_{DF}-WHO_{98}	77.7	76.8
Total TCDD	413	413
Total PeCDD	281	281
Total HxCDD	221	221
Total HpCDD	105	105
Total OCDD	43	43
Total TCDF	1,880	1,880
Total PeCDF	1,021	1,021
Total HxCDF	492	492
Total HpCDF	169	169
Total OCDF	32	30
Total CDD/CDF	4,657	4,656

a Listed values are the arithmetic averages of seven tests for the congeners and the averages of five tests for the congener groups.

Source: Lemieux (2000); Gullett et al. (1999; 2000a; 2000b).

Table 6-3. PCDD/PCDF Analysis for Composite Ash Samples from Barrel Burning (ng/kg of ash)

Congener/Congener Group	Average Concentration in Composite Ash Sample		I-TEQ_{DF}		TEQ_{DF}-WHO_{98}	
	Avid Recycler	Non-Recycler	Avid Recycler	Non-Recycler	Avid Recycler	Non-Recycler
2,3,7,8-TCDD	31	9	31	9	31	9
1,2,3,7,8-PeCDD	230	53	115	26.5	230	53
1,2,3,4,7,8-HxCDD	270	44	27	4.4	27	4.4
1,2,3,6,7,8-HxCDD	420	74	42	7.4	42	7.4
1,2,3,7,8,9-HxCDD	300	56	30	5.6	30	5.6
1,2,3,4,6,7,8-HpCDD	4,000	630	40	6.3	40	6.3
OCDD	9,600	690	9.6	0.69	0.96	0.069
2,3,7,8-TCDF	830	220	83	22	83	22
1,2,3,7,8-PeCDF	1,000	270	50	13.5	50	13.5
2,3,4,7,8-PeCDF	2,500	690	1,250	345	1,250	345
1,2,3,4,7,8-HxCDF	2,300	480	230	48	230	48
1,2,3,6,7,8-HxCDF	2,100	490	210	49	210	67
2,3,4,6,7,8-HxCDF	2,900	670	290	67	290	15
1,2,3,7,8,9-HxCDF	810	150	81	15	81	21
1,2,3,4,6,7,8-HpCDF	12,000	2,100	120	21	120	1.7
1,2,3,4,7,8,9-HpCDF	1,400	170	14	1.7	14	0.056
OCDF	8,200	560	8.2	0.56	0.82	
Total TCDD	2,500	490	-	-	-	-
Total PeCDD	4,100	740	-	-	-	-
Total HxCDD	5,600	1,300	-	-	-	-
Total HpCDD	7,600	1,300	-	-	-	-
Total OCDD	9,600	690	-	-	-	-
Total TCDF	25,000	8,200	-	-	-	-
Total PeCDF	21,000	6,600	-	-	-	-
Total HxCDF	19,000	4,600	-	-	-	-
Total HpCDF	17,000	2,900	-	-	-	-
Total OCDF	8,200	560	-	-	-	-
Total CDD	14,851	1,556	-	-	-	-
Total CDF	34,040	5,800	-	-	-	-
Total CDD/CDF	48,891	7,356	-	-	-	-

Table 6-4. PCB Analysis for Composite Ash Samples from Barrel Burning
(ng/kg of ash)

Compound	Avid Recycler	Non-Recycler
2-Chlorobiphenyl	<2,500	4,900
2,3'-Dichlorobiphenyl	3,700	4,700
2,2',6-Trichlorobiphenyl	<500	5,600
2,2',5-Trichlorobiphenyl	32,000	6,300
2,3',5-Trichlorobiphenyl	800	800
2,3',4-Trichlorobiphenyl	<500	700
2,4',5-Trichlorobiphenyl	1,500	900
2,4,4'-Trichlorobiphenyl	<500	500
2,2',4,6'-Tetrachlorobiphenyl	<500	1,500
2,2',3,6'-Tetrachlorobiphenyl	5,300	1,300
2,2',5,5'-Tetrachlorobiphenyl	3,100	1,800
2,2',3,5'-Tetrachlorobiphenyl	2,600	1,200
2,2',4,4',5-Pentachlorobiphenyl	3,400	1,300
2,2',3,3',5-Pentachlorobiphenyl	400	<500
2,2',3,4,5,5'-Hexachlorobiphenyl	1,200	<500

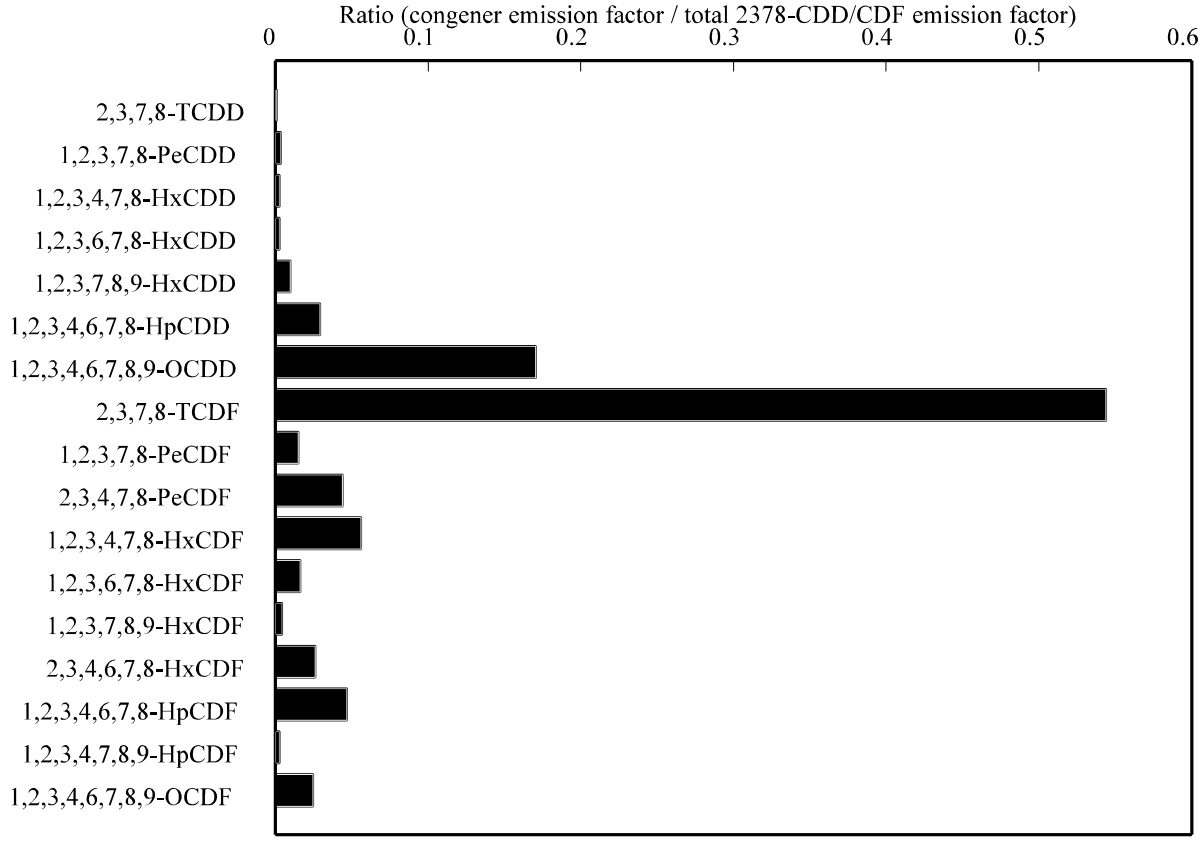
Table 6-5. CDD/CDF in Dust Fall and Ashes from Volcanoes

2,3,7,8-Substituted Congener Group	Dust Fall (mg/km^2/month)[a]		Volcanic Ash (ng/kg)[b]	
	July 1992	Oct. 1992	Ash No. 1	Ash No. 2
TCDD	<0.5	<0.5	<0.1	<0.1
PeCDD	<0.5	<0.5	<0.1	<0.1
HxCDD	<0.5	<0.5	<0.1	<0.1
HpCDD	9.2	5.2	2.5	1.8
OCDD	14	11	1.7	2.2
TCDF	<0.5	<0.5	<0.1	<0.1
PeCDF	<0.5	<0.5	<0.1	<0.1
HxCDF	<0.5	<0.5	<0.1	<0.1
HpCDF	1.9	2.8	1.2	1.2
OCDF	4.2	1.8	<0.5	<0.5

a Dust fall measured from the active volcano, Fugendake.

b Volcanic ash measured from active volcano, Sakurajima.

Source: Takizawa et al. (1994).



Source: CARB (1990d).

Figure 6-1. Congener Profile for Landfill Flare Air Emissions

7. METAL SMELTING AND REFINING SOURCES OF CDD/CDF

7.1. PRIMARY NONFERROUS METAL SMELTING/REFINING

Little information has been published on the potential for the formation and environmental release of CDD/CDFs from primary nonferrous metal manufacturing facilities. Norwegian investigators (Oehme et al., 1989) have reported the presence of CDD/CDFs in the wastewater of a magnesium refining facility and in the receiving water sediments downstream of a nickel refining facility in Norway. Insufficient information is available from this study for evaluating CDD/CDF emissions, if any, from the smelting/refining of magnesium and nickel in the United States. The potential for formation and release of CDD/CDFs by primary copper smelters in the United States has been reported by Environmental Risk Sciences (1995) to be negligible. Lexen et al. (1993) reported finding few or no CDD/CDFs in solid wastes from a primary aluminum smelter. Bramley (1998) indicated that the smelting/refining of titanium may be a source of CDD/CDFs. The findings of these studies are discussed in the following subsections.

7.1.1. Primary Copper Smelting and Refining

Environmental Risk Sciences (1995) prepared an analysis for the National Mining Association on the potential for CDD/CDF emissions from the primary copper smelting industry. The analysis included reviewing the process chemistry and technology of primary copper smelting, identifying operating conditions, and comparing process stream compositions from seven of the eight U.S. primary copper smelters that are members of the National Mining Association. The analysis also included stack testing for CDD/CDFs at two facilities. The stack testing (Secor International Inc., 1995a and 1995b) involved the principal off-gas streams for copper smelters: main stack, plant tail gas stack, and the vent fume exhaust. The two facilities that were tested (Phelps Dodge Mining Co. in Playas, New Mexico, and Cyprus Miami Mining Co. in Claypool, Arizona) were selected as representative of the other facilities in the industry because of their similarity to the other facilities in terms of process chemistry, process stream composition, and process stream temperatures.

The results of the assessment of the process chemistry and technology and the operating conditions and process stream compositions indicate that although there is some

potential for CDD/CDF formation in this industry, several factors lessen the probability of CDD/CDF formation. These factors include (a) most of the energy used to melt copper is derived from oxidation of copper sulfide ore minerals (i.e., $CuFeS_2$) rather than carbon (i.e., fossil fuels); (b) low concentrations of organic carbon and chloride are present in raw materials and reagents; (c) high concentrations of sulfur dioxide are present in process gases (6 to 40 percent SO_2 by volume); (d) high temperatures are maintained in the furnaces and converters (1,100 to 1,500°C); and (e) copper (II) chloride is apparently absent in process emissions.

The results of this assessment were supported by the stack test data from the two tested facilities. CDD/CDFs were not detected in the air emissions from either facility. In 1995, eight primary smelters were in operation in the United States, one of which closed at the end of the year (Edelstein, 1995). Total refinery production was 1.60 million metric tons in 1995, including 0.36 million metric tons from scrap material (Edelstein, 1995) and 1.13 million metric tons in 1987 (USGS, 1997c). Conservatively assuming that all nondetected values were present at one-half the detection limits, Environmental Risk Sciences (1995) calculated the annual TEQ emission to air to be less than 0.5 g I-TEQ_{DF} in 1995 for the seven facilities (out of a total of eight) belonging to the National Mining Association. Assuming that feed and processing materials were similar in 1987, 1987 releases can be estimated at less than 0.5 g I-TEQ_{DF} as well. The activity level estimates are assigned a high confidence rating and the emission factor estimate a medium rating.

7.1.2. Primary Magnesium Smelting and Refining

Oehme et al. (1989) reported that the production of magnesium can lead to the formation of CDDs and CDFs. Oehme et al. (1989) estimated that 500 g of I-TEQ_{DF} were released in wastewater to the environment and 6 g I-TEQ_{DF} were released to air annually from a magnesium production facility studied in Norway; CDFs predominated with a CDF to CDD concentration ratio of 10:1. At the time of sampling, the magnesium production process involved formation of MgO (magnesium oxide) from calcinated dolomite followed by a step in which $MgCl_2$ was produced by heating MgO/coke pellets in a shaft furnace in a pure chlorine atmosphere to about 700 to 800°C. The $MgCl_2$ was then electrolyzed to form metallic magnesium and Cl_2. The Cl_2 excess from the $MgCl_2$ process and the Cl_2 formed during electrolysis were collected by water scrubbers and directly discharged to

the environment. The discharged wastewater contained 200–500 ppm of suspended particulate matter. All but trace quantities of the hexa- through octa- congeners were associated with the particulates; up to 10 percent of the tetra- and penta- congeners were present in the water phase.

A recent study by the firm operating the facility (Musdalslien et al., 1998) indicates that installation of a water treatment system has reduced annual emissions to water to less than 1 g Nordic TEQ and emissions to air have been reduced to less than 2 g Nordic TEQ. This study also presented results demonstrating that the carbon reducing agent used in the $MgCl_2$ production step and the operating conditions of the shaft furnace greatly affect the formation of CDD/CDFs. Gases from the furnace were measured nine times over sampling periods of 6 to 8 hours. The calculated emission factor to air (i.e., before any APCD controls) ranged from 468 to 3,860 ng Nordic TEQ per kg of $MgCl_2$ produced. The APCD controls consist of three water scrubbers, a wet ESP, and an incinerator.

U.S. production of primary magnesium was 142,000 metric tons in 1995. This production was about 98 percent of the rated capacity of the three U.S. magnesium production facilities. The United States has been the world's largest producer of metallic magnesium for the past five decades (Kramer, 1996). Similar to the Norwegian plant, an electrolytic process (i.e., electrolysis of magnesium chloride) is used at the plants in Texas (capacity of 65,000 kkg/yr) and Utah (capacity of 40,000 kkg/yr) to recover metallic magnesium from $MgCl_2$. However, these two facilities reportedly use seawater and lake brines as the source of magnesium, and the procedures to obtain and purify $MgCl_2$ do not involve chlorinating furnaces and carbonized pellets (Lockwood et al., 1981). A thermic process is used to recover magnesium from dolomite at the facility in Washington (capacity of 40,000 kkg/yr) (Kramer, 1995). In thermic processes, magnesium oxide (MgO), a component of calcinated dolomite, is reacted with a metal such as silicon (usually alloyed with iron) to produce metallic magnesium.

Monitoring of wastewater discharges for CDD/CDF content from U.S. magnesium production facilities has not been reported. Wastewater discharge of CDD/CDF reported for the Norwegian facility, discussed in the previous paragraphs, are not adequate to support development of wastewater emission factors for U.S. facilities because of

possible differences in the processes used to manufacture $MgCl_2$ and pollution control equipment.

Monitoring of air emissions for CDD/CDF content has recently been reported for one of the three U.S. primary magnesium production facilities, the Magnesium Corporation of America facility near Rowley, Utah. The average emission rates (for three tests) reported for the melt reactor stack and the cathode stack were 0.31 mg I-TEQ_{DF}/hr and 0.16 mg I-TEQ_{DF}/hr, respectively (Western Environmental Services and Testing, Inc., 2000). The confidence in the degree to which the one tested facility represents the emissions from the other two U.S. facilities is currently very low. Therefore, the emissions data were judged inadequate for developing at this time national emission estimates that could be included in the national inventory. However, a preliminary estimate of potential TEQ annual emissions from U.S. primary magnesium production facilities can be made by assuming that the average total emission factor for the Utah facility (i.e., 0.47 mg I-TEQ_{DF}/hr) measured in May of 2000 is representative of the other two facilities on a magnesium production basis. Specifically, if it is assumed that this facility operated for 24 hours per day and 365 days in 1995, then the annual release in 1995 would have been 4.1 g I-TEQ_{DF}. If it is further assumed that this facility operated at 98 percent of it's rated capacity of 40,000 kkg/yr, then the production-based emission factor is 105 ng I-TEQ_{DF}/kg of magnesium produced. Applying this emission factor to 98 percent of the industry's production capacity in 1995 (i.e., 142,000 kkg) yields an annual emission estimate of 14.6 g I-TEQ_{DF} in 1995. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the magnitude of these emissions.

7.1.3. Primary Nickel Smelting and Refining

Oehme et al. (1989) reported that certain primary nickel refining processes generate CDDs and CDFs, primarily CDFs. Although the current low-temperature process used at the Norwegian facility is estimated to result in releases to water of only 1 g I-TEQ_{DF} per year, a high temperature (i.e., 800°C) $NiCl_2$ to NiO conversion process that had been used for 17 years at the facility is believed to have resulted in significant releases in earlier years based on the ppb levels of CDFs detected in aquatic sediments downstream of the facility (Oehme et al., 1989).

The only nickel mining and smelting complex in the United States is located in Oregon. This facility restarted operations in April 1995 and produced 8,290 metric tons of nickel that year. The facility had been on standby since August 1993 and had no production in 1994. The smelter has a capacity of 16,000 metric tons per year (Kuck, 1995).

Monitoring of discharges for CDD/CDF content at this one U.S. facility has not been reported. Emissions of CDD/CDF were reported for a Norwegian facility in the late 1980s, as discussed in Section 7.1.4. The emissions information contained in the Norwegian study, Oehme et al. (1989), is not adequate to support development of emission factors for the U.S. facility.

7.1.4. Primary Aluminum Smelting and Refining

No sampling of air emissions from this industry for the presence of CDD/CDFs has been reported. Lexen et al. (1993) reported that samples of filter powder and sludge from a lagoon at the only primary aluminum production plant in Sweden showed no or little CDD/CDF. A brief summary of the processes involved in primary aluminum smelting is presented in the following paragraphs.

Bauxite ore, a hydrated oxide of aluminum consisting of 30 to 56 percent alumina (Al_2O_3), is refined into alumina by the Bayer Process and the alumina is then shipped to a primary aluminum smelter for electrolytic reduction to aluminum. Electrolytic reduction of alumina occurs in shallow rectangular cells, or "pots," which are steel shells lined with carbon. Carbon electrodes (petroleum coke mixed with a pitch binder) extending into the pot serve as the anodes, and the carbon lining serves as the cathode. Three types of pots are used: prebaked anode cell, horizontal stud Soderberg anode cell, and vertical stud Soderberg anode cell. Most of the aluminum produced in the United States is produced using the prebaked cells. Molten cryolite (Na_3AlF_6) functions as both the electrolyte and the solvent for the aluminum. Aluminum is deposited at the cathode as molten metal (U.S. EPA, 1998a).

Prior to casting, the molten aluminum may be batch treated in reverberatory furnaces (like those used in secondary aluminum smelting) to remove oxides, gaseous impurities, and active metals such as sodium and magnesium. One process consists of

adding a flux of chloride and fluoride salts and then bubbling chlorine gas through the molten mixture (U.S. EPA, 1998a).

U.S. production of primary aluminum was 3.343 million metric tons in 1987 and 3.375 million metric tons in 1995. In 1995, 13 companies operated 22 primary aluminum reduction plants (USGS, 1997d, 1997e).

7.1.5. Primary Titanium Smelting and Refining

No sampling of emissions or products from this industry for CDD/CDF content has been reported. However, Bramley (1998) and the Peer Review Panel (Eastern Research Group, 1998) suggested that carbochlorination processes used in this industry may be a source of CDD/CDFs. A brief summary of the processes used in this industry is presented in the following paragraphs.

Titanium oxide ores and concentrates are chlorinated in fluidized-bed reactors in the presence of coke at 925 to 1,010°C to form titanium tetrachloride ($TiCl_4$). The $TiCl_4$ is separated from other chlorides by double distillation. The $TiCl_4$ is then either oxidized at 985°C to form pigment-grade titanium dioxide or is reduced using sodium or magnesium to form titanium sponge (i.e., metallic titanium) (Knittel, 1983). Titanium ingot is produced by melting titanium sponge or scrap or a combination of both using electron beam, plasma, and vacuum arc methods. Scrap currently supplies about 50 percent of ingot feedstock (Gambogi, 1996).

Titanium sponge is currently produced at two facilities in the United States, one in Albany, Oregon, and the other in Henderson, Nevada. In 1995, the U.S. production volume of titanium sponge was withheld to avoid disclosing company proprietary data; domestic sponge capacity was 29,500 metric tons per year. In 1987, U.S. production of titanium sponge was 17,849 metric tons. The majority of titanium dioxide (i.e., greater than 90 percent) is produced using the process described above. Titanium dioxide is produced at nine facilities in the United States. Production volumes in 1987 and 1995 were 821,000 and 1,180,000 metric tons, respectively (Gambogi, 1996; USGS, 1997f).

7.2. SECONDARY NONFERROUS METAL SMELTING

Secondary smelters primarily engage in the recovery of nonferrous metals and alloys from new and used scrap and dross. The principal metals of this industry both in

terms of volume and value of product shipments are aluminum, copper, lead, zinc, and precious metals (U.S. DOC, 1990a). Scrap metal and metal wastes may contain organic impurities such as plastics, paints, and solvents. Secondary smelting/refining processes for some metals (e.g., aluminum, copper, and magnesium) use chemicals such as NaCl, KCl, and other salts. The combustion of these impurities and chlorine salts in the presence of various types of metal during reclamation processes can result in the formation of CDDs and CDFs, as evidenced by the detection of CDDs and CDFs in the stack emissions of secondary aluminum, copper, and lead smelters (Aittola et al., 1992; U.S. EPA, 1987a, 1997b).

7.2.1. Secondary Aluminum Smelters

Secondary aluminum smelters reclaim aluminum from scrap. This recycling involves two processes—precleaning and smelting. Both processes may produce CDD/CDF emissions.

Precleaning processes involve sorting and cleaning scrap to prepare it for smelting. Cleaning processes that may produce CDD/CDF emissions use heat to separate aluminum from contaminates and other metals; these techniques are "roasting" and "sweating." Roasting uses rotary dryers with a temperature high enough to vaporize organic contaminants, but not high enough to melt aluminum. An example of roasting is the delacquering and processing of used beverage cans. Sweating involves heating aluminum-containing scrap metal to a temperature above the melting point of aluminum, but below the melting temperature of other metals such as iron and brass. The melted aluminum trickles down and accumulates in the bottom of the sweat furnace and is periodically removed (U.S. EPA, 1997b).

After precleaning, the treated aluminum scrap is smelted and refined. This usually takes place in a reverberatory furnace. Once smelted, flux is added to remove impurities. The melt is "demagged" to reduce the magnesium content of the molten aluminum by the addition of chlorine gas. The molten aluminum is then transferred to a holding furnace and alloyed to final specifications (U.S. EPA, 1997b).

CDD/CDF emissions to air have been measured at six U.S. secondary aluminum operations. Four facilities were tested in 1995 and two facilities were tested in 1992. Three of the four 1995 tests were conducted by EPA in conjunction with The Aluminum

Association for the purpose of identifying emission rates from facilities with potentially MACT-grade operations and APCD equipment; the other test performed in 1995 (U.S. EPA, 1995h) was performed by EPA. Two facilities tested by the California Air Resources Board in 1992 were reported in two confidential reports.

The first facility tested in 1995 was a top-charge melt furnace (Advanced Technology Systems, Inc., 1995). During testing, the charge material to the furnace was specially formulated to contain no oil, paint, coatings, rubber, or plastics (other than incidental amounts). The CDD/CDF emissions from such a clean charge, 0.26 ng I-TEQ_{DF}/kg charge material (0.27 ng TEQ_{DF}-WHO_{98}/kg), would be expected to represent the low end of the normal industry range.

The second facility operated a sweat furnace to preclean the scrap and a reverberatory furnace to smelt the precleaned aluminum (U.S. EPA, 1995h). Stack emissions were controlled by an afterburner operated at 1,450° F. The TEQ emission factor for this facility was 3.22 ng I-TEQ_{DF}/kg aluminum produced (3.37 ng TEQ_{DF}-WHO_{98}/kg).

The third facility employed a crusher/roasting dryer as a precleaning step, followed by a reverberatory furnace (Galson Corporation, 1995). The emissions from the two units were vented separately. The exhaust from the crusher/dryer was treated with an afterburner and a baghouse. The exhaust from the furnace passed through a baghouse with lime injection. Both stack exhausts were tested and the combined TEQ emission factor was 12.95 ng I-TEQ_{DF}/kg aluminum produced (13.55 ng TEQ_{DF}-WHO_{98}/kg). Because the activity level of the facility at the time of sampling was treated as confidential business information, the calculated emission factor was based on the reported typical production rates of the two operations, 26,000 lbs/hr for the crusher/dryer and 6,700 lbs/hr for the furnace.

The fourth facility operated a scrap roasting dryer followed by a sidewell reverberatory furnace (Envisage Environmental Inc., 1995). The emissions from the two units were vented separately. Exhaust from the dryer passed through an afterburner and a lime-coated baghouse. The exhaust from the furnace passed through a lime-coated baghouse. Both stack exhausts were tested and the combined TEQ emission factor was 36.03 ng I-TEQ_{DF}/kg of charge material (37.94 ng TEQ_{DF}-WHO_{98}/kg). Problems with the

scrap dryer were discovered after the testing was completed. Also, operating conditions during testing were reported to represent more worst-case than typical operations.

Two facilities tested by CARB in 1992 and reported in two confidential reports (CARB, 1992a, as reported in U.S. EPA, 1997b; CARB, 1992b, as reported in U.S. EPA, 1997b) were reported to have TEQ emission factors of 52.21 and 21.67 ng I-TEQ_{DF}/kg of scrap aluminum consumed (55.68- and 23.44-ng TEQ_{DF}-WHO_{98}/kg). One facility was equipped with a venturi scrubber; the other was assumed in U.S. EPA (1997b) to be uncontrolled.

The congener and congener group emission factors derived from these stack tests are presented in Table 7-1. The average congener and congener group profiles are presented in Figure 7-1. The average of the TEQ emission factors measured at the six tested facilities (including the facility at which a specially formatted clean charge was used) is 21.1 ng I-TEQ_{DF}/kg of scrap feed (22.4 ng TEQ_{DF}-WHO_{98}/kg). [Note: Although the emission factors at two of the facilities tested in 1995 are based on the output rather than input rate, the two rates are assumed, for purposes of this report, to be roughly equivalent.] Although the testing was recently conducted at U.S. facilities, a low confidence rating is assigned to this average emission factor because it is based on the results of testing at only six facilities, several of which may have more effective APCD than the other facilities in the industry.

For comparison purposes, The European Commission uses 22 ng I-TEQ_{DF}/kg scrap aluminum as the "typical" emission factor for the European Dioxin Inventory (Quab and Fermann, 1997). Umweltbundesamt (1996) reported stack testing results for 25 aluminum smelters/foundries in Germany. Sufficient data were provided in Umweltbundesamt (1996) to enable calculation of TEQ emission factors for 11 of the tested facilities. The calculated emission factors ranged from 0.01 to 167 ng I-TEQ_{DF}/kg of scrap feed. Three facilities had emission factors exceeding 100 ng I-TEQ_{DF}/kg, and two facilities had emission factors less than 1 ng I-TEQ_{DF}/kg. The mean emission factor for the 11 facilities was 42 ng I-TEQ_{DF}/kg.

An approximate total of 727,000 metric tons of scrap aluminum were consumed by 67 secondary aluminum smelters in 1987 (U.S. DOC, 1995c). In 1995, consumption of scrap aluminum by the 76 facilities that compose the secondary aluminum smelting industry had nearly doubled to 1.3 million metric tons (USGS, 1997a; The Aluminum

Association, 1997). A high confidence rating is assigned to these production estimates, because they are based on government survey data. Applying the I-TEQ_{DF} emission factor of 21.1 ng TEQ/kg of scrap feed to these consumption values yields estimated annual emissions of 15.3 g I-TEQ_{DF} in 1987 and 27.4 g I-TEQ_{DF} in 1995. Applying the TEQ_{DF}-WHO_{98} emission factor of 22.4 ng TEQ/kg to the consumption values yields estimated annual emissions of 16.3 g TEQ_{DF}-WHO_{98} in 1987 and 29.1 g TEQ_{DF}-WHO_{98} in 1995.

It should be noted that a significant amount of scrap aluminum is also consumed by other segments of the aluminum industry. However, this scrap is generally scrap from metal manufacturing processes, including metal and alloy production (e.g., borings, turnings, and dross), rather than old scrap that results from consumer products (e.g., cans, radiators, auto shredders). Integrated aluminum companies consumed 1.4 million metric tons of scrap aluminum in 1995, and independent mill fabricators consumed 0.68 million metric tons (USGS, 1997a).

7.2.2. Secondary Copper Smelters

Secondary copper smelting is part of the scrap copper, brass, and bronze reprocessing industry. Brass is an alloy of copper and zinc; bronze is an alloy of copper and tin. Facilities in this industry fall into three general classifications: secondary smelting, ingot making, and remelting. Similar process equipment may be used at all three types of facilities, so the distinguishing features are not immediately apparent (U.S. EPA, 1994g).

The feature that distinguishes secondary smelters from ingot makers and remelters is the extent to which pyrometallurgical purification is performed. A typical charge at a secondary smelter may contain from 30 to 98 percent copper. The secondary smelter upgrades the material by reducing the quantity of impurities and alloying materials, thereby increasing the relative concentration of copper. This degree of purification and separation of the alloying constituents does not occur at ingot makers and remelters. Feed material to a secondary copper smelter is a mixture of copper-bearing scrap such as tubing, valves, motors, windings, wire, radiators, turnings, mill scrap, printed circuit boards, telephone switching gear, and ammunition casings. Nonscrap items like blast furnace slags and drosses from ingot makers or remelters may represent a portion of the charge. The secondary smelter operator uses a variety of processes to separate the

alloying constituents. Some purify the scrap in the reductive atmosphere of a blast furnace. The charge may be subsequently purified in the oxidizing atmosphere of a converter. Other secondary smelters perform all purification by oxidation in top-blown rotary converters or in reverberatory furnaces (U.S. EPA, 1994g).

The ingot makers blend and melt scrap copper, brass, and bronze of various compositions to produce a specification brass or bronze ingot. When necessary, the ingot makers add ingots of other metals (e.g., zinc or tin) to adjust the metallurgy of the final product. The feed materials for ingot makers contain relatively high amounts of copper. Examples of feed materials include copper tubing, valves, brass and bronze castings, ammunition shell casings, and automobile radiators. "Fire-refined" anode copper or cathode copper may also be charged. Items such as motors, telephone switchboard scrap, circuit board scrap, and purchased slags are not used by ingot makers. The reductive step (melting in a reducing atmosphere, as in a blast furnace) that some secondary smelters employ is not used by ingot makers. Ingot makers do, however, use some of the other types of furnaces used by secondary smelters, including direct-fired converters, reverberatory furnaces, and electric induction furnaces (U.S. EPA, 1994g).

Remelting facilities do not conduct any substantial purification of the incoming feeds. These facilities typically just melt the charge and cast or extrude a product. The feeds to a remelter are generally alloy material of approximately the desired composition of the product (U.S. EPA, 1994g).

Emissions Data

Stack emissions of CDD/CDFs from a secondary copper smelter were measured by EPA during 1984–1985 as part of the National Dioxin Tier 4 Study (U.S. EPA, 1987a). The facility chosen for testing was estimated to have high potential for CDD/CDF emissions because of the abundance of chlorinated plastics in the feed. This facility ceased operations in 1986. The tested facility was chosen for testing by EPA because the process technology and air pollution control equipment in place were considered typical for the source category. Copper and iron-bearing scrap were fed in batches to a cupola blast furnace, which produced a mixture of slag and black copper. Four to 5 tons of metal-bearing scrap were fed to the furnace per charge, with materials typically being charged 10 to 12 times per hour. Coke fueled the furnace and represented approximately

14 percent by weight of the total feed. During the stack tests, the feed consisted of electronic telephone scrap and other plastic scrap, brass and copper shot, iron-bearing copper scrap, precious metals, copper-bearing residues, refinery by-products, converter furnace slag, anode furnace slag, and metallic floor-cleaning material. The telephone scrap made up 22 percent by weight of the feed and was the only scrap component that contained plastic materials. Oxygen-enriched combustion air for combustion of the coke was blown through tuyeres (nozzles) at the bottom of the furnace. At the top of the blast furnace were four natural gas–fired afterburners to aid in completing combustion of the exhaust gases. Fabric filters controlled particulate emissions, and the flue gas then was discharged into a common stack. The estimated emission factors derived for this site are presented in Table 7-2. The emission factors are based on the total weight of scrap fed to the furnace. The TEQ emission factor, based on the measured congener and congener group emission factors, is 779 ng I-TEQ_{DF}/kg of scrap metal smelted (810 ng $TEQ_{DF}WHO_{98}$/kg). Figure 7-2a presents the congener group profile based on these emission factors.

In 1992, stack testing of the blast furnace emissions of a secondary smelter located in Philadelphia, Pennsylvania (Franklin Smelting and Refining Co.), was conducted by Applied Geotechnical & Environmental Services Corporation (AGES, 1992). Similar to the facility tested by EPA in 1984–1985, this facility processed low-purity copper-bearing scrap, telephone switch gear, and slags, as well as higher copper content materials (U.S. EPA, 1994g). The facility used a blast (cupola-type) furnace coupled with a pair of rotary converters to produce blister copper. The blast furnace used coke as both the fuel and the agent to maintain a reducing atmosphere. The black copper/slag mixture from the blast furnace was charged to the rotary converters for further refining with the aid of oxygen, sand, and oak logs (AGES, 1992; U.S. EPA, 1994g). The APCD equipment installed on the blast furnace included an afterburner, cooling tower, and baghouse. During testing, the afterburner was reported to be operating erratically and was particularly low during one of the two sampling episodes. Stack gas flow was also low during both sampling episodes because one or more baghouse compartments were inoperable (AGES, 1992). The estimated emission factors derived for this site from the AGES results are presented in Table 7-2. The emission factors are based on the total weight of scrap fed to the blast furnace. The TEQ emission factor was 16,618 ng I-

TEQ_{DF}/kg of scrap (16,917 ng TEQ_{DF}-WHO_{98}/kg). Figure 7-2b presents the congener and congener group profiles based on these emission factors.

In 1991, stack testing of the rotary furnace stack emissions of a secondary smelter located in Alton, Illinois (Chemetco, Inc.) was conducted by Sverdrup Corp. (1991). The Chemetco facility used four tap down rotary (i.e., oxidizing) furnaces. Furnace process gas emissions were controlled by a primary quencher and a venturi scrubber. The feed was relatively high-purity copper scrap containing minimal, if any, plastics. The same manufacturing process and APCD equipment were in place in 1987 and 1995 (U.S. EPA, 1994g). Because this facility operated under oxidizing rather than reducing conditions and processed relatively high-purity scrap, the potential for CDD/CDF formation and release was expected to be dramatically different than that of the two tested facilities reported above. The estimated emission factors derived for this site from the results of Sverdrup Corp. (1991) are presented in Table 7-2. The emission factors are based on the total weight of scrap feed to the furnace. The TEQ emission factor was 3.60 ng I-TEQ_{DF}/kg of scrap (3.66 ng TEQ_{DF}-WHO_{98}/kg).

Only limited data on emissions from secondary copper smelters are reported in the European Dioxin Inventory (LUA, 1997). I-TEQ_{DF} emission factors reported for German shaft furnaces/converters and reverberatory furnaces range from 5.6 to 110 ng I-TEQ_{DF}/kg and from 0.005 to 1.56 ng I-TEQ_{DF}/kg. Emission factors reported for two "smelter and casting furnaces" in Sweden in which "relatively clean scrap is used as input" are 0.024 and 0.04 ng I-TEQ_{DF}/kg. A smelter in Austria is reported to have an I-TEQ emission factor of 4 ng I-TEQ_{DF}/kg. The minimum, typical, and maximum default emission factors selected in LUA (1997) are 5, 50, and 400 ng I-TEQ_{DF}/kg, respectively.

Activity Level Information

In 1987, four secondary copper smelters were in operation: Franklin Smelting and Refining Co. (Philadelphia, PA), Chemetco (Alton, IL), Southwire Co. (Carrollton, GA), and a facility located in Gaston, SC, that was owned by American Telephone and Telegraph (AT&T) until 1990 when it was purchased by Southwire Co. In 1987, estimated smelter capacities were 13,600 kkg for the Franklin Smelting and Refining Co. facility, 120,000 kkg for the Chemetco facility, 48,000 kkg for the Southwire Co. facility, and 85,000 kkg for the AT&T facility (Edelstein, 1999). In 1995, only three of these four facilities were in

operation. The Southwire facility in Gaston (previously owned by AT&T) was closed in January 1995. The Franklin facility subsequently ceased operations in August 1997. Estimated smelter capacities in 1995 were 16,000 kkg for the Franklin Smelting and Refining Co. facility, 135,000 kkg for the Chemetco facility, and 92,000 kkg for the Southwire Co. facility (Edelstein, 1999).

Emission Estimates

Although little research has been performed to define the CDD/CDF formation mechanism(s) in secondary copper smelting operations, two general observations have been made (Buekens et al., 1997). The presence of chlorinated plastics in copper scraps used as feed to the smelters is believed to increase the CDD/CDF formation. Second, the reducing or pyrolytic conditions in blast furnaces can lead to high CDD/CDF concentrations in the furnace process gases. As noted in "Emission Data," above, two of the U.S. facilities that have been tested (i.e., U.S. EPA, 1987a; AGES, 1992) each had the following characteristics. Both processed low-purity scrap containing significant quantities of plastics, and both facilities used blast furnaces. The APCD equipment at both facilities consisted of an afterburner, cooling tower (Franklin facility only), and a baghouse (U.S. EPA, 1994g). The other tested U.S. facility (i.e., Sverdrup, 1991) used oxidizing rather than reducing conditions and processed relatively high purity scrap.

For purposes of this report, the TEQ emission factor measured at the Franklin Smelting and Refining Co. facility in 1992 is considered to be representative of the TEQ emission factor in 1987 and 1995. Combining this emission factor (16,618 ng I-TEQ_{DF}/kg scrap feed, or 16,917 ng TEQ_{DF}-WHO_{98}/kg) with the estimated smelter capacities (data are not available on the amount of scrap processed) for this facility in 1987 (13,600 kkg) and 1995 (16,000 kkg) yields I-TEQ_{DF} emission estimates of 226 g (230 g TEQ_{DF}-WHO_{98}) in 1987 and 266 g (271 g TEQ_{DF}-WHO_{98}) in 1995. This facility ceased operations in 1997.

Similarly, for purposes of this report, the TEQ emission factor for the Chemetco, Inc., facility is considered to be representative of the TEQ emission factor in 1987 and 1995. Combining this emission factor (3.60 ng I-TEQ_{DF}/kg scrap feed or 3.66 ng TEQ_{DF}-WHO_{98}/kg) with the estimated smelter capacities (data are not available on the amount of scrap processed) for this facility in 1987 (120,000 kkg) and 1995 (135,000 kkg) yields I-

TEQ_{DF} estimates of 0.43 g (0.44 g TEQ_{DF}-WHO_{98}) in 1987 and 0.49 g (0.49 g TEQ_{DF}-WHO_{98}) in 1995.

The facility in Gaston, South Carolina, was in operation during 1987, but not in 1995. Prior to 1990, when this facility was owned by AT&T, the plant processed a great deal of high-plastics-content scrap (such as whole telephones). This scrap was fed to a pyrolysis unit prior to entering the blast furnace. In addition to a blast furnace, the facility also had an oxidizing reverberatory furnace for processing higher purity scrap. The facility had separate baghouses for the blast furnace, the converters, and the reverberatory furnace (U.S. EPA, 1994g). Because this facility processed low-purity, high-plastics-content scrap in 1987, and presumably processed much of this in the reducing atmosphere of a pyrolysis unit and blast furnace, the average of the TEQ emission factors for the Tier 4 (U.S. EPA, 1987a) and Franklin facilities (8,700 ng I-TEQ_{DF}/kg, or 8,860 ng TEQ_{DF}-WHO_{98}/kg) was used to estimate potential emissions in 1987 of 740 g I-TEQ_{DF} or 753 g TEQ_{DF}-WHO_{98} (assuming an activity level of 85,000 kkg). This activity level is the estimated capacity of the facility; data are not available on the amount of scrap processed.

The Southwire facility in Carrollton, Georgia, had both a blast furnace and a reverberatory furnace. In 1992, approximately 50 percent of incoming scrap was processed in each furnace (U.S. EPA, 1994g). Unlike the two tested facilities and the Gaston facility, the Southwire facility stopped processing plastic-coated scrap in the 1970s. In addition, this facility had a more complex APCD system, which may have reduced the formation and release of CDD/CDFs. The blast furnace process gases passed through an afterburner (1,600°F), U-tube coolers, and an evaporative spray system before entering the baghouse at a temperature of 225 to 375°F. For these reasons, EPA has determined that the existing emissions data for secondary smelters cannot reliably be used to generate a quantitative estimate of potential emissions during 1987 and 1995 for this facility.

A high confidence rating is assigned to the production estimates, because they are based on government survey data. A low confidence rating is assigned to the TEQ emission estimates because they are based on limited measurements made at three smelters, one of which was not in operation in 1987 or 1995.

It should be noted that a significant amount of scrap copper is consumed by other segments of the copper industry. In 1995, brass mills and wire-rod mills consumed 886,000 metric tons of copper-based scrap; foundries and miscellaneous manufacturers consumed 71,500 metric tons (USGS, 1997a). As noted above, however, these facilities generally do not conduct any significant purification of the scrap. Rather, the scrap consumed is already of alloy quality and processes employed typically involve only melting, casting and extruding. Thus, the potential for formation of CDD/CDFs is expected to be much less than the potential during secondary smelting operations.

7.2.3. Secondary Lead Smelters

The secondary lead smelting industry produces elemental lead through the chemical reduction of lead compounds in a high-temperature furnace (1,200 to 1,260° C). Smelting is performed in reverberatory, blast, rotary, or electric furnaces. Blast and reverberatory furnaces are the most common types of smelting furnaces used by the 23 facilities that make up the current secondary lead smelting industry in the United States. Of the 45 furnaces at these 23 facilities, 15 are reverberatory furnaces, 24 are blast furnaces, 5 are rotary furnaces, and 1 is an electric furnace. The one electric furnace and 11 of the 24 blast furnaces are co-located with reverberatory furnaces, and most share a common exhaust and emissions control system (U.S. EPA, 1994h).

Furnace charge materials consist of lead-bearing raw materials, lead-bearing slag and drosses, fluxing agents (blast and rotary furnaces only), and coke. Scrap motor vehicle lead-acid batteries represent about 90 percent of the lead-bearing raw materials at a typical lead smelter. Fluxing agents consist of iron, silica sand, and limestone or soda ash. Coke is used as fuel in blast furnaces and as a reducing agent in reverberatory and rotary furnaces. Organic emissions from co-located blast and reverberatory furnaces are more similar to the emissions of a reverberatory furnace than the emissions of a blast furnace (U.S. EPA, 1994h).

The total annual production capacity of the 23 companies that make up the U.S. lead smelting industry is 1.36 million metric tons. Blast furnaces not co-located with reverberatory furnaces account for 21 percent of capacity (or 0.28 million metric tons). Reverberatory furnaces and blast and electric furnaces co-located with reverberatory furnaces account for 74 percent of capacity, or 1.01 million metric tons. Rotary furnaces

account for the remaining 5 percent of capacity, or 0.07 million metric tons (U.S. EPA, 1994h). Actual production volume statistics by furnace type are not available. However, if it is assumed that the total actual production volume of the industry, 0.97 million metric tons in 1995 (USGS, 1997a) and 0.72 million metric tons in 1987 (U.S. EPA, 1994h), reflect the production capacity breakdown by furnace type, then the estimated actual production volumes of blast furnaces (not co-located), reverberatory and co-located blast/ electric and reverberatory furnaces, and rotary furnaces were 0.20, 0.72, and 0.05million metric tons, respectively, in 1995, and 0.15, 0.53, and 0.04 million metric tons, respectively, in 1987. In 1987, the industry consisted of 24 facilities.

CDD/CDF emission factors can be estimated for lead smelters using the results of emission tests recently performed by EPA at three smelters (a blast furnace, a co-located blast/reverberatory furnace, and a rotary kiln furnace) (U.S. EPA, 1992e, 1995d, 1995e). The air pollution control systems at the three tested facilities consisted of both baghouses and scrubbers. Congener-specific measurements were made at both APCD exit points at each facility. Table 7-3 presents the congener and congener group emission factors from the baghouse and the scrubber for each site. Figure 7-3 presents the corresponding profiles for the baghouse emissions from the tested blast furnace and reverberatory furnace. Although all 23 smelters employ baghouses, only 9 employ scrubber technology. Facilities that employ scrubbers account for 14 percent of the blast furnace (not co-located) production capacity, 52 percent of the reverberatory and co-located furnace production capacity, and 57 percent of the rotary furnace production capacity. TEQ emission factors (ng TEQ/kg lead processed) from the reported data for each of the three furnace configurations are presented below as a range reflecting the presence or absence of a scrubber.

Emission factors when nondetected values are set equal to zero:

- Blast furnace:
  - 0.63 to 8.31 ng I-TEQ_{DF}/kg lead produced
  - 0.64 to 8.81 ng TEQ_{DF}-WHO_{98}/kg lead produced
- Reverberatory/co-located furnace:
  - 0.05 to 0.41 ng I-TEQ_{DF}/kg lead produced
  - 0.05 to 0.42 ng TEQ_{DF}-WHO_{98}/kg lead produced

- Rotary furnace:
  - 0.24 to 0.66 ng I-TEQ_{DF}/kg lead produced
  - 0.24 to 0.66 ng TEQ_{DF}-WHO_{98}/kg lead produced

If it is assumed that these ranges of emission rates are representative of those at nontested facilities with the same basic furnace configuration and presence or absence of scrubbers, then combining these emission rate ranges with the estimated volume of secondary lead production derived above and the percentage of each configuration type that have scrubbers, yields the following estimated air emissions in units of grams TEQ per year:

Configuration	Estimated Annual TEQ Emissions (g TEQ)*			
	Ref. Year 1995		Ref. Year 1987	
	I-TEQ_{DF}	TEQ_{DF}-WHO_{98}	I-TEQ_{DF}	TEQ_{DF}-WHO_{98}
Blast furnaces w/scrubbers	0.018	0.018	0.013	0.013
Blast furnaces w/o scrubbers	1.429	1.515	1.072	1.136
Reverberatory furnaces w/ scrubbers	0.019	0.019	0.014	0.014
Reverberatory furnaces w/o scrubbers	0.142	0.145	0.104	0.106
Rotary furnaces w/ scrubbers	0.019	0.019	0.015	0.015
Rotary furnaces w/o scrubbers	0.005	0.005	0.004	0.004
	1.632	1.721	1.223	1.288

* Calculated using emission factors based on nondetected values set equal to zero.

A medium confidence rating is assigned to the emission factors derived above because stack test data were available for 3 of the 23 smelters in the United States (of which only 16 were in operation as of December 1993), and the stack test data used represent the three major furnace configurations. The activity level estimate has been assigned a medium confidence rating because, although it is based on a U.S. Department of Commerce estimate of total U.S. production, no production data were available on a furnace type or furnace configuration basis.

7.3. PRIMARY FERROUS METAL SMELTING/REFINING

Iron is manufactured from its ores (i.e., magnetic pyrites, magnetite, hematite, and carbonates of iron) in a blast furnace, and the iron obtained from this process is further refined in steel plants to make steel. The primary production of iron and steel involves two operations identified by European researchers as potential emission sources of CDD/CDFs: iron ore sinter production and coke production. Each of these potential sources is discussed in the following subsections.

7.3.1. Sinter Production

At some iron manufacturing facilities, iron ores and waste iron-bearing materials undergo sintering to convert the materials to usable feed for the blast furnace. In the sintering process, iron ore fines and waste materials are mixed with coke fines, and the mixture is placed on a grate, which is then heated to a temperature of 1,000–1,400°C. The heat generated during combustion sinters the small particles. Iron-bearing dusts and slags from processes in the steel plant are the types of iron-bearing waste materials used as a feed mix for the sinter plant (Knepper, 1981; Capes, 1983; U.S. EPA, 1995b).

Several European investigators have reported that iron ore sinter plants are major sources of airborne emissions CDD/CDFs (Rappe, 1992b; Lexen et al., 1993; Lahl, 1993, 1994). Lahl (1993, 1994) reports that the management practice of recycling dusts and scraps from other processes in the steel plant into the sintering plant introduces traces of chlorine and organic compounds that generate the CDD/CDFs found in these plants.

Organic compounds that are potential precursors to CDD/CDF formation come primarily from the oil, which is found in mill scale, as well as some blast furnace sludges that are used as part of the sinter feed mixture. Most U.S. plants limit the amount of oil because it increases emissions of volatile organic compounds (VOCs) and may create a fire hazard. In addition, plants with baghouses must limit the oil content because the oil tends to blind the fabric filters. Typical oil contents of the feed at U.S. sinter plants range from 0.1 to 0.75 percent (Calcagni et al., 1998).

Sinter plants in Sweden were reported to emit up to 3 ng I-TEQ_{DF}/Nm^3 stack gas or 2 to 4 g I-TEQ_{DF}/yr per plant to the air (Rappe, 1992b; Lexen et al., 1993). Bremmer et al. (1994) reported the results of stack testing at three iron ore sintering plants in The Netherlands. One facility equipped with wet scrubbers had an emission factor of 1.8 ng

I-TEQ_{DF}/dscm (at 11 percent O_2). The other two facilities, both equipped with cyclones, had emission factors of 6.3 and 9.6 ng I-TEQ_{DF}/dscm (at 7 percent O_2). Lahl (1993, 1994) reports stack emissions for sintering plants in Germany (after passage through mechanical filters and electrostatic precipitators) ranging from 3 to 10 ng I-TEQ_{DF}/Nm^3. A recent compilation of emission measurements by the German Federal Environmental Agency indicates stack emission concentrations ranging from 1.2 to 60.6 ng I-TEQ_{DF}/m^3 (at 7 percent O_2); the majority of emissions in 1996 were around 3 ng I-TEQ_{DF}/m^3 (Umweltbundesamt, 1996).

EPA conducted tests at two of the nine U.S. sinter plants operating in 1997 in order to quantify emissions of CDD/CDFs (Calcagni et al., 1998). In choosing representative plants for testing, EPA considered a variety of issues, including the types and quantities of feed materials, types of emission controls, and the oil content of the sinter feed. EPA decided to test a plant with a baghouse and a plant with a venturi (or wet) scrubber. Baghouses and wet scrubbers are the principal air pollution control devices employed to control emissions from the sinter plant windbox. Four plants used a baghouse and five plants used a wet scrubber. The types of feed materials and oil content at the two selected plants were determined to be representative of other plants in the industry. Sampling was performed over 3 days (4 hours per day) at each plant.

The average CDD/CDF TEQ concentrations measured in the stack emissions were 0.19 ng I-TEQ_{DF}/Nm^3 and 0.81 ng I-TEQ_{DF}/Nm^3 for the wet scrubber and baghouse, respectively. The corresponding TEQ emission factors are 0.55 ng I-TEQ_{DF}/kg sinter (0.62 ng TEQ_{DF}-WHO_{98}/kg) and 4.14 ng I-TEQ_{DF}/kg sinter (4.61 ng TEQ_{DF}-WHO_{98}/kg), respectively, for wet scrubbers and baghouses. These emission factors are assigned a high rating because they are based on recent EPA testing at two facilities considered by EPA to be representative of both current and 1995 standard industry practices. Congener-specific emission factors for these two facilities are presented in Table 7-4. Figure 7-4 presents the congener profiles for these facilities. Although concentrations were higher from the baghouse than from the scrubber, both concentrations are low relative to what had been reported from testing at German, Dutch, and Swedish sinter plants. These differences may be due to differences between the operation or APCD of U.S. sinter plants and the tested European plants. Most of the U.S. integrated iron and steel plants, including those with sinter plants, have eliminated the purchase and use of

chlorinated organics in their facilities. Their rolling mill oils (lubricants and hydraulic fluids) do not contain chlorinated compounds. In addition, routine analysis of waste materials going to the sinter plant have not detected any chlorinated solvents. Finally, none of the U.S. plants currently use an electrostatic precipitator to control emissions from the sinter windbox (Calcagni et al., 1998).

In 1996 (data were not readily available for 1995), 11 sintering plants were operating in the United States, with a total annual production capacity of about 17.6 million metric tons (Metal Producing, 1996). Over the past two decades, the size of this industry has decreased dramatically. In 1982, 33 facilities operated with a combined total capacity of 48.3 million metric tons (U.S. EPA, 1982b). The nine currently operating U.S. sinter plants have a combined capacity of 15.6 million metric tons (Calcagni et al., 1998). In 1987, sinter consumption by iron and steel plants was 14.5 million metric tons (AISI, 1990); in 1995, consumption was 12.4 million metric tons (Fenton, 1995), or approximately 70 percent of production capacity, assuming that production capacity in 1995 was the same as in 1996. These activity level estimates are assigned a confidence rating of medium.

As shown in Table 7-5, 59 percent of current (i.e., 1998) sinter production capacity is at facilities with wet scrubbers and 41 percent is at facilities with baghouses. If it is assumed that these same relative proportions of APCD to production capacity existed in 1995, and it is assumed that actual production in 1995 was equal to sinter consumption at iron and steel plants (i.e., 12.4 million metric tons), then estimated TEQ emissions from wet scrubber-equipped facilities were 4.0 g I-TEQ_{DF} (4.5 g TEQ_{DF}-WHO_{98}) and emissions from baghouse-equipped facilities were 21.0 g I-TEQ_{DF} (23.4 g TEQ_{DF}-WHO_{98}), for a total of 25.1 g I-TEQ_{DF} (28.0 g TEQ_{DF}-WHO_{98}). These emission estimates are assigned an overall medium confidence rating on the basis of the medium rating for the activity level estimates.

If these same assumptions are applied to the 1987 sinter consumption rate of 14.5 million metric tons, then estimated TEQ emissions from wet scrubber-equipped facilities were 4.7 g I-TEQ_{DF} (5.3 g TEQ_{DF}-WHO_{98}) and emissions from baghouse-equipped facilities were 24.6 g I-TEQ_{DF} (27.4 g TEQ_{DF}-WHO_{98}), for a total of 29.3 g I-TEQ_{DF} (32.7 g TEQ_{DF}-WHO_{98}). These emission estimates are less certain than the estimates for 1995 because of uncertainties concerning actual APCD in place in 1987 and content of waste feed (i.e.,

oil content and presence of chlorinated organics in the oil) at that time. Consequently, a low confidence rating is assigned to the emission factor.

7.3.2. Coke Production

Coke is the principal fuel used in the manufacture of iron and steel. Coke is the solid carbonaceous material produced by the destructive distillation of coal in high-temperature ovens. No testing of CDD/CDF emissions from U.S. coke facilities has been reported. However, at a facility in The Netherlands, Bremmer et al. (1994) measured a CDD/CDF emission rate to air during the water quenching of hot coke of 0.23 ng I-TEQ_{DF}/kg of coal consumed. Minimal CDD/CDF air emissions, 0.002 ng I-TEQ_{DF}/kg of coal, were estimated by Bremmer et al. (1994) for flue gases generated during the charging and emptying of the coke ovens.

In 1995, an estimated 30 million metric tons of coal were consumed by coke plants in the United States (EIA, 1997b). No testing of CDD/CDF emissions from U.S. coke plants has been reported upon which to base an estimate of national emissions. The limited data available were thus judged inadequate for developing national emission estimates that could be included in the national inventory. However, a preliminary estimate of potential TEQ annual emissions from U.S. coke plants can be made by combining the consumption value of 30 million metric tons and the emission factor reported by Bremmer et al. (1994) for a Dutch coke plant (0.23 ng I-TEQ_{DF}/kg of coal consumed). This calculation yields an annual emission of 6.9 g I-TEQ_{DF} in 1995. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions.

7.4 SECONDARY FERROUS METAL SMELTING/REFINING

Electric arc furnaces (EAFs) have been reported to be sources of CDD/CDF emissions in Europe; no testing has been reported at U.S. facilities. EAFs are used to produce carbon and steel alloys primarily from scrap material. The production of steel in an EAF is a batch process, and the input material is typically 100 percent scrap. Scrap, alloying agents, and fluxing materials are loaded into the cylindrical, refractory-lined EAF, and then carbon electrodes are lowered into the EAF. The current of the opposite polarity

electrodes generates heat between the electrodes and through the scrap. Processing time of a batch ranges from about 1.5 to 5 hours to produce carbon steel and from 5 to 10 hours to produce alloy steel (U.S. EPA, 1995b).

The melting of scrap ferrous material contaminated with metalworking fluids and plastics that contain chlorine provides the conditions conducive to formation of CDD/CDFs. Tysklind et al. (1989) studied the formation and releases of CDD/CDFs at a pilot 10 ton electric furnace in Sweden. Scrap ferrous metal feedstocks containing varying amounts of chlorinated compounds (i.e., PVC plastics, cutting oils, or $CaCl_2$) were charged into the furnace under different operating conditions (i.e., continuous feed, batch feed into the open furnace, or batch feed through the furnace lid). During continuous charging operations, the highest emissions, 1.5 ng Nordic TEQ/dry Nm^3 (i.e., after a baghouse filter), were observed with a feedstock consisting of scrap metal with PVC plastics (1.3 g of chlorine per kg of feedstock). This emission equates to 7.7 ng Nordic TEQ/kg of feedstock. The highest emissions during batch charging also occurred when the scrap metal with PVC plastic was combusted (0.3 ng Nordic TEQ/dry Nm^3 or 1.7 ng Nordic TEQ/kg of feedstock). Much lower emissions (0.1 ng Nordic TEQ/dry Nm^3 or 0.6 ng Nordic TEQ/kg of feedstock) were observed when scrap metal with cutting oils that contained chlorinated additives (0.4 g of chlorine per kg of feedstock) was melted. Although these cutting oil-related emissions were not significantly different than the emissions observed from the melting of no-chlorine scrap metal, relatively high levels of CDD/CDF (i.e., 110-ng Nordic TEQ/dry Nm^3) were detected in flue gases prior to the baghouse. The congener profiles of raw flue gas samples (i.e., prior to APCD) showed that CDFs, rather than CDDs, were predominant in all three feedstock types. The congener profile from the test burn with PVC-containing feedstock showed a higher chlorinated congener content than was observed with the other feedstocks.

Eduljee and Dyke (1996) used a range of 0.7 to 10 ng I-TEQ_{DF}/kg of scrap feed to estimate national emissions for the United Kingdom. The range was assumed to be representative of no-chlorine and high-chlorine operations. However, Eduljee and Dyke (1996) provided little information on the supporting emission test studies (i.e., tested facility operational materials, feed rates, congener-specific emission rates).

Umweltbundesamt (1996) reported stack testing results for a variety of EAFs in Germany. Sufficient data were provided in Umweltbundesamt (1996) to enable

calculation of TEQ emission factors for six of the tested facilities. Two facilities had emission factors exceeding 1 ng I-TEQ_{DF}/kg of scrap processed, and two facilities had emission factors less than 0.1 ng I-TEQ_{DF}/kg of scrap. The mean emission factor was 1.15 ng I-TEQ_{DF}/kg of scrap. The TEQ concentrations in the stack gases at these facilities (corrected to 7 percent O_2) ranged from less than 0.1 to 1.3 ng I-TEQ_{DF}/m^3.

In 1995, electric arc furnaces accounted for 40.4 percent of U.S. steel production (or 38.4 of the total 95.2 million metric tons of raw steel produced) (Fenton, 1996). No testing of CDD/CDF emissions from U.S. electric arc furnaces has been reported upon which to base an estimate of national emissions, and the limited European data available were thus judged inadequate for developing national emission estimates that could be included in the national inventory. However, a preliminary estimate of potential TEQ annual emissions from U.S. electric arc furnaces can be made by combining the production estimate of 38.4 million metric tons and the average emission factor derived from the data reported in Umweltbundesamt (1996) for six EAFs (i.e., 1.15 ng I-TEQ_{DF}/kg scrap). This calculation yields an annual emission estimate of 44.3 g I-TEQ_{DF} in 1995. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions.

7.5. FERROUS FOUNDRIES

Ferrous foundries produce high-strength iron and steel castings used in industrial machinery, pipes, and heavy transportation equipment. Iron and steel castings are solid solutions of iron, carbon, and various alloying materials. Castings are produced by injecting or pouring molten metal into cavities of a mold made of sand, metal, or ceramic material. Metallic raw materials are pig iron, iron and steel scrap, foundry returns, and metal turnings (U.S. EPA, 1995b, 1997b).

The melting process takes place primarily in cupola (or blast) furnaces and to a lesser extent in electric arc furnaces. About 70 percent of all iron castings are produced using cupolas, although steel foundries rely almost exclusively on EAFs or induction furnaces for melting. The cupola is typically a vertical, cylindrical steel shell with either a refractory-lined or water-cooled inner wall. Charges are loaded at the top of the unit; the iron is melted as it flows down the cupola, and is removed at the bottom. (EAFs are

discussed in Section 7.4.3.) Electric induction furnaces are batch-type furnaces in which the charge is melted by a fluctuating electromagnetic charge produced by electrical coils surrounding the unit (U.S. EPA, 1995b, 1997b).

Iron and steel foundries, particularly those using EAFs, are highly dependent on iron and steel scrap. Of the estimated 72 million metric tons of iron and steel scrap consumed by the iron and steel industry in 1995, 25 percent (or 18 million metric tons) were used by ferrous foundries. The other 75 percent were used by primary ferrous metal smelters (principally those using EAFs) (USGS, 1997b). Thus, foundries face the same potential for CDD/CDF emissions as EAFs because of their use of scrap that contains chlorinated solvents, plastics, and cutting oils. (See Section 7.4.3.) The potential for formation and release of CDD/CDFs during the casting process (i.e., pouring of molten metal into molds and cores made of sand and various organic binders and polymers) is not known.

The results of emissions testing have been reported for only one U.S. ferrous foundry (CARB, 1993a, as reported in U.S. EPA, 1997b). The tested facility consisted of a batch-operated, coke-fired cupola furnace charged with pig iron, scrap iron, scrap steel, coke, and limestone. Emission control devices operating during the testing were an oil-fired afterburner and a baghouse. The congener and congener group emission factors derived from the testing are presented in Table 7-6. The calculated TEQ emission factor for this set of tests is 0.37 ng I-TEQ_{DF}/kg of metal charged to the furnace (0.42 ng TEQ_{DF}-WHO_{98}).

Umweltbundesamt (1996) reported stack testing results for a variety of ferrous foundries in Germany. Sufficient data were provided in Umweltbundesamt (1996) to enable calculation of TEQ emission factors for eight of the tested facilities. Three facilities had emission factors exceeding 1 ng I-TEQ_{DF}/kg of metal charge, and four facilities had emission factors less than 0.1 ng I-TEQ_{DF}/kg of metal charge. The emission factors span more than four orders of magnitude. The mean emission factor was 1.26 ng I-TEQ_{DF}/kg of metal feed.

Because of the wide range of emissions for the tested German foundries reported in Umweltbundesamt (1996), the confidence in the degree to which the one tested U.S. facility represents the mean emission factor for the approximate 1,000 U.S. foundries is considered very low. Therefore, the limited data available were judged inadequate for developing national emission estimates that could be included in the national inventory.

However, a preliminary estimate of potential TEQ annual emissions from U.S. ferrous foundries can be made by combining the mean emission factor derived from the data reported in Umweltbundesamt (1996) for eight foundries (1.26 ng I-TEQ_{DF}/kg of metal feed) with an activity level for U.S. foundries. In 1995, U.S. shipments from the approximate 1,000 U.S. ferrous foundries were 13.9 million metric tons, of which about 90 percent were iron castings and 10 percent were steel castings (Fenton, 1996). This calculation yields an annual emission estimate of 17.5 g I-TEQ_{DF} in 1995. This estimate should be regarded as a preliminary indication of possible emissions from this source category; further testing is needed to confirm the true magnitude of these emissions.

7.6. SCRAP ELECTRIC WIRE RECOVERY

The objective of wire recovery is to remove the insulating material and reclaim the metal (e.g., copper, lead, silver, and gold) in the electric wire. The recovery facility then sells the reclaimed metal to a secondary metal smelter. Wire insulation commonly consists of a variety of plastics, asphalt-impregnated fabrics, or burlap. Chlorinated organics are used to preserve the cable casing in ground cables. The combustion of chlorinated organic compounds in the cable insulation, catalyzed by the presence of wire metals such as copper and iron, can lead to the formation of CDDs and CDFs (Van Wijnen et al., 1992).

Although in the past, scrap electric wire was commonly recovered using thermal processing to burn off the insulating material, current recovery operations no longer typically involve thermal treatment according to industry and trade association representatives. Instead, scrap electric wire is mechanically chopped into fine particles. The insulating material is then removed by air blowing and, followed by gravitational settling of the heavier metal (telephone conversations between T. Leighton, Versar, Inc., R. Garino, Institute of Scrap Recycling Industries, March 2, 1993; and J. Sullivan, Triple F. Dynamics, March 8, 1993).

EPA measured dioxin-like compounds emitted to the air from a scrap wire reclamation incinerator during its 1986 National Dioxin Study of combustion sources (U.S. EPA, 1987a). Testing determined that the facility was typical of this industrial source category at that time. Insulated wire and other metal-bearing scrap material were fed to the incinerator on a steel pallet. The incinerator operated in a batch mode, with the

combustion cycles for each batch of scrap feed lasting between 1 and 3 hours. Natural gas was used to incinerate the material. Although most of the wire had a tar-based insulation, PVC-coated wire was also fed to the incinerator. Temperatures during combustion in the primary chamber furnace were about 570°C. The tested facility was equipped with a high-temperature natural gas-fired afterburner (980 to 1,090°C). Emission factors estimated for this facility are presented in Table 7-7. The estimated TEQ emission factor (based only on 2,3,7,8-TCDD, 2,3,7,8-TCDF, OCDD, and OCDF) is 16.9 ng I-TEQ_{DF}/kg scrap feed (15.8 ng TEQ_{DF}-WHO_{98}). Figure 7-5 presents a congener group profile based on these emission factors.

Bremmer et al. (1994) reported emission factors for three facilities in The Netherlands, which have subsequently ceased operations. Emission rates at a facility burning underground cables and cables containing PVC ranged from 3.7 ng I-TEQ_{DF}/kg to 14 ng I-TEQ_{DF}/kg. The emission rate at a second facility ranged from 21 ng I-TEQ_{DF}/kg of scrap (when burning copper core coated with greasy paper) to 2,280 ng I-TEQ_{DF}/kg of scrap (when burning lead cable). The third facility, which burned motors, was reported to have an emission rate of 3,300 ng I-TEQ_{DF}/kg of scrap. On the basis of these measurements, Bremmer et al. (1994) used emission rates of 40 ng I-TEQ_{DF}/kg of scrap and 3,300 ng I-TEQ_{DF}/kg of scrap for estimating national emissions in The Netherlands for facilities burning wires and cables and those burning motors.

Although limited emission testing has been conducted at one U.S. facility, the activity level for this industry sector in reference years 1987 and 1995 is unknown; therefore, an estimate of national emissions cannot be made. It is uncertain how many facilities still combust scrap wire in the United States. Trade association and industry representatives state that U.S. scrap wire recovery facilities now burn only minimal quantities of scrap wire. However, a recent inventory of CDD/CDF sources in the San Francisco Bay area noted that two facilities in the Bay area thermally treat electric motors to recover electrical windings (BAAQMD, 1996).

In addition to releases from regulated recovery facilities, CDD/CDF releases from small-scale burning of wire at unregulated facilities and open air sites have occurred; however, the current magnitude of small-scale, unregulated burning of scrap wire in the United States is not known. For example, Harnly et al. (1995) analyzed soil/ash mixtures from three closed metal recovery facilities and from three closed sites of open burning for

copper recovery near a California desert town. The geometric mean of the total CDD/CDF concentrations at the facility sites and the open burning sites was 86,000 and 48,500 ng/kg, respectively. The geometric mean TEQ concentrations were 2,900 and 1,300 ng I-TEQ_{DF}/kg, respectively. A significantly higher geometric mean concentration (19,000 ng I-TEQ_{DF}/kg) was found in fly ash located at two of the facility sites. The congener-specific and congener group results from this study are presented in Table 7-8. The results show that the four dominant congeners in the soil samples at both the facility and open burning sites were OCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8-HxCDF, and 2,3,7,8-TCDF. A slightly different profile was observed in the fly ash samples, with 1,2,3,7,8-PeCDF and 1,2,3,4,7,8,9-HpCDF replacing OCDD and 2,3,7,8-TCDF as dominant congeners.

Van Wijnen et al. (1992) reported similar results for soil samples collected from unpermitted incineration sites of former scrap wire and cars in The Netherlands. Total CDD/CDF concentrations in the soil ranged from 60 to 98,000 ng/kg, with 9 of the 15 soil samples having levels above 1,000 ng/kg. Chen et al. (1986) reported finding high levels of CDD/CDFs in residues from open air burning of wire in Taiwan, and Huang et al. (1992) reported elevated levels in soil near wire scrap recovery operations in Japan. Bremmer et al. (1994) estimated an emission rate to air of 500 ng I-TEQ_{DF}/kg of scrap for illegal, unregulated burning of cables in The Netherlands.

7.7. DRUM AND BARREL RECLAMATION FURNACES

Hutzinger and Fiedler (1991b) reported detecting CDD/CDFs in stack gas emissions from drum and barrel reclamation facilities at levels ranging from 5 to 27 ng/m^3. EPA measured dioxin-like compounds in the stack gas emissions of a drum and barrel reclamation furnace as part of the National Dioxin Study (U.S. EPA, 1987a).

Drum and barrel reclamation furnaces operate a burning furnace to thermally clean used 55-gallon steel drums of residues and coatings. The drums processed at these facilities come from a variety of sources in the petroleum and chemical industries. The thermally cleaned drums are then repaired, repainted, relined, and sold for reuse. The drum-burning process subjects used drums to an elevated temperature in a tunnel furnace for a sufficient time so that the paint, interior linings, and previous contents are burned or disintegrated. The furnace is fired by auxiliary fuel. Used drums are loaded onto a conveyor that moves at a fixed speed. As the drums pass through the preheat and

ignition zone of the furnace, additional contents of the drums drain into the furnace ash trough. A drag conveyor moves these sludges and ashes to a collection pit. The drums are air cooled as they exit the furnace. Exhaust gases from the burning furnace are typically drawn through a breeching fan to a high-temperature afterburner.

The afterburner at the facility tested by EPA operated at an average of 827°C during testing and achieved a 95 percent reduction in CDD/CDF emissions (U.S. EPA, 1987a). Emission factors estimated for this facility are presented in Table 7-9. On the basis of the measured congener and congener group emissions, the average TEQ emission factor is estimated to be 16.5 ng I-TEQ_{DF} per drum (17.5 ng TEQ_{DF}-WHO_{98}/drum). The congener group profile is presented in Figure 7-6.

Approximately 2.8 to 6.4 million 55-gallon drums are incinerated annually in the United States (telephone conversation between C. D'Ruiz, Versar, Inc., and P. Rankin, Association of Container Reconditioners, December 21, 1992). This estimate is based on the following assumptions: (1) 23 to 26 incinerators are currently in operation; (2) each incinerator, on average, handles 500 to 1,000 drums per day; and (3) on average, each incinerator operates 5 days per week, with 14 days downtime per year for maintenance activities. The weight of 55-gallon drums varies considerably; however, on average, a drum weighs 38 lbs (or 17 kg); therefore, an estimated 48 to 109 million kg of drums are incinerated annually. Assuming that 4.6 million drums are burned each year (i.e., the midpoint of the range) and applying the emission factors developed above, the estimated annual emission of TEQ is 0.08 g I-TEQ_{DF} (0.08 g TEQ_{DF}-WHO_{98}). No activity level data are available that would enable annual emission estimates to be made specifically for reference years 1987 and 1995.

A low confidence rating is assigned to the activity level estimate because it is based on expert judgment rather than a published reference. A low confidence rating is also assigned to the emission factor, because it was developed from stack tests conducted at just one U.S. drum and barrel furnace and thus may not represent average emissions from current operations in the United States.

7.8. SOLID WASTE FROM PRIMARY/SECONDARY IRON/STEEL MILLS/FOUNDRIES

Literature on the Identification of Relevant Industrial Sources of Dioxins and Furans in Europe (Quab, 1997), Table 17, contains summary data on the typical annual quantities

and ranges of TEQ (Norwegian-TEQ [NTEQ] and I-TEQ) from various solid residuals from the metallurgical industries in Europe. No support information accompanies the tabular data. Specific congeners are not discussed. However, the summary data for annual TEQ generation in grams are as follows:

Grey Iron Foundries: baghouse dust and scrubber sludge	0.817 NTEQ
Steel Mill Coke Oven Door Leakage Dust	0.31 NTEQ
Steel Mill Coke Oven Door Leakage Dust	0.04 I-TEQ
Pig Iron Tapping Slag	0.041 NTEQ
Basic Oxygen Furnace Scrubber Sludge	1.53 NTEQ (range of 0.30 - 7.81)
Electric Furnace Baghouse Dust	3.1 I-TEQ (range of 0.4 - 2.4)
Electric Furnace Slag or Baghouse Dust	19.2 NTEQ

Table 7-1. CDD/CDF Emission Factors for Secondary Aluminum Smelters

Congener/Congener Group	Mean Facility Emission Factor (ng/kg scrap feed) (Ref. 1)	Mean Facility Emission Factor (ng/kg scrap feed) (Ref. 2)	Mean Facility Emission Factor (ng/kg scrap feed) (Ref. 3)	Mean Facility Emission Factor (ng/kg scrap feed) (Ref. 4)	Mean Facility Emission Factor (ng/kg scrap feed) (Ref. 5)	Mean Facility Emission factor (ng/kg scrap feed) (Ref. 5)
2,3,7,8-TCDD	ND (0.01)	0.13	0.51	2.17	1.97	0.845
1,2,3,7,8-PeCDD	0.02	0.39	1.19	3.84	7.10	3.64
1,2,3,4,7,8-HxCDD	0.05	0.24	1.35	2.88	4.26	2.82
1,2,3,6,7,8-HxCDD	0.13	0.86	1.52	5.39	5.30	4.12
1,2,3,7,8,9-HxCDD	0.15	1.26	2.51	7.22	5.30	2.02
1,2,3,4,6,7,8-HpCDD	0.51	7.67	2.60	18.01	28.9	19.3
OCDD	0.42	14.97	1.01	NR	33.2	24.3
2,3,7,8-TCDF	0.44	0.74	14.20	47.12	23.2	4.84
1,2,3,7,8-PeCDF	0.06	1.51	10.47	20.01	33.8	1.18
2,3,4,7,8-PeCDF	0.17	2.44	11.06	29.60	48.0	23.3
1,2,3,4,7,8-HxCDF	0.32	2.44	21.84	52.32	46.1	17.6
1,2,3,6,7,8-HxCDF	0.11	2.69	7.10	16.31	46.1	16.9
1,2,3,7,8,9-HxCDF	0.02	1.02	0.47	1.20	22.0	1.35
2,3,4,6,7,8-HxCDF	0.30	3.82	7.09	22.96	39.0	16.0
1,2,3,4,6,7,8-HpCDF	0.07	11.39	14.61	35.29	122	42.6
1,2,3,4,7,8,9-HpCDF	0.03	5.50	1.21	5.17	27.1	6.20
OCDF	0.30	30.40	3.15	18.77	60.5	29.5
*Total I-TEQ_{DF}	0.26	3.22	12.95	36.03	52.21	21.67
*Total TEQ_{DF}-WHO_{98}	0.27	3.37	13.55	37.94	55.68	23.44
Total TCDD	NR	3.30	46.03	NR	47.8	0.845
Total PeCDD	NR	4.91	28.07	NR	64.0	3.64
Total HxCDD	NR	11.45	35.51	NR	78.0	8.95
Total HpCDD	NR	14.71	6.01	NR	58.5	19.3
Total OCDD	0.42	14.97	1.01	NR	33.2	24.3
Total TCDF	NR	29.67	161.80	NR	620	4.84
Total PeCDF	NR	28.73	222.75	NR	585	35.1
Total HxCDF	NR	32.23	115.32	NR	515	52.0
Total HpCDF	NR	39.44	39.94	NR	247	48.8
Total OCDF	0.30	30.40	3.15	18.77	60.5	29.5
Total CDD/CDF	NR	209.81	659.60	NR	2,309	227

* TEQ calculations assume not-detected values are zero.
NR = Not reported.
ND = Not detected (value in parenthesis is the emission at the detection limit).
Sources: Ref. 1: Advanced Technology Systems, Inc. (1995)
Ref. 2: U.S. EPA (1995h)
Ref. 3: Galson Corporation (1995)
Ref. 4: Envisage Environmental, Inc. (1995)
Ref. 5: CARB (1992a, 1992b), as reported in U.S. EPA (1997b)

Table 7-2. CDD/CDF Emission Factors for Secondary Copper Smelters

Congener/Congener Group	Mean EPA Tier 4 Emission Factor[a,b] (ng/kg scrap feed)	Franklin Smelting Facility Mean Emission Factor[d] (ng/kg scrap feed)	Chemetco Smelting Facility Mean Emission Factor[e] (ng/kg scrap feed)
2,3,7,8-TCDD	127	227	ND (0.05)
1,2,3,7,8-PeCDD	NR	846	0.21
1,2,3,4,7,8-HxCDD	NR	1,476	0.39
1,2,3,6,7,8-HxCDD	NR	1,746	0.70
1,2,3,7,8,9-HxCDD	NR	2,132	1.26
1,2,3,4,6,7,8-HpCDD	NR	17,065	8.95
OCDD	1,350	55,668	22.45
2,3,7,8-TCDF	2,720	4,457	2.11
1,2,3,7,8-PeCDF	NR	9,455	1.47
2,3,4,7,8-PeCDF	NR	5,773	2.63
1,2,3,4,7,8-HxCDF	NR	70,742	7.30
1,2,3,6,7,8-HxCDF	NR	20,524	2.15
1,2,3,7,8,9-HxCDF	NR	5,362	4.06
2,3,4,6,7,8-HxCDF	NR	12,082	0.27
1,2,3,4,6,7,8-HpCDF	NR	37,251	11.48
1,2,3,4,7,8,9-HpCDF	NR	7,570	2.74
OCDF	2,520	82,192	21.61
*Total I-TEQ_{DF}	779[c]	16,618	3.60
*Total TEQ_{DF}-WHO_{98}	810[c]	16,917	3.66
Total TCDD	736	14,503	3.05
Total PeCDD	970	30,248	5.19
Total HxCDD	1,260	55,765	9.62
Total HpCDD	2,080	38,994	16.71
Total OCDD	1,350	55,668	22.45
Total TCDF	13,720	108,546	46.42
Total PeCDF	8,640	71,136	27.99
Total HxCDF	4,240	164,834	27.96
Total HpCDF	3,420	66,253	23.38
Total OCDF	2,520	82,192	21.61
Total CDD/CDF	38,890	688,139	204.33

* TEQ calculations assume not-detected values are zero.
NR = Not reported.
ND = Not detected (value in parenthesis is the emission at the detection limit).

a No nondetected values were reported for 2,3,7,8-TCDD, 2,3,7,8-TCDF, or any congener group in the three test runs.
b Source: U.S. EPA (1987a).
c Estimated using the measured data for 2,3,7,8-TCDD, 2,3,7,8-TCDF, OCDD, and OCDF and congener group emissions (i.e., for the penta-, hexa-, and hepta-CDDs and CDFs, it was assumed that the measured emission factor within a congener group was the sum of equal emission factors for all congeners in that group, including non-2,3,7,8-substituted congeners).
d Source: AGES (1992).
e Source: Sverdrup Corp. (1991).

Table 7-3. CDD/CDF Emission Factors for Secondary Lead Smelters

Congener/Congener Group	Blast Furnace (Ref. A) (ng/kg lead produced)		Blast/reverb (Ref. B) (ng/kg lead produced)		Rotary kiln (Ref. C) (ng/kg lead produced)	
	Before Scrubber	After Scrubber	Before Scrubber	After Scrubber	Before Scrubber	After Scrubber
2,3,7,8-TCDD	2.11	0.25	0.00	0.00	0.10	0.24
1,2,3,7,8-PeCDD	0.99	0.03	0.00	0.00	0.01	0.00
1,2,3,4,7,8-HxCDD	0.43	0.00	0.00	0.00	0.00	0.00
1,2,3,6,7,8-HxCDD	0.99	0.03	0.00	0.00	0.00	0.00
1,2,3,7,8,9-HxCDD	1.55	0.03	0.00	0.00	0.00	0.00
1,2,3,4,6,7,8-HpCDD	2.06	0.08	0.10	0.06	0.00	0.22
OCDD	1.40	0.39	0.57	0.55	0.24	2.41
2,3,7,8-TCDF	8.73	0.93	1.46	0.49	0.40	1.20
1,2,3,7,8-PeCDF	3.88	0.43	0.24	0.02	0.14	0.40
2,3,4,7,8-PeCDF	6.65	0.36	0.31	0.00	0.14	0.46
1,2,3,4,7,8-HxCDF	5.83	0.37	0.63	0.00	0.11	0.27
1,2,3,6,7,8-HxCDF	1.67	0.11	0.19	0.00	0.02	0.10
1,2,3,7,8,9-HxCDF	0.11	0.00	0.00	0.00	0.04	0.13
2,3,4,6,7,8-HxCDF	2.06	0.11	0.15	0.00	0.00	0.00
1,2,3,4,6,7,8-HpCDF	2.34	0.19	0.48	0.00	0.03	0.13
1,2,3,4,7,8,9-HpCDF	0.63	0.06	0.00	0.00	0.00	0.00
OCDF	1.39	0.18	0.29	0.00	0.00	0.00
Total 2,3,7,8-CDD	9.52	0.82	0.68	0.61	0.35	2.87
Total 2,3,7,8-CDF	33.28	2.74	3.75	0.51	0.88	2.68
Total I-TEQ_{DF} (nondetects = 0)	8.31	0.63	0.41	0.05	0.24	0.66
Total TEQ_{DF}-WHO_{98} (nondetects = 0)	8.81	0.64	0.42	0.05	0.24	0.66
Total TCDD	74.33	7.39	0.97	1.58	3.40	7.90
Total PeCDD	39.29	1.73	0.15	0.16	0.29	0.27
Total HxCDD	20.05	0.81	0.14	0.02	0.10	0.23
Total HpCDD	4.20	9.72	0.09	0.09	0.01	0.29
Total OCDD	1.39	0.18	0.57	0.55	0.24	2.41
Total TCDF	145.71	17.34	8.21	4.71	10.82	28.57
Total PeCDF	69.59	3.45	3.07	0.36	1.69	5.04
Total HxCDF	19.73	1.02	1.14	0.19	0.15	0.73
Total HpCDF	4.74	0.11	0.72	0.01	0.05	0.14
Total OCDF	1.39	0.18	0.29	0.00	0.00	0.00
Total CDD/CDF (nondetects = 0)	380.43	41.92	15.36	7.66	16.76	45.57
Total CDD/CDF (nondetects = ½ DL)	380.44	42.27	15.36	7.74	16.80	45.62

Note: Except where noted, emission factors were calculated assuming nondetected values are zero.

Sources: Ref. A: U.S. EPA (1995e)
Ref. B: U.S. EPA (1992e)
Ref. C: U.S. EPA (1995d)

Table 7-4. CDD/CDF Emission Factors for Sinter Plants

Congener/Congener Group	Wet Scrubber APCD (ng/kg sinter)		Baghouse APCD (ng/kg sinter)	
	ND = 0	ND = 1/2DL	ND = 0	ND = 1/2DL
2,3,7,8-TCDD	0.049	0.049	0.406	0.406
1,2,3,7,8-PeCDD	0.138	0.138	0.937	0.937
1,2,3,4,7,8-HxCDD	0.030	0.030	0.135	0.135
1,2,3,6,7,8-HxCDD	0.612	0.612	1.469	1.469
1,2,3,7,8,9-HxCDD	0.288	0.288	0.609	0.609
1,2,3,4,6,7,8-HpCDD	0.696	0.696	0.698	0.698
OCDD	0.496	0.496	0.695	0.695
2,3,7,8-TCDF	0.602	0.602	10.232	10.232
1,2,3,7,8-PeCDF	0.343	0.343	3.518	3.518
2,3,4,7,8-PeCDF	0.349	0.349	3.228	3.228
1,2,3,4,7,8-HxCDF	0.421	0.421	1.382	1.382
1,2,3,6,7,8-HxCDF	0.164	0.164	0.495	0.495
1,2,3,7,8,9-HxCDF	0.011	0.014	0.029	0.057
2,3,4,6,7,8-HxCDF	0.142	0.142	0.285	0.285
1,2,3,4,6,7,8-HpCDF	0.247	0.247	0.316	0.316
1,2,3,4,7,8,9-HpCDF	0.036	0.036	0.000	0.115
OCDF	0.103	0.103	0.050	0.192
Total 2,3,7,8-CDD	2.309	2.309	4.949	4.949
Total 2,3,7,8-CDF	2.418	2.421	19.535	19.820
Total I-TEQ_{DF}	0.55	0.55	4.14	4.14
Total TEQ_{DF}-WHO_{98}	0.62	0.62	4.61	4.61
Total TCDD	NR	NR	NR	NR
Total PeCDD	NR	NR	NR	NR
Total HxCDD	NR	NR	NR	NR
Total HpCDD	NR	NR	NR	NR
Total OCDD	0.496	0.496	0.695	0.695
Total TCDF	NR	NR	NR	NR
Total PeCDF	NR	NR	NR	NR
Total HxCDF	NR	NR	NR	NR
Total HpCDF	NR	NR	NR	NR
Total OCDF	0.103	0.103	0.050	0.192
Total CDD/CDF[a]	4.73	4.73	24.48	24.77

a The listed values for total CDD/CDF include only the 17 toxic congeners.

Source: Calcagni et al. (1998)

Table 7-5. Operating Parameters for U.S. Iron Ore Sinter Plants

Company	Location	1998 Capacity (1,000 kkg/yr)	Current APCD
A.K. Steel Corp.	Middleton, OH	907	WS
A.K. Steel Corp.*	Ashland, KY	816*	NA
Bethlehem Steel	Burns Harbor, IN	2,676	WS
Bethlehem Steel	Sparrows Point, MD	3,856	WS
Geneva Steel	Provo, UT	816	BH
Inland Steel	East Chicago, IN	1,089	BH
LTV Steel	East Chicago, IN	1,270	WS
U.S. Steel	Gary, IN	3,992	BH
Weirton Steel*	Weirton, WV	1,179*	NA
Wheeling-Pittsburgh Steel	East Steubenville, WV	519	WS
WCI Steel	Warren, OH	477	BH
TOTALS		17,597**	

NA = Not available.
WS = Wet scrubber.
BH = Baghouse.

* Not in operation during 1998 (Calcagni et al., 1998)
** Total 1998 capacity was 15,600 thousand metric tons (i.e., excluding the Ashland, KY, and Weirton, WV, facilities).

Sources: Metal Producing (1991, 1996); Calcagni et al. (1998)

Table 7-6. CDD/CDF Emission Factors for a Ferrous Foundry

Congener/Congener Group	Mean Facility Emission Factor (ng/kg scrap feed) (CARB, 1993a)
2,3,7,8-TCDD	0.033
1,2,3,7,8-PeCDD	0.086
1,2,3,4,7,8-HxCDD	NR
1,2,3,6,7,8-HxCDD	0.051
1,2,3,7,8,9-HxCDD	NR
1,2,3,4,6,7,8-HpCDD	0.093
OCDD	NR
2,3,7,8-TCDF	0.520
1,2,3,7,8-PeCDF	0.305
2,3,4,7,8-PeCDF	0.350
1,2,3,4,7,8-HxCDF	0.190
1,2,3,6,7,8-HxCDF	0.170
1,2,3,7,8,9-HxCDF	NR
2,3,4,6,7,8-HxCDF	0.101
1,2,3,4,6,7,8-HpCDF	0.193
1,2,3,4,7,8,9-HpCDF	NR
OCDF	0.059
Total 2,3,7,8-CDD	0.262
Total 2,3,7,8-CDF	1.888
Total I-TEQ_{DF} (for reported congeners)	0.372
Total TEQ_{DF}-WHO_{98}	0.415
Total TCDD	3.96
Total PeCDD	1.76
Total HxCDD	0.55
Total HpCDD	0.19
Total OCDD	NR
Total TCDF	25.8
Total PeCDF	850
Total HxCDF	1.74
Total HpCDF	0.24
Total OCDF	0.06
Total CDD/CDF (not including OCDD)	884.3

NR = Not reported.

Source: CARB (1993a), as reported in U.S. EPA, 1997b

Table 7-7. CDD/CDF Emission Factors for a Scrap Wire Incinerator

Congener/Congener Group	Mean Facility Emission Factor [a] (ng/kg scrap feed)
2,3,7,8-TCDD	0.374
1,2,3,7,8-PeCDD	NR
1,2,3,4,7,8-HxCDD	NR
1,2,3,6,7,8-HxCDD	NR
1,2,3,7,8,9-HxCDD	NR
1,2,3,4,6,7,8-HpCDD	NR
OCDD	1,000
2,3,7,8-TCDF	2.67
1,2,3,7,8-PeCDF	NR
2,3,4,7,8-PeCDF	NR
1,2,3,4,7,8-HxCDF	NR
1,2,3,6,7,8-HxCDF	NR
1,2,3,7,8,9-HxCDF	NR
2,3,4,6,7,8-HxCDF	NR
1,2,3,4,6,7,8-HpCDF	NR
1,2,3,4,7,8,9-HpCDF	NR
OCDF	807
Total 2,3,7,8-CDD	NR
Total 2,3,7,8-CDF	NR
Total I-TEQ_{DF}	16.9[b]
Total TEQ_{DF}-WHO_{98}	15.8
Total TCDD	4.42
Total PeCDD	13.7
Total HxCDD	71.1
Total HpCDD	347
Total OCDD	1,000
Total TCDF	107
Total PeCDF	97.4
Total HxCDF	203
Total HpCDF	623
Total OCDF	807
Total CDD/CDF	3,273

NR = Not reported.

a No nondetected values were reported for 2,3,7,8-TCDD, 2,3,7,8-TCDF, or any congener group in the three test runs.

b Estimated based on the measured data for 2,3,7,8-TCDD, 2,3,7,8-TCDF, OCDD, and OCDF and congener group emissions (i.e., for the penta-, hexa-, and hepta-CDDs and CDFs, it was assumed that the measured emission factor within a congener group was the sum of equal emission factors for all congeners in that group, including non-2,3,7,8-substituted congeners).

Source: U.S. EPA (1987a)

Table 7-8. Geometric Mean CDD/CDF Concentrations in Fly Ash and Ash/Soil at Metal Recovery Sites

Congener/Congener Group	Metal Recovery Facilities				Open Burn Sites	
	Fly ash (2 sites)		Ash/Soil (3 sites)		Ash/Soil (3 sites)	
	Geom. mean (μg/kg)	Relative % of Total CDD/CDF	Geom. mean (μg/kg)	Relative % of Total CDD/CDF	Geom. mean (μg/kg)	Relative % of Total CDD/CDF
2,3,7,8-TCDD	*		*		*	
1,2,3,7,8-PeCDD	400	0.1%	0.24	0.3%	0.24	0.5%
1,2,3,4,7,8-HxCDD	1,200	0.2%	0.25	0.3%	0.13	0.3%
1,2,3,6,7,8-HxCDD	2,300	0.5%	0.49	0.6%	0.33	0.7%
1,2,3,7,8,9-HxCDD	1,700	0.3%	1.3	1.5%	0.39	0.8%
1,2,3,4,6,7,8-HpCDD	12,000	2.4%	2.6	3.1%	1.2	2.5%
OCDD	18,000	3.5%	7.2	8.5%	3.4	7.0%
2,3,7,8-TCDF	15,000	2.9%	6.4	7.5%	1.7	3.5%
1,2,3,7,8-PeCDF	35,000	6.9%	2.9	3.4%	0.58	1.2%
2,3,4,7,8-PeCDF	10,000	2.0%	1.4	1.6%	0.66	1.4%
1,2,3,4,7,8-HxCDF	46,000	9.0%	5.9	6.9%	2.7	5.6%
1,2,3,6,7,8-HxCDF	12,000	2.4%	1.8	2.1%	0.76	1.6%
1,2,3,7,8,9-HxCDF	5,000	1.0%	0.92	1.1%	0.66	1.4%
2,3,4,6,7,8-HxCDF	5,000	1.0%	1.6	1.9%	0.49	1.0%
1,2,3,4,6,7,8-HpCDF	71,000	13.9%	12	14.1%	4.3	8.9%
1,2,3,4,7,8,9-HpCDF	25,000	4.9%	3	3.5%	0.71	1.5%
OCDF	100,000	19.6%	14	16.5%	6.6	13.6%
Total TCDD	*	*	*	*	*	*
Total PeCDD	2,000	0.4%	1.4	1.6%	2.8	5.8%
Total HxCDD	4,000	0.8%	2.7	3.2%	0.98	2.0%
Total HpCDD	24,000	4.7%	4.1	4.8%	2.0	4.1%
Total OCDD	18,000	3.5%	7.2	8.5%	3.4	7.0%
Total TCDF	23,000	4.5%	14	16.5%	5.6	11.5%
Total PeCDF	110,000	21.6%	12	14.1%	7.0	14.4%
Total HxCDF	88,000	17.3%	12	14.1%	7.6	15.7%
Total HpCDF	110,000	21.6%	17	20.0%	7.4	15.3%
Total OCDF	100,000	19.6%	14	16.5%	6.6	13.6%
Total I-TEQ_{DF}	19,000		2.9		1.3	
Total CDD/CDF	510,000		85		48.5	

* Analytical method used had low sensitivity for TCDDs; results were not reported.

Source: Harnly et al. (1995)

Table 7-9. CDD/CDF Emission Factors for a Drum and Barrel Reclamation Furnace

Congener/Congener Group	Mean Facility Emission Factor[a] (ng/drum)
2,3,7,8-TCDD	2.09
1,2,3,7,8-PeCDD	NR
1,2,3,4,7,8-HxCDD	NR
1,2,3,6,7,8-HxCDD	NR
1,2,3,7,8,9-HxCDD	NR
1,2,3,4,6,7,8-HpCDD	NR
OCDD	37.5
2,3,7,8-TCDF	36.5
1,2,3,7,8-PeCDF	NR
2,3,4,7,8-PeCDF	NR
1,2,3,4,7,8-HxCDF	NR
1,2,3,6,7,8-HxCDF	NR
1,2,3,7,8,9-HxCDF	NR
2,3,4,6,7,8-HxCDF	NR
1,2,3,4,6,7,8-HpCDF	NR
1,2,3,4,7,8,9-HpCDF	NR
OCDF	22.4
Total 2,3,7,8-CDD	NR
Total 2,3,7,8-CDF	NR
Total I-TEQ_{DF}	16.5[b]
Total TEQ_{DF}-WHO_{98}	17.5
Total TCDD	50.29
Total PeCDD	29.2
Total HxCDD	32.2
Total HpCDD	53.4
Total OCDD	37.5
Total TCDF	623
Total PeCDF	253
Total HxCDF	122
Total HpCDF	82.2
Total OCDF	22.4
Total CDD/CDF	1,303

NR = Not reported.

a No nondetected values were reported for 2,3,7,8-TCDD, 2,3,7,8-TCDF, or any congener group in the three test runs.

b Estimated based on the measured data for 2,3,7,8-TCDD, 2,3,7,8-TCDF, OCDD, and OCDF and congener group emissions (i.e., for the penta-, hexa-, and hepta-CDDs and CDFs, it was assumed that the measured emission factor within a congener group was the sum of equal emission factors for all congeners in that group, including non-2,3,7,8-substituted congeners).

Source: U.S. EPA (1987a)

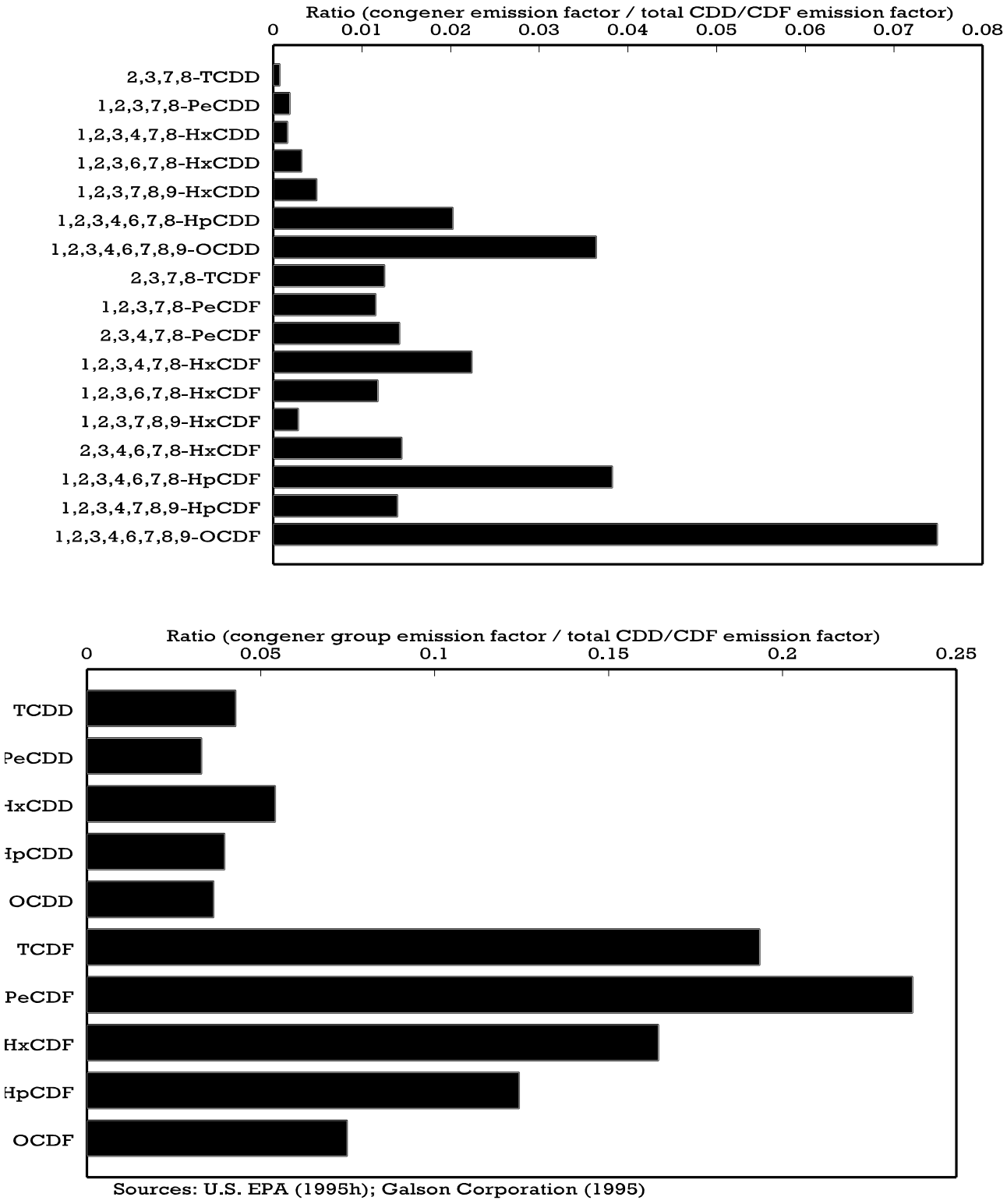


Figure 7-1. Congener and Congener Group Profiles for Air Emissions from Secondary Aluminum Smelters

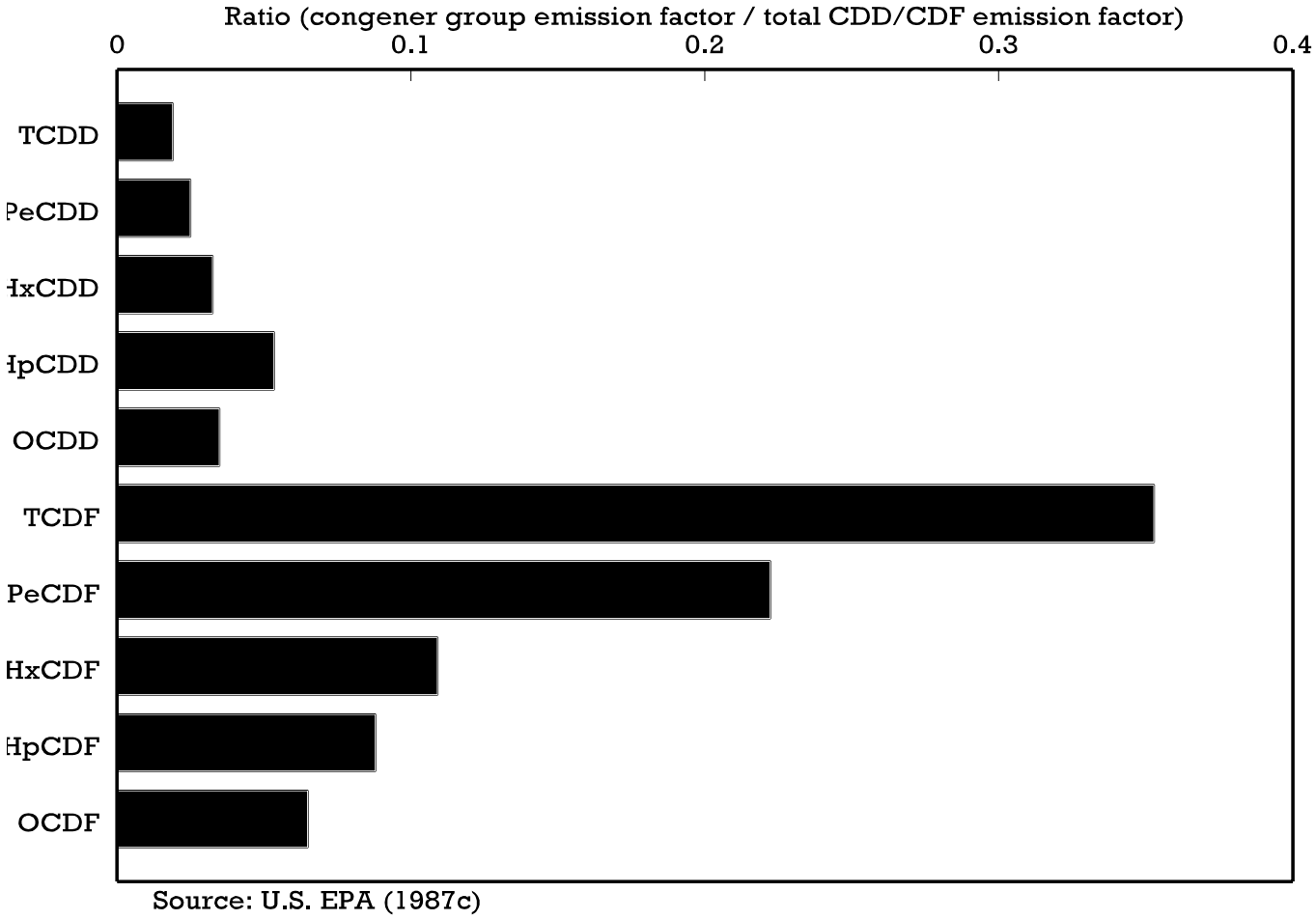


Figure 7-2a. Congener Group Profile for Air Emissions from a Secondary Copper Smelter

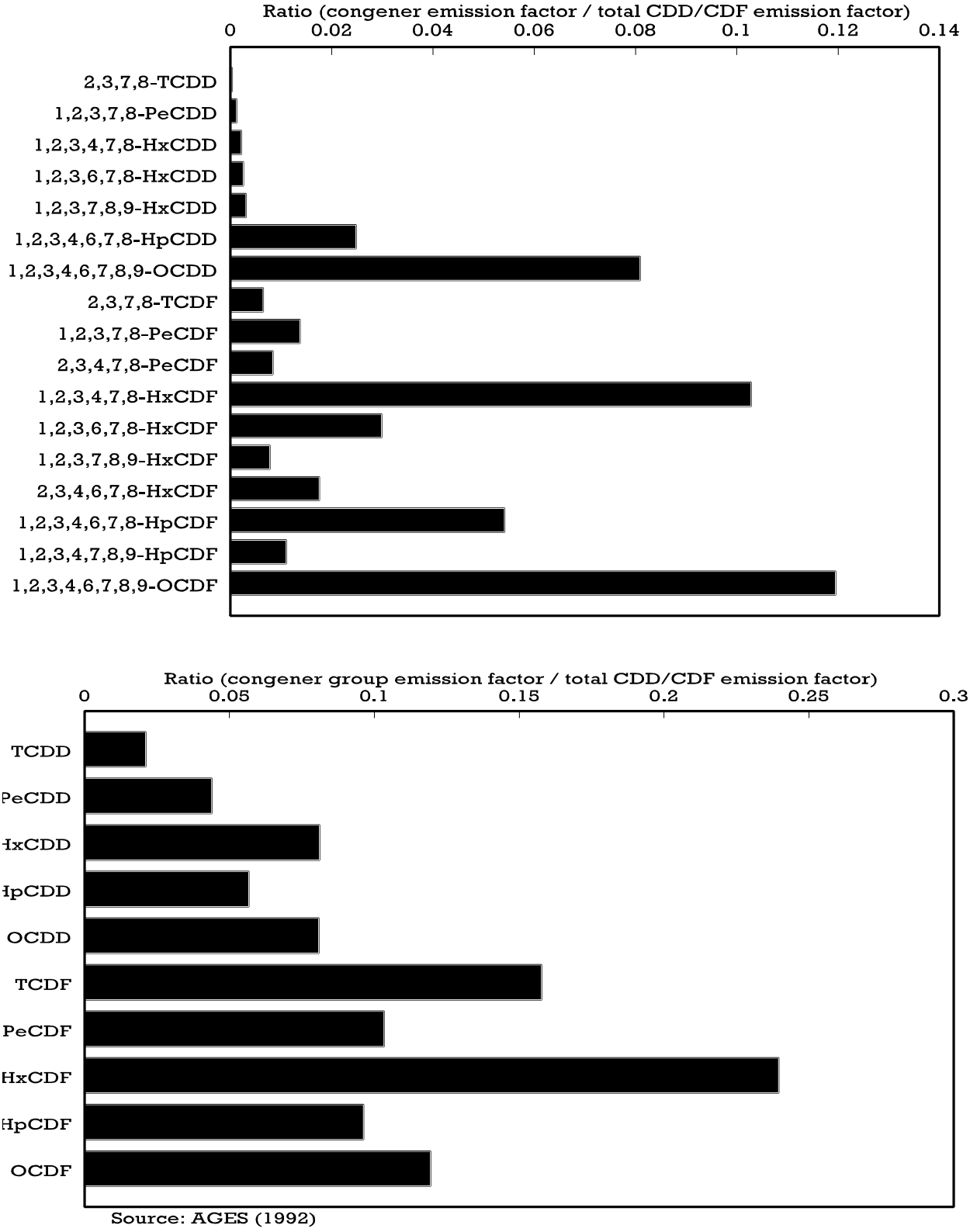


Figure 7-2b. Congener and Congener Group Profiles for a Closed Secondary Copper Smelter

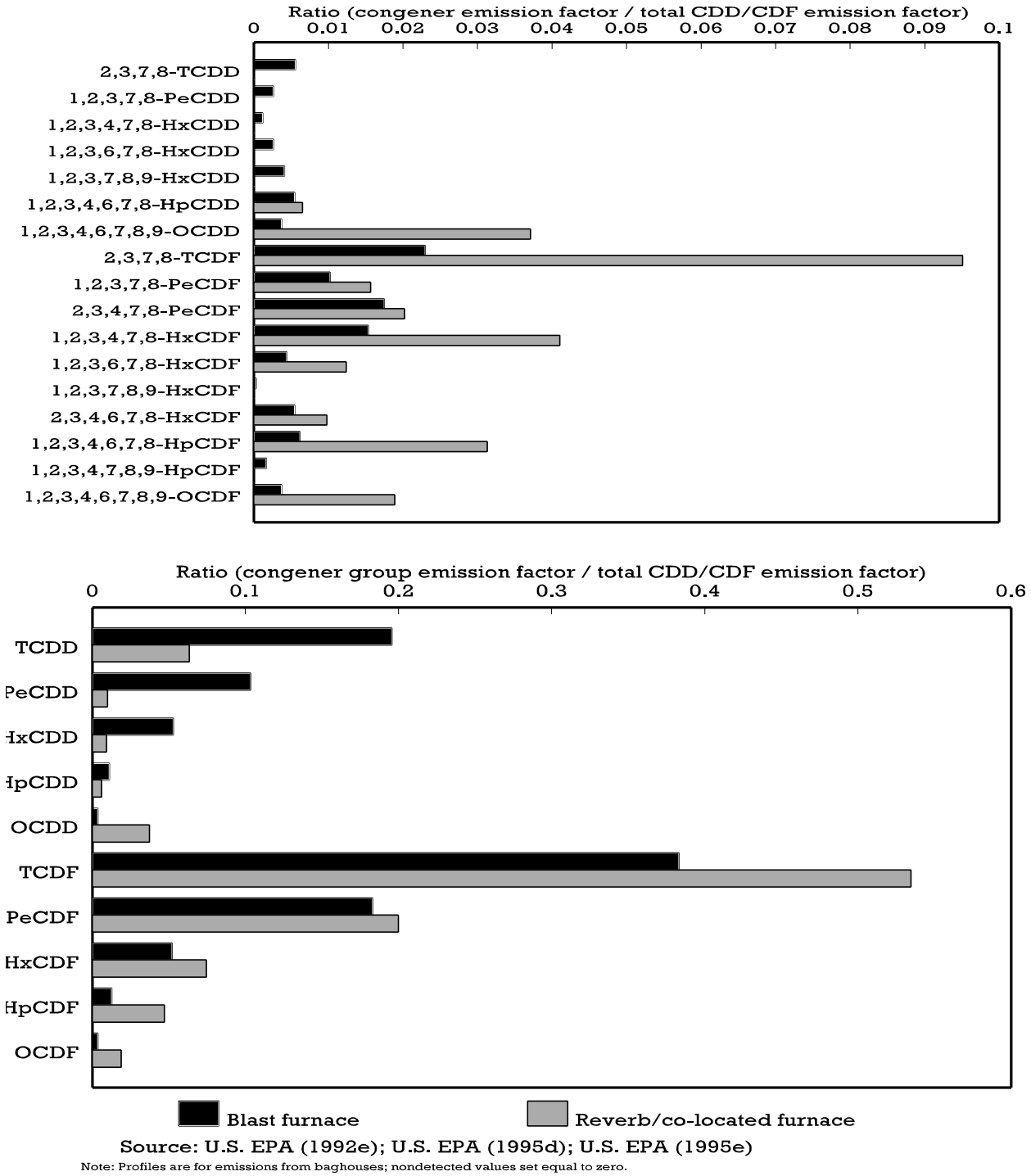


Figure 7-3. Congener and Congener Group Profiles for Air Emissions from Secondary Lead Smelters

Figure 7-4. Congener Profiles for Air Emissions from U.S. Iron Ore Sinter Plants

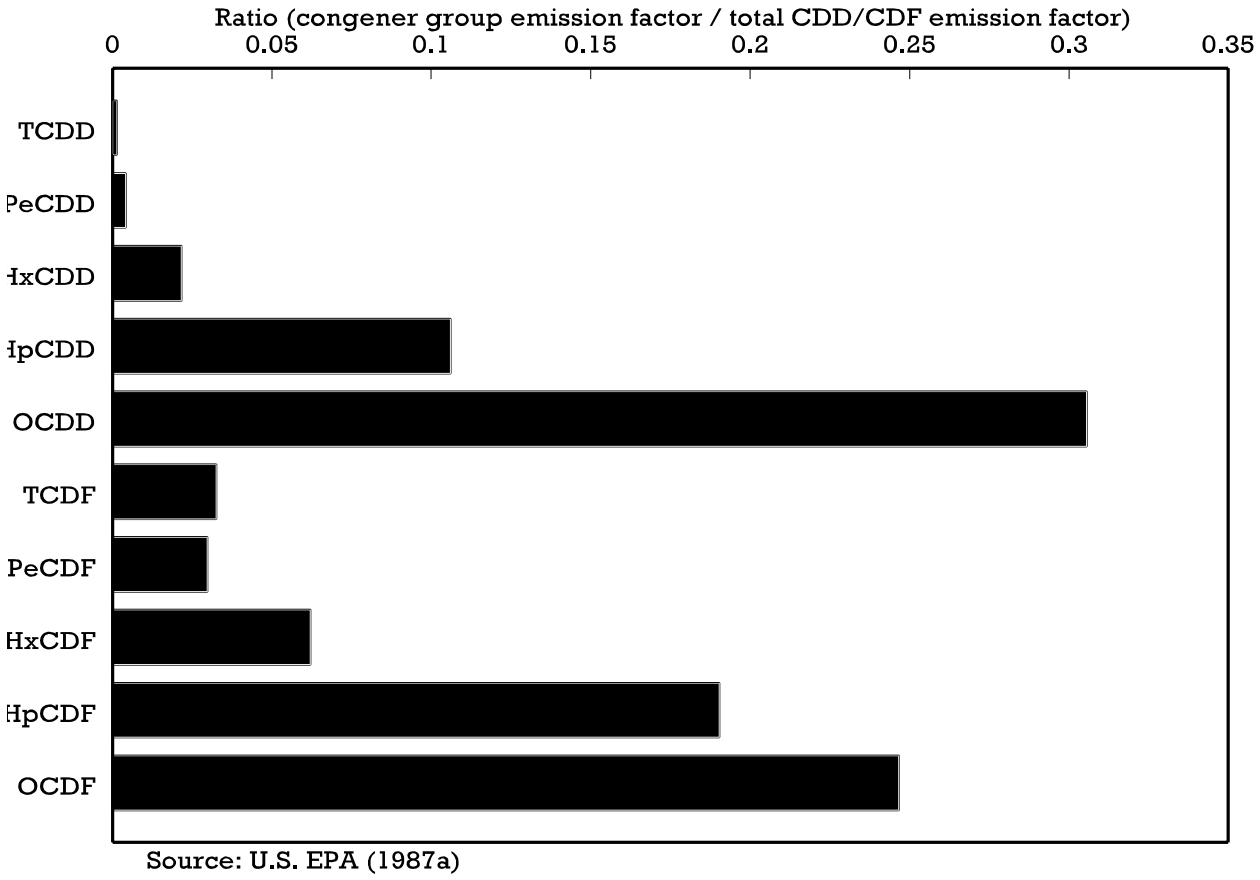
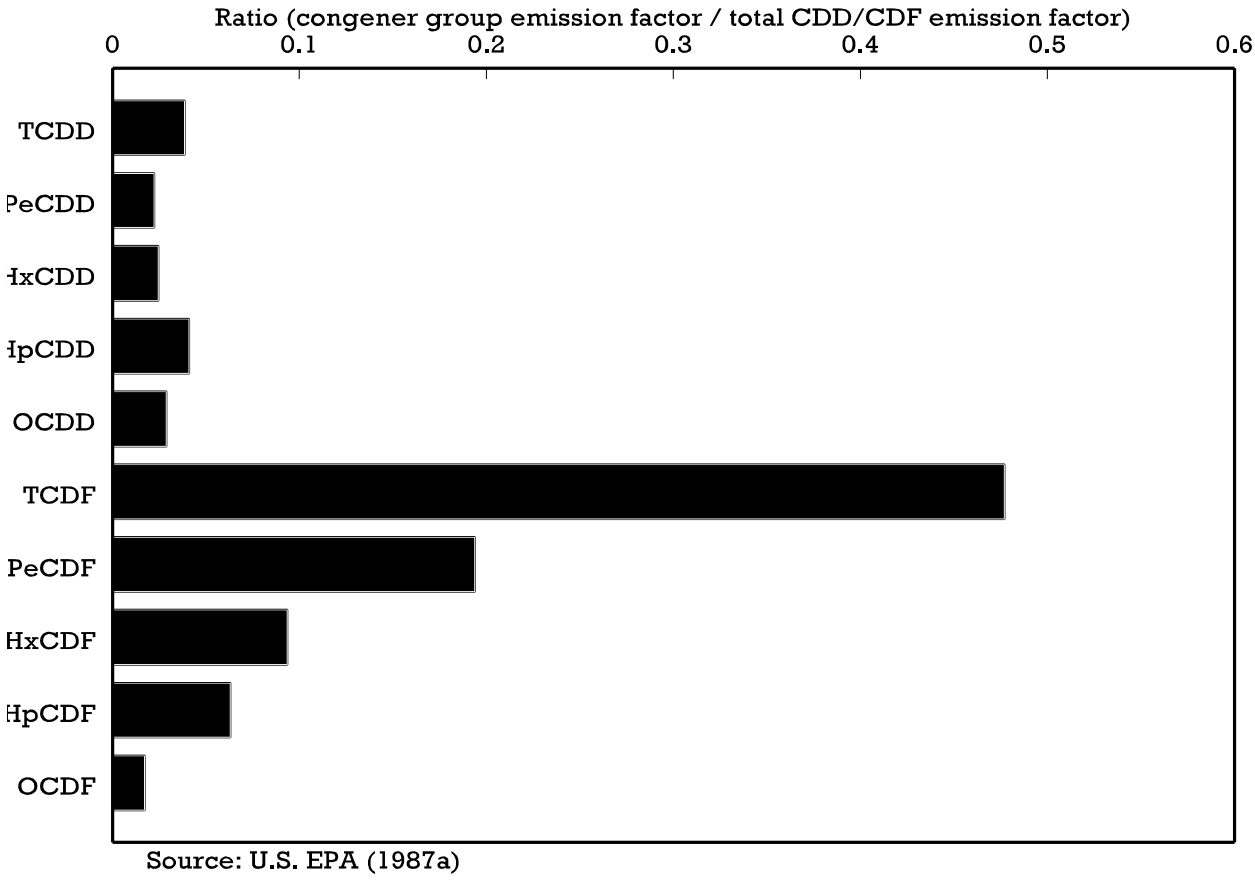


Figure 7-5. Congener Group Profile for Air Emissions from a Scrap Wire Incinerator



Source: U.S. EPA (1987a)

Figure 7-6. Congener Group Profile for Air Emissions from a Drum Incinerator

8. CHEMICAL MANUFACTURING AND PROCESSING SOURCES

8.1. BLEACHED CHEMICAL WOOD PULP AND PAPER MILLS

In March 1988, EPA and the U.S. pulp and paper industry jointly released the results from a screening study that provided the first comprehensive data on formation and discharge of CDDs and CDFs from pulp and paper mills (U.S. EPA, 1988d). This early screening study of five bleached kraft mills ("Five Mill Study") confirmed that the pulp bleaching process was primarily responsible for the formation of the CDDs and CDFs. The study results showed that 2,3,7,8-TCDD was present in seven of nine bleached pulps, five of five wastewater treatment sludges, and three of five treated wastewater effluents. The study results also indicated that 2,3,7,8-TCDD and 2,3,7,8-TCDF were the principal CDDs and CDFs formed.

To provide EPA with more complete data on the release of these compounds by the U.S. industry, EPA and the U.S. pulp and paper industry jointly conducted a survey during 1988 of 104 pulp and paper mills in the United States to measure levels of 2,3,7,8-TCDD and 2,3,7,8-TCDF in effluent, sludge, and pulp. This study, commonly called the 104 Mill Study, was managed by the National Council of the Paper Industry for Air and Stream Improvement, Inc. (NCASI), with oversight by EPA, and included all U.S. mills where chemically produced wood pulps were bleached with chlorine or chlorine derivatives. The final study report was released in July 1990 (U.S. EPA, 1990a).

An initial phase of the 104 Mill Study involved the analysis of bleached pulp (10 samples), wastewater sludge (9 samples), and wastewater effluent (9 samples) from eight kraft mills and one sulfite mill for all 2,3,7,8-substituted CDDs and CDFs. These analyses were conducted to test the conclusion drawn in the Five Mill Study that 2,3,7,8-TCDD and 2,3,7,8-TCDF were the principal CDDs and CDFs found in pulp, wastewater sludge, and wastewater effluent on a toxic equivalents basis. Although at the time of this study there were no reference analytical methods for many of the 2,3,7,8-substituted CDDs/CDFs, the data obtained were considered valid by EPA for the purposes intended because of the identification and quantification criteria used, duplicate sample results, and limited matrix spike experiments. Table 8-1 presents a summary of the results obtained in terms of the median concentrations and the range of concentrations observed for each matrix (i.e., pulp, sludge, and effluent). Figures 8-1 through 8-3 present congener profiles

for each matrix (normalized to total CDD/CDF and to total I-TEQ_{DF}) using the median reported concentrations. After examination of the raw, mill-specific data, EPA (1990a) concluded that the congener profiles were fairly consistent across matrices within mills and that 2,3,7,8-TCDD and 2,3,7,8-TCDF account for the majority of TEQ in the samples. Using the median concentrations and treating nondetected values as either zero or one-half the detection limit, EPA concluded that 2,3,7,8-TCDF accounted for 95.8 to 99.0 percent of the total I-TEQ_{DF} in pulp (95.4 to 99.5 percent of TEQ_{DF}-WHO_{98}), 94.1 to 95.8 percent of the I-TEQ_{DF} in sludge (94.1 to 96.5 percent of TEQ_{DF}-WHO_{98}), and 81.1 to 91.7 of the I-TEQ_{DF} in effluent (81.7 to 96.4 percent of TEQ_{DF}-WHO_{98}).

NCASI reported on a similar full-congener analysis study for samples collected from eight mills during the mid-1990s (Gillespie, 1997). The results of these analyses are presented in Table 8-2. The frequencies of detection of 2,3,7,8-TCDD and 2,3,7,8-TCDF were significantly lower than in the 1988 study. Therefore, deriving meaningful summary statistics concerning the relative importance of 2,3,7,8-TCDD and 2,3,7,8-TCDF to the total TEQ is difficult. With all nondetected values assumed to be zero, 2,3,7,8-TCDD and 2,3,7,8-TCDF account for 91 percent of the total effluent I-TEQ_{DF} (97 percent of TEQ_{DF}-WHO_{98}), 46 percent of the total sludge I-TEQ_{DF} (53 percent of TEQ_{DF}-WHO_{98}), and 87 percent of the total pulp I-TEQ_{DF} (87 percent of TEQ_{DF}-WHO_{98}). Because of the high frequency of nondetects, when all nondetected values are one-half the detection limits, 2,3,7,8-TCDD and 2,3,7,8-TCDF account for only 13 percent of the total effluent I-TEQ_{DF}, 13 percent of the total sludge I-TEQ_{DF}, and 28 percent of the total pulp I-TEQ_{DF}.

In 1992, the pulp and paper industry conducted its own NCASI-coordinated survey of 2,3,7,8-TCDD and 2,3,7,8-TCDF emissions (NCASI, 1993). Ninety-four mills participated in the NCASI study, and NCASI assumed that the remaining 10 (of 104) operated at the same levels as measured in the 1988 104 Mill Study. All nondetected values were counted as half the detection limit. If detection limits were not reported, they were assumed to be 10 pg/L for effluent and 1 ng/kg ppt for sludge or bleached pulp. The data used in the report were provided by individual pulp and paper companies that had been requested by NCASI to generate the data using the same protocols used in the 104 Mill Study.

As part of its efforts to develop revised effluent guidelines and standards for the pulp, paper, and paperboard industry, EPA in 1993 published the development document

for the guidelines and standards being proposed for this industry (U.S. EPA, 1993d). The development document presents estimates of the 2,3,7,8-TCDD and 2,3,7,8-TCDF annual discharges in wastewater from the mills in this industry as of January 1, 1993. To estimate these discharges, EPA used the most recent information about each mill from four databases (104 Mill Study, EPA short-term monitoring studies at 13 mills, EPA long-term monitoring studies at 8 mills, and industry self-monitoring data submitted to EPA). The 104 Mill Study data were used for only those mills that did not report making any process changes subsequent to the 104 Mill Study and did not submit any more recent effluent monitoring data.

Gillespie (1994, 1995) reported the results of 1993 and 1994 updates, respectively, to the 1992 NCASI survey. As in the 1992 survey, companies were requested to follow the same protocols for generating data used in the 104 Mill Study. Gillespie (1994, 1995) reported that less than 10 percent of mills had 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations in effluent above the nominal detection limits of 10 pg/L and 100 pg/L, respectively. EPA obtained similar results in its short- and long-term sampling for 18 mills; 2,3,7,8-TCDD was detected at four mills, and 2,3,7,8-TCDF was detected at nine mills (U.S. EPA, 1993d). Gillespie (1994) reported that wastewater sludges at most mills (i.e., 90 percent) contained less than 31 ng/kg of 2,3,7,8-TCDD and less than 100 ng/kg of 2,3,7,8-TCDF. Gillespie (1995) also reported that 90 percent of the mills reported 2,3,7,8-TCDD and 2,3,7,8-TCDF concentrations in sludge of less than 17 ng/kg and 76 ng/kg, respectively, in 1994. U.S. EPA (1993d) reported similar results but found detectable levels of 2,3,7,8-TCDD and 2,3,7,8-TCDF in sludges from 64 percent and 85 percent of the facilities sampled, respectively. Gillespie (1994) reported that nearly 90 percent of the bleached pulps contained less than 2 ng/kg of 2,3,7,8-TCDD and less than 160 ng/kg of 2,3,7,8-TCDF. Gillespie (1995) reported that 90 percent of the bleached pulps contained 1.5 ng/ng or less of 2,3,7,8-TCDD and 5.9 ng/kg or less of 2,3,7,8-TCDF. The final levels in white paper products would correspond to levels in bleached pulp, so bleached paper products would also be expected to contain less than 2 ng/kg of 2,3,7,8-TCDD.

On April 15, 1998, EPA promulgated effluent limitations guidelines and standards for certain segments of the pulp, paper and paperboard industry (Federal Register, 1998c). The industry segments covered by this rulemaking (i.e., the bleached papergrade kraft and

soda subcategory and the papergrade sulfite subcategory) are those segments responsible for more than 90 percent of the bleached chemical pulp production in the United States. For this rule, EPA updated the estimates of baseline loadings made in 1993 for the proposed rule by using more recent data collected by EPA, NCASI (including the 1994 NCASI survey), and individual facilities (U.S. EPA, 1997f). These revised estimates are presented in the last column in Table 8-3. EPA projects that, after full compliance with these rules, annual TEQ discharges will be reduced to 5 grams in effluent and 7 grams in sludge.

Estimates of National Emissions in 1987 and 1995 - The U.S. annual discharges of 2,3,7,8-TCDD and 2,3,7,8-TCDF are summarized in Table 8-3 for each of the six surveys discussed above. The release estimates for 1995 from U.S. EPA (1997f) and for 1988 from U.S. EPA (1990a) are believed to best represent emissions in the reference years 1995 and 1987, respectively. During the period between EPA's 104 Mill Study and issuance of the development document (U.S. EPA, 1993d), the U.S. pulp and paper industry reduced releases of CDD/CDFs primarily by instituting numerous process changes to reduce the formation of CDD/CDFs during the production of chemically bleached wood pulp. Details on the process changes implemented are provided in U.S. EPA (1993d) and Gillespie (1995). Much of the reduction between 1988 and 1995 can be attributed to process changes for pollution prevention.

The confidence ratings for these release estimates were judged to be high because direct measurements were made at virtually all facilities, indicating a high level of confidence in both the production and emission factor estimates. The best estimates of annual emissions in 1995 (i.e., the 1995 estimates presented in Table 8-3) are 28 g TEQ/yr for effluent, 50 g TEQ/yr for sludge, and 40 g TEQ/yr for pulp (i.e., TEQs that will enter the environment in the form of paper products). The best estimates of annual emissions in 1987 (i.e., the 1988 estimates presented in Table 8-3) are 356 g TEQ/yr for effluent, 343 g TEQ/yr for sludge, and 505 g TEQ/yr for pulp.

In 1990, the majority of the wastewater sludge generated by these facilities was placed in landfills or in surface impoundments (75.5 percent), with the remainder incinerated (20.5 percent), applied to land directly or as compost (4.1 percent), or distributed as a commercial product (less than 1 percent) (U.S. EPA, 1993e). Data more recent than 1995 or earlier than 1988 are not available on disposition of wastewater

sludges. On the basis of these statistics, the best estimate of TEQ applied to land (i.e., not incinerated or landfilled) in 1995 is 2.0 g (i.e., 4.1 percent of 50 g). The estimate for 1987 is 14.1 g TEQ (i.e., 4.1 percent of 343 g).

8.2. MANUFACTURE OF CHLORINE, CHLORINE DERIVATIVES, AND METAL CHLORIDES

No testing of CDD/CDF emissions to air, land, or water from U.S. manufacturers of chlorine, chlorine derivatives, and metal chlorides has been reported on which to base estimates of national emissions. Sampling of graphite electrode sludges from European chlorine manufacturers indicates high levels of CDFs. Limited sampling of chlorine derivatives and metal chlorides in Europe indicates low-level contamination in some products.

8.2.1. Manufacture of Chlorine

Chlorine gas is produced by electrolysis of brine electrolytic cells. Until the late 1970s, the primary type of electrolytic process used in the chloralkali industry to produce chlorine consisted of mercury cells containing graphite electrodes. As shown in Table 8-4, high levels of CDFs have been found in several samples of graphite electrode sludge from facilities in Europe. The CDFs predominate in these sludges, and the 2,3,7,8-substituted congeners account for a large fraction of the respective congener totals (Rappe et al., 1990b; Rappe et al., 1991; Rappe, 1993; Strandell et al., 1994). During the 1980s, titanium metal anodes were developed to replace graphite electrodes (U.S. EPA, 1982a; Curlin and Bommaraju, 1991). Currently, no U.S. facility is believed to use graphite electrodes in the production of chlorine gas (telephone conversation between L. Phillips, Versar, Inc., and T. Fielding, U.S. EPA, Office of Water, February 1993).

Although the origin of the CDFs in graphite electrode sludge is uncertain, chlorination of the cyclic aromatic hydrocarbons (such as dibenzofuran) present in the coal tar used as a binding agent in the graphite electrodes has been proposed as the primary source (Strandell et al., 1994). For this reason, sludges produced using metal electrodes were not expected to contain CDFs. However, results of an analysis of metal electrode sludge from a facility in Sweden, analyzed as part of the Swedish Dioxin Survey, showed the sludge contained high levels of CDFs (similar to those of the graphite sludge) and

primarily nondetectable levels of CDDs (Strandell et al., 1994). The sludge showed the same type of CDF congener pattern reported by Rappe et al. (1991) and Rappe (1993). Strandell et al. (1994) suggested that chlorination of PAHs present in the rubber linings of the electrolytic cell may have formed the CDFs found in the one sample analyzed.

Although EPA does not regulate CDD/CDFs specifically, it issued restrictions under the Resource Conservation and Recovery Act (RCRA) on the land disposal of wastewater and sludges generated by chlorine manufacturers that use the mercury cell process and the diaphragm process (with graphite electrodes) (Waste Codes K071, K073, and K106) (40 CFR 268).

8.2.2. Manufacture of Chlorine Derivatives and Metal Chlorides

The limited sampling of chlorine-derivative products indicates that these products contain very low, if any, concentrations of CDD/CDFs. Rappe et al. (1990c) analyzed a sample of chlorine bleach consisting of 4.4 percent sodium hypochlorite. Most of the 2,3,7,8-substituted CDD/CDF congeners were below the limits of detection (0.3 to 7 pg/L for all congeners, except OCDD and OCDF, which were 12 and 20 pg/L, respectively). No 2,3,7,8-substituted CDDs were detected. Tetra-, penta-, and hexa-CDFs were detected at levels of 13 pg/L or lower. The TEQ content of the sample was 4.9 pg I-TEQ_{DF}/L. Hutzinger and Fiedler (1991a) reported finding no CDD/CDFs at a detection limit of 4 μg/kg in chlorine gas or in samples of 10 percent sodium hypochlorite, 13 percent sodium hypochlorite, and 31–33 percent hydrochloric acid at a detection limit of 1 μg/kg.

Hutzinger and Fiedler (1991a) reported the results of analyses of samples of $FeCl_2$, $AlCl_3$, $CuCl_2$, CuCl, $SiCl_4$, and $TiCl_4$ for their content of HpCDF, OCDF, HpCDD, and OCDD. The sample of $FeCl_3$ contained HpCDF and OCDF in the low μg/kg range, but no HpCDD or OCDD were detected at a detection limit of 0.02 μg/kg. One of the two samples of $AlCl_3$ analyzed also contained a low μg/kg concentration of OCDF. The samples of $CuCl_2$ and CuCl contained concentrations of HpCDF, OCDF, and OCDD less that 1 μg/kg. The results are presented in Table 8-5.

8.3. MANUFACTURE OF HALOGENATED ORGANIC CHEMICALS

Several chemical production processes generate CDDs and CDFs (Versar, 1985; Hutzinger and Fiedler, 1991a). CDDs and CDFs can be formed during the manufacture of

chlorophenols, chlorobenzenes, and chlorobiphenyls (Versar, 1985; Ree et al., 1988). Consequently, disposal of industrial wastes from manufacturing facilities producing these compounds may result in the release of CDDs and CDFs to the environment. Also, the products themselves may contain these compounds, and their use or consumption, may result in additional releases to the environment. CDD and CDF congener distribution patterns indicative of noncombustion sources have been observed in sediments in southwest Germany and The Netherlands. According to Ree et al (1988), the congener patterns found suggest that wastes from the production of chlorinated organic compounds may be important historical sources of CDD and CDF contamination in these regions. The production and use of many of the chlorophenols, chlorophenoxy herbicides, and PCB products are now banned or strictly regulated in most countries. However, these products may have been a source of the environmental contamination that occurred prior to the 1970s and may continue to be a source of environmental releases under certain limited use and disposal conditions (Rappe, 1992a).

8.3.1. Chlorophenols

Chlorophenols have been widely used for a variety of pesticidal applications. The higher chlorinated phenols (i.e., tetrachlorophenol and pentachlorophenol) and their sodium salts have been used primarily for wood preservation. The lower chlorinated phenols have been used primarily as chemical intermediates in the manufacture of other pesticides. For example, 2,4-dichlorophenol is used to produce the herbicides 2,4-Dichlorophenoxyacetic acid (2,4-D), 4-(2,4-Dichlorophenoxy)butanoic acid (2,4-DB), 2-(2,4-Dichlorophenoxy)-propanoic acid (2,4-DP), Nitrophen, Genite, and Zytron, and 2,4,5-trichlorophenol was used to produce hexachlorophene, 2,4,5-T, Silvex, Erbon, Ronnel, and Gardona (Gilman et al., 1988; Hutzinger and Fiedler, 1991a). [Note: Sections 8.3.7 and 8.3.8 contain information on EPA actions to control CDD/CDF contamination of pesticides (including pentachlorophenol and its salts) and to obtain additional data on CDD/CDF contamination of pesticides.]

The two major commercial methods used to produce chlorophenols are (1) electrophilic chlorination of molten phenol by chlorine gas in the presence of catalytic amounts of a metal chloride and organic chlorination promoters and stabilizers, and (2) alkaline hydrolysis of chlorobenzenes under heat and pressure using aqueous methanolic

sodium hydroxide. Other manufacturing methods include conversion of diazonium salts of various chlorinated anilines, and chlorination of phenolsulfonic acids and benzenesulfonic acids, followed by the removal of the sulfonic acid group (Gilman et al., 1988; Hutzinger and Fiedler, 1991a).

Because of the manufacturing processes employed, commercial chlorophenol products can contain appreciable amounts of impurities (Gilman et al., 1988). During the direct chlorination of phenol, CDD/CDFs can form either by the condensation of tri-, tetra-, and pentachlorophenols or by the condensation of chlorophenols with hexachlorocyclohexadienone (which forms from excessive chlorination of phenol). During alkaline hydrolysis of chlorobenzenes, CDD/CDFs can form through chlorophenate condensation (Ree et al., 1988; Gilman et al., 1988; Hutzinger and Fiedler, 1991a).

The limited information on CDD/CDF concentrations in chlorophenols published in the 1970s and early 1980s was compiled by Versar (1985) and Hutzinger and Fiedler (1991a). The results of several major studies cited by these reviewers (Firestone et al., 1972; Rappe et al., 1978a, 1978b) are presented in Table 8-6. Typically, CDD/CDFs were not detected in monochlorophenols (MCP) and dichlorophenols (DCP) but were reported in trichlorophenols (TrCP) and tetrachlorophenols (TeCP). More recent results of testing of 2,4-dichlorophenol (2,4-DCP), performed in response to the Toxic Substances Control Act (TSCA) Dioxin/Furan Test Rule, showed no detectable concentrations of 2,3,7,8-substituted tetra- through hepta-CDD/CDFs. Other than a study by Hagenmaier (1986) that reported finding 2,3,7,8-TCDD at a concentration of 0.3 μg/kg in a sample of 2,3,4,5-tetrachlorophenol, no more recent data on concentrations of CDDs and CDFs could be found in the literature for the mono- through tetra-chlorophenols. Tables 8-7 and 8-8 present summaries of several studies that reported CDD/CDF concentrations in PCP and in PCP-Na products, respectively. Many of these studies do not report congener-specific concentrations, and many are based on products obtained from non-U.S. sources.

Regulatory Actions - Section 8.3.8 of this report describes regulatory actions taken by EPA to control the manufacture and use of chlorophenol-based pesticides.

In the mid-1980s, EPA's Office of Solid Waste promulgated land disposal restrictions on wastes under RCRA (i.e., wastewaters and nonwastewaters) resulting from the manufacture of chlorophenols (40 CFR 268). Table 8-9 lists all wastes in which CDDs and CDFs are specifically regulated as hazardous constituents by EPA, including

chlorophenol wastes (waste codes F020 and F021). The regulations prohibit the land disposal of these wastes until they are treated to a level below the routinely achievable detection limits in the waste extract listed in Table 8-9 for each of the following congener groups: TCDDs, PeCDDs, HxCDDs, TCDFs, PeCDFs, and HxCDFs. Wastes from PCP-based wood-preserving operations (waste codes K001 and F032) are also regulated as hazardous wastes under RCRA (40 CFR 261).

EPA's Office of Water promulgated effluent limitations for facilities that manufacture chlorinated phenols and discharge treated wastewater (40 CFR 414.70). These effluent limitations do not specifically regulate CDDs and CDFs. The effluent limitations for the individually regulated chlorinated phenols are less than or equal to 39 μg/L for facilities that use biological end-of-pipe treatment.

DCPs and TrCPs are subject to reporting under the Dioxin/Furan Test Rule, which is discussed in Section 8.3.7 of this report. Since the effective date of that rule (i.e., June 5, 1987), only the 2,4-DCP isomer has been commercially produced (or imported) in the United States, and as noted in Table 8-6, no CDD/CDFs were detected in the product. Testing is required for the other DCPs and TrCPs, if manufacture or importation resumes. Similarly, TeCPs were subject to reporting under the Dioxin/Furan Pesticide Data Call-In or DCI (discussed in Section 8.3.8 of this report). Since issuance of the DCI, the registrants of TeCP-containing pesticide products have elected to no longer support the registration of their products in the United States.

In January 1987, EPA entered into a Settlement Agreement with pentachlorophenol (PCP) manufacturers, which set limits on allowed uses of PCP and its salts and set maximum allowable concentrations of 2,3,7,8-TCDD and HxCDDs, effective in February 1989. Section 8.3.8 discusses the 1987 PCP Settlement Agreement and estimates current releases of CDD/CDFs associated with use of PCP in the United States. Section 12.3.1 provides an estimate of the amount of CDD/CDFs that may have entered the environment or that are contained within treated wood products as a result of prior use of PCP and PCP-Na.

Since the late 1980s, U.S. commercial production of chlorophenols has been limited to 2,4-dichlorophenol (2,4-DCP) and PCP. As noted above, disposal of wastes generated during the manufacture of chlorophenols is strictly regulated, and thus releases to the environment are expected to be negligible. With regards to releases associated

with the use of 2,4-DCP, no CDD/CDFs have been detected in 2,4-DCP. Releases associated with the use of PCP are presented in Sections 8.3.8 and 12.3.1.

8.3.2. Chlorobenzenes

Chlorobenzenes have been produced in the United States since 1909. U.S. production operations were developed primarily to provide chemical raw materials for the production of phenol, aniline, and various pesticides based on the higher chlorinated benzenes. Because of [incremental] changes in the processes used to manufacture phenol and aniline and the phaseout of highly chlorinated pesticides such as DDT and hexachlorobenzene, by 1988 U.S. production of chlorobenzenes had decreased to 50 percent of the peak production level in 1969.

Chlorobenzenes can be produced via three methods: (1) electrophilic substitution of benzene (in liquid or vapor phase) with chlorine gas in the presence of a metal salt catalyst; (2) oxidative chlorination of benzene with HCl at 150–300°C in the presence of a metal salt catalyst; and (3) dehydrohalogenation of hexachlorocyclohexane wastes at 200–240°C with a carbon catalyst to produce trichlorobenzene, which can be further chlorinated to produce higher chlorinated benzenes (Ree et al., 1988; Hutzinger and Fiedler, 1991a; Bryant, 1993).

All chlorobenzenes currently manufactured in the United States are produced using the electrophilic substitution process using liquid-phase benzene (i.e., temperature is at or below 80°C). Ferric chloride is the most common catalyst employed. Although this method can be used to produce mono- through hexachlorobenzene, the extent of chlorination is controlled to yield primarily MCBz and DCBz. The finished product is a mixture of chlorobenzenes, and refined products must be obtained by distillation and crystallization (Bryant, 1993).

CDD/CDFs can be produced inadvertently during the manufacture of chlorobenzenes by nucleophilic substitution and pyrolysis mechanisms (Ree et al., 1988). The criteria required for production of CDD/CDFs via nucleophilic substitution are (1) oxygen as a nuclear substituent (i.e., presence of chlorophenols) and (2) production or purification of the substance under alkaline conditions. Formation via pyrolysis requires reaction temperatures above 150°C (Ree et al., 1988; Hutzinger and Fiedler, 1991a). The liquid-phase electrophilic substitution process currently used in the United States does not

meet either of these criteria. Although Ree et al. (1988) and Hutzinger and Fiedler (1991a) state that the criteria for formation of CDD/CDFs via nucleophilic substitution may be present in the catalyst neutralization and purification/distillation steps of the manufacturing process, Opatick (1995) states that the chlorobenzene reaction product in U.S. processes remains mildly acidic throughout these steps.

Table 8-10 summarizes the very limited published information on CDD/CDF contamination of chlorobenzene products. The presence of CDD/CDFs has been reported in TCBz, PeCBz, and HCBz. No CDD/CDFs have been reported in monochlorobenzene (MCBz) and DCBz. Conflicting data exist concerning the presence of CDD/CDFs in TCBz. One study (Villanueva et al., 1974) detected no CDD/CDFs in one sample of 1,2,4-TCBz at a detection limit of 0.1 μg/kg. Hutzinger and Fiedler (1991a) reported unpublished results of Dr. Hans Hagenmaier showing CDD/CDF congener group concentrations ranging from 0.02 to 0.074 μg/kg in a sample of mixed TCBz. Because the TCBz examined by Hagenmaier contained about 2 percent hexachlorocyclohexane, it is reasonable to assume that the TCBz was produced by dehydrohalogenation of hexachlorocyclohexane (a manufacturing process not currently used in the United States).

Regulatory Actions - EPA has determined, as part of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Pesticide Data Call-In (discussed in Section 8.3.8), that the 1,4-DCBz manufacturing processes used in the United States are not likely to form CDD/CDFs. MCBz, DCBz, and TCBz are listed as potential precursor chemicals under the TSCA Dioxin/Furan Test Rule and are subject to reporting. (See Section 8.3.7.) In addition, EPA issued a Significant New Use Rule (SNUR) under Section 5(a)(2) of TSCA on December 1, 1993 (effective January 14, 1994) for PeCBz and 1,2,4,5-TeCBz (Federal Register, 1993c). This rule requires persons to submit a notice to EPA at least 90 days before manufacturing, importing, or processing either of these compounds in amounts of 10,000 pounds or greater per year per facility for any use. All registrations of pesticide products containing HCBz were cancelled in the mid-1980s (Carpenter et al., 1986).

EPA's Office of Solid Waste promulgated land disposal restrictions on wastes (i.e., wastewaters and nonwastewaters) resulting from the manufacture of chlorobenzenes (40 CFR 268). Table 8-9 lists all solid wastes for which EPA specifically regulates CDDs and CDFs as hazardous constituents, including chlorobenzene wastes. The regulations prohibit the land disposal of these wastes until they are treated to a level below the routinely

achievable detection limits in the waste extract listed in Table 8-9 for each of the following congener groups: TCDDs, PeCDDs, HxCDDs, TCDFs, PeCDFs, and HxCDFs.

EPA's Office of Water promulgated effluent limitations for facilities that manufacture chlorinated benzenes and discharge treated wastewater (40 CFR 414.70). These effluent limitations do not specifically address CDDs and CDFs. The following chlorinated benzenes are regulated: chlorobenzene; 1,2-dichlorobenzene; 1,3-dichlorobenzene; 1,4-dichlorobenzene; 1,2,4-trichlorobenzene; and hexachlorobenzene. The effluent limitations for the individual regulated chlorinated benzenes are less than or equal to 77 μg/L for facilities that use biological end-of-pipe treatment and are less than or equal to 196 μg/L for facilities that do not use biological end-of-pipe treatment.

Since at least 1993, U.S. commercial production of chlorobenzenes has been limited to MCBz, 1,2-dichlorobenzene (1,2-DCBz), 1,4-dichlorobenzene (1,4-DCBz), and, to a much lesser extent, 1,2,4-trichlorobenzene (1,2,4-TCBz). As noted above, CDD/CDF formation is not expected under the normal operating conditions of the processes currently used in the United States to produce these four chemicals. No tetra-, penta-, or hexachlorinated benzenes are now intentionally produced or used in the United States (Bryant, 1993). Thus, releases of CDD/CDFs from manufacture of chlorobenzenes in 1995 were estimated to be negligible. Because the information available on CDD/CDF content of MCBz to PeCBz is very limited and is based primarily on unpublished European data, and because information on the chlorobenzene manufacturing processes in place during 1987 is not readily available, no emission estimates can be made for 1987.

8.3.3. Chlorobiphenyls

PCBs are manufactured by the direct batch chlorination of molten biphenyl in the presence of a catalyst, followed by separation and purification of the desired chlorinated biphenyl fractions. During the manufacture of PCBs, the inadvertent production of CDFs also occurrs. This section addresses potential releases of CDD/CDFs associated with leaks and spills of PCBs. CDFs have been shown to form when PCB-containing transformers and capacitors undergo malfunctions or are subjected to fires that result in accidental combustion of the dielectric fluid. This combustion source of PCB-associated CDFs is discussed in Section 6.6. Section 11.2 addresses releases of dioxin-like PCBs.

PCB production is believed to have occurred in 10 countries. The total amount of PCBs produced worldwide since 1929 (i.e., the first year of known production) is estimated to total 1.5 billion kg. Initially, PCBs were primarily used as dielectric fluids in transformers. After World War II, PCBs found steadily increasing use as dielectric fluids in capacitors, as heat-conducting fluids in heat exchangers, and as heat-resistant hydraulic fluids in mining equipment and vacuum pumps. PCBs also were used in a variety of "open" applications (i.e., uses from which PCBs cannot be re-collected) including in plasticizers, carbonless copy paper, lubricants, inks, laminating agents, impregnating agents, paints, adhesives, waxes, additives in cement and plaster, casting agents, dedusting agents, sealing liquids, fire retardants, immersion oils, and pesticides (DeVoogt and Brinkman, 1989).

PCBs were manufactured in the United States from 1929 until 1977. U.S. production peaked in 1970, with a volume of 85 million pounds. Monsanto Corporation, the major U.S. producer, voluntarily restricted the use of PCBs in 1971, and annual production fell to 40 million pounds in 1974. Monsanto ceased PCB manufacture in mid-1977 and shipped the last inventory in October 1977. Regulations issued by EPA beginning in 1977, principally under TSCA (40 CFR 761), strictly limited the production, import, use, and disposal of PCBs. (See Section 4.1 for details on TSCA regulations.) The estimated cumulative production and consumption volumes of PCBs in the United States from 1930 to 1975 were 1,400 million pounds produced; 3 million pounds imported (primarily from Japan, Italy, and France), 1,253 million pounds sold in the United States; and 150 million pounds exported (ATSDR, 1993; DeVoogt and Brinkman, 1989).

Monsanto Corporation marketed technical-grade mixtures of PCBs primarily under the trade name Aroclor. The Aroclors are identified by a four-digit numbering code in which the last two digits indicate the chlorine content by weight percent. The exception to this coding scheme is Aroclor 1016, which contains only mono- through hexachlorinated congeners with an average chlorine content of 41 percent. The following list shows the percentages of total Aroclor production, by Aroclor mixture, during 1957 to 1977, as reported by Brown (1994).

Aroclor	1957–1977 U.S. Production (%)
1221	0.96
1016	12.88
1232	0.24
1242	51.76
1248	6.76
1254	15.73
1260	10.61
1262	0.83
1268	0.33

The trade names of the major commercial technical-grade mixtures of PCBs manufactured in other countries included *Clophen* (Germany), *Fenclor* and *Apirolio* (Italy), *Kanechlor* (Japan), *Phenoclor* and *Pyralene* (France), *Sovtel* (USSR), *Delor* and *Delorene* (Czechoslovakia), and *Orophene* (German Democratic Republic) (DeVoogt and Brinkman, 1989). Some of the mixtures marketed under these trade names were similar in terms of chlorine content (by weight percent and average number of chlorines per molecule) to various Aroclors, as shown below. Mixtures that are comparable in terms of chlorine content were marketed under several trade names, as shown below.

Aroclor	Clophen	Pyralene	Phenoclor	Fenclor	Kanechlor
1232		2000			200
1242	A-30	3000	DP-3	42	300
1248	A-40		DP-4		400
1254	A-50		DP-5	54	500
1260	A-60		DP-6	64	600

During the commercial production of PCBs, thermal oxidative cyclization under alkaline conditions resulted in the inadvertent production of CDFs in most of the commercial PCB mixtures (Brown et al., 1988; ATSDR, 1993). Bowes et al. (1975a) first reported detection of CDFs in Aroclor products; samples of unused Aroclors manufactured in 1969 and 1970 were found to have CDF (i.e., TCDF through HxCDF) concentrations ranging from 0.8 to 2.0 mg/kg. Bowes et al. (1975b) employed congener-specific analytical methodology and detected 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF at concentrations ranging from 0.11 to 0.33 mg/kg and 0.12 to 0.83 mg/kg, respectively, in unused samples of Aroclor 1254 and Aroclor 1260. The presence of CDDs in commercial

PCB mixtures, although at much lower concentrations than those of the CDFs, was reported by Hagenmaier (1987) and Malisch (1994). Table 8-11 presents the CDF and CDD congener group concentrations reported by Bowes et al. (1975a) and those reported in subsequent years for unused PCBs by Erickson (1986), ATSDR (1993), Hagenmaier (1987), and Malisch (1994).

Several researchers reported concentrations of specific CDD/CDF congeners in commercial PCB mixtures (Bowes et al., 1975b; Brown et al., 1988; Hagenmaier, 1987; Malisch, 1994). Only the Hagenmaier (1987) and Malisch (1994) studies, however, reported the concentrations of all 2,3,7,8-substituted CDDs and CDFs. Table 8-12 presents the results of these four studies. It is evident from the table that major variations are found in the levels of 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF in the Clophen mixtures reported by Hagenmaier (1987) and Malisch (1994) and the corresponding levels in the Aroclor mixtures reported by Bowes et al. (1975b) and Brown et al. (1988).

Brown et al. (1988) compared the levels of 2,3,7,8-TCDF, 2,3,4,7,8-PeCDF, and 1,2,3,7,8,9-HxCDF in used samples (i.e., samples from previously used capacitors and transformers) and unused samples of Aroclors 1016, 1242, 1254, and 1260. The concentration ranges reported for the used and unused Aroclors were similar, leading Brown et al. (1988) to conclude that CDFs are not formed during the normal use of PCBs in electrical equipment.

Amounts of CDD/CDF TEQ that may have been released to the environment during 1987 and 1995 from spills and leaks of in-service PCBs cannot be accurately estimated because reliable data regarding leaked and spilled PCBs are not available. However, preliminary estimates can be made using the release data reported to EPA's Toxics Release Inventory (TRI) by those manufacturing facilities required to submit annual reports to TRI. Table 11-6 in Section 11 lists the amounts of PCBs reported to TRI to have been released to the environment during 1988 through 1996. These TRI data include emissions to the air, discharges to bodies of water, and releases to land. On the basis of these data, annual emissions of PCBs to air during 1988 and 1996 could have been as high as 2.7 kg and as low as 0 kg, respectively. If it is further assumed that the ratio of TEQ (I-TEQ_{DF} and TEQ_{DF}-WHO_{98}) to total PCB in the air emissions was 0.17:1,000,000 (i.e., the average of the TEQ contents for Clophen A-30 and Clophen A-50, or 170 μg/kg, as reported by Hagenmaier (1987) and presented in Table 8-12), then annual emissions of I-TEQ_{DF} to air

in 1988 and 1995 could have been 0.5 and 0 mg, respectively. Similar assumptions for PCB releases to water of 4.5 kg in 1988 and 0 kg in 1995 yield estimated TEQ emissions during 1988 and 1995 of 0.8 and 0 mg, respectively. For land releases of 341 kg in 1988 and 0 kg in 1995, estimated TEQ emissions during 1988 and 1995 are 58 and 0 mg, respectively. All of these estimated releases are considered to be negligible.

8.3.4. Polyvinyl Chloride

Polyvinyl chloride (PVC) resins are produced when free radical initiators are used to induce the polymerization of vinyl chloride monomer (VCM). VCM is typically produced by the thermal dehydrochlorination (commonly known as cracking) of ethylene dichloride (EDC). One plant in the United States still uses the catalytic reaction of acetylene and HCl to manufacture VCM directly. The cracking of EDC requires elevated pressure (20 to 30 atmospheres) and temperature (450 to 650°C) and yields VCM and HCl at about a 1:1 molar ratio. EDC is produced by two different methods: (1) direct chlorination of ethylene with chlorine in the presence of a catalyst at a temperature of 50 to 60°C and pressure of 4 to 5 atmospheres; and (2) oxychlorination, which involves reaction of ethylene with HCl and oxygen in the presence of a catalyst at temperatures generally less than 325°C. The primary source of HCl for the oxychlorination process is the HCl produced from the cracking of EDC to form VCM; all VCM plants, with the exception of the one facility noted above, are integrated with EDC production facilities (The Vinyl Institute, 1998).

Although it has generally been recognized that CDD/CDFs are formed during the manufacture of EDC/VCM/PVC, manufacturers and environmental public interest groups have disagreed as to the quantity of CDD/CDFs that are formed and released to the environment in wastes and possibly in PVC products. Although EPA regulates emissions from EDC/VCM production facilities under the Clean Water Act (40 CFR 61), the Clean Air Act (40 CFR 414), and RCRA (40 CFR 268 - Waste Codes F024, K019, and K020), CDD/CDFs are not specifically regulated pollutants; as a consequence, monitoring data for CDD/CDFs in emissions are generally lacking.

In 1993, Greenpeace International issued a report on CDD/CDF emissions associated with the production of EDC/VCM (Greenpeace, 1993). Greenpeace estimated that 5 to 10 g I-TEQ_{DF} are released to the environment (air, water, and ground combined) annually for every 100,000 metric tons of VCM produced. This emission factor was

based on data gathered by Greenpeace on four European plants. The Vinyl Institute responded with a critique of the Greenpeace report (ChemRisk, 1993). Miller (1993) summarized the differing views of the two parties. According to Miller (1993), European PVC manufacturers claim the emission factor is 0.01 to 0.5 g I-TEQ_{DF}/100,000 metric tons of VCM. Although Greenpeace (1993) and ChemRisk (1993) used basically the same monitoring information to develop their emission factors, Greenpeace adjusted the emission factor to account for unquantified fugitive emissions and waste products that contain unspecified amounts of CDD/CDFs.

In 1995, Greenpeace issued another report reiterating the organization's concern that the generation and emission of CDD/CDFs may be significant and urging that further work be initiated to quantify and prevent emissions (Stringer et al., 1995). Stringer et al. (1995) presented the results of analyses of three samples of chlorinated wastes obtained from U.S. EDC/VCM manufacturing facilities. The three wastes were characterized according to EPA hazardous waste classification numbers as follows: (1) an F024 waste (i.e., waste from the production of short chain aliphatics by free radical catalyzed processes), (2) a K019 waste (i.e., heavy ends from the distillation of ethylene from EDC production), and a probable K020 waste (i.e., heavy ends from distillation of VC in VCM manufacture). Table 8-13 presents the analytical results reported by Stringer et al. (1995). This study acknowledged that because EDC/VCM production technologies and waste treatment and disposal practices are very site-specific, the limited information available on CDD/CDF generation and emissions made it difficult to quantify amounts of CDD/CDFs generated and emitted.

In response to the lack of definitive studies and at the recommendation of EPA, U.S. PVC manufacturers initiated an extensive monitoring program, the Dioxin Characterization Program, to evaluate the extent of any CDD/CDF releases to air, water, and land, as well as any product contamination. Manufacturers performed emission and product testing at various facilities that were representative of various manufacturing and process control technologies. The Vinyl Institute has completed studies of CDD/CDF releases in wastewater, wastewater treatment plant solids, and stack gases, as well as studies of CDD/CDF content of products (i.e., PVC resins and "sales" EDC). The following subsections discuss the results for each of these media (The Vinyl Institute, 1998).

The Vinyl Institute created an External Advisory Group to advise the institute on the conduct of the Dioxin Characterization Program and to provide an independent review of the Program results. In their final evaluation report, the Advisory Group judged the industry's coverage, in terms of the number of facilities and waste streams sampled, to be fairly comprehensive. The number of samples of PVC product, stack emissions, wastewaters, and wastewater sludges obtained from the different types of manufacturing facilities was deemed by the Advisory Group to provide a sufficient database to evaluate industrywide annual releases. The Advisory Group concluded that the process established by The Vinyl Institute to ensure that data collected as part of its Dioxin Characterization Program are representative of normal process operations was a good one. After auditing The Vinyl Institute's estimates of annual releases, the Advisory Group concluded that the data were properly validated and the results were extrapolated to annual industrywide release estimates in a creditable, scientific manner.

EPA has reviewed The Vinyl Institute (1998) study and concurs with the conclusions of the External Advisory Group. EPA assigns a high confidence rating to the activity level estimates and a medium confidence rating to the emission factor estimates developed by The Vinyl Institute (1998).

Wastewater - The Vinyl Institute (1998) presented results for treated wastewater samples collected during April and May of 1995 at six sites that manufactured only PVC, at three sites that manufactured EDC and VCM, and at one site that manufactured EDC, VCM, and PVC. In terms of production, the six PVC-only sites represent approximately 15 percent of the total estimated 1995 U.S. and Canadian PVC production. The three EDC/VCM sites and the one EDC/VCM/PVC site together represent 27 percent of the total estimated 1995 U.S. EDC production. Samples taken from PVC-only sites were taken from sites that manufactured suspension PVC resin as well as sites that manufactured dispersion PVC resin. Samples for the other four sites were taken from sites that used direct and oxychlorination processes, fixed and fluidized beds, and low- and high-temperature direct chlorination. The wastewater samples from one of the EDC/VCM sites, one of the PVC-only sites, and the EDC/VCM/PVC site were taken from effluents derived from process areas not limited to EDC/VCM, EDC/VCM/PVC, or PVC manufacturing.

The results of the sampling are presented in Table 8-14. The method detection limits (MDLs) for all congeners except OCDD and OCDF in all samples were 10 pg/L or

less. The MDLs for OCDD and OCDF were 50 pg/L or less. CDD/CDFs were detected in two of the six samples from PVC-only sites (0.52 and 2.0 pg I-TEQ_{DF}/L, assuming ND = 0). The overall mean TEQ concentrations were 0.88 pg I-TEQ_{DF}/L (ND = 0) and 4.7 pg I-TEQ_{DF}/L (ND = 1/2 MDL). CDD/CDFs were detected in all four of the samples from EDC/VCM/PVC sites. The overall mean TEQ concentrations were 0.42 pg I-TEQ_{DF}/L (ND = 0) and 4.4 pg I-TEQ_{DF}/L (ND = 1/2 MDL).

Based on these sample results, The Vinyl Institute developed I-TEQ_{DF} emission factors for PVC-only and EDC/VCM/PVC manufacturing facilities. First, individual site release rates were estimated using the treated wastewater effluent flow rate recorded by the site during sampling and assuming that the site continuously releases CDD/CDFs at its calculated total I-TEQ_{DF}, 24 hours per day, 360 days per year, at the recorded water effluent rate. The total releases from each site-type category (i.e., PVC-only or EDC/VCM/PVC facilities) were then estimated by averaging the individual release rates on a per-1,000-metric-ton-of-PVC basis or per-1,000-metric-ton-of-EDC basis using the estimated 1995 PVC and EDC production statistics for the sampled sites. These values were then "scaled up" to estimate total U.S. releases in treated wastewater from the site-type categories. It is not possible using the data presented in the Vinyl Institute (1998) to calculate emission factors for TEQ_{DF}-WHO_{98}. However, because 1,2,3,7,8-PeCDD was not detected in any wastewater sample, the TEQ_{DF}-WHO_{98} emission factors would be lower than the I-TEQ_{DF} emission factors.

The mean emission factors derived from the sample results for the PVC-only facilities are 2.3 μg I-TEQ_{DF}/1,000 metric tons of PVC (ND = 0) and 29 μg I-TEQ_{DF}/1,000 metric tons of PVC (ND = 1/2 MDL). The mean emission factors for the EDC/VCM/PVC facilities are 2.9 μg I-TEQ_{DF}/1,000 metric tons (ND = 0) and 15 μg I-TEQ_{DF}/1,000 metric tons of EDC (ND = 1/2 MDL).

The Vinyl Institute (1998) combined these emission factors with 1995 industry production statistics (i.e., 5,212 thousand metric tons of PVC and 11,115 thousand metric tons of EDC), to yield release estimates of 0.011 grams I-TEQ_{DF} (ND = 0) and 0.15 g I-TEQ_{DF} (ND = 1/2 DL) from PVC-only manufacturing sites and 0.032 g I-TEQ_{DF} (ND = 0) and 0.17 g I-TEQ_{DF} (ND = 1/2 DL) from EDC/VCM and EDC/VCM/PVC facilities for a total I-TEQ_{DF} release in 1995 of 0.043 g (ND = 0) and 0.32 g (ND = 1/2 DL).

Wastewater Treatment Plant Solids - The Vinyl Institute (1998) presented results for 14 samples collected in 1996 from 9 EDC/VCM/PVC manufacturing sites. Samples were collected from 4 of the 5 U.S. sites that manufactured EDC, VCM, and PVC; 3 of the 7 U.S. sites that manufactured EDC and VCM, but not PVC; and 2 of the 21 sites that manufacture PVC, but not EDC or VCM. On the basis of 1995 production data, the two PVC-only sites manufactured approximately 4.7 percent of the total estimated U.S. and Canadian PVC resin production. The sampled EDC/VCM and EDC/VCM/PVC sites manufactured 56 percent of the total estimated 1995 U.S. EDC production. Samples from the PVC-only sites were taken from sites that manufactured suspension PVC resin as well as sites that manufactured dispersion PVC resin. Samples taken from the EDC/VCM and EDC/VCM/PVC sites were taken from sites that used direct and oxychlorination processes; fixed and fluidized EDC reactor beds; low- and high-temperature direct chlorination; and air, oxygen, and mixed air/oxygen feeds.

Using the sample results and their determination that the results for facilities using different EDC reactor bed technologies (i.e., fluidized bed vs. fixed bed) appear to differ significantly, The Vinyl Institute developed annual I-TEQ_{DF} emission estimates for three categories: PVC-only, EDC/VCM/PVC fixed bed, and EDC/VCM/PVC fluidized bed facilities. Nine U.S. sites use fixed bed technology and six use fluidized bed technology. Four of each type of facility were sampled by The Vinyl Institute. It is not possible using the data presented in The Vinyl Institute (1998) to calculate emission factors for TEQ_{DF}-WHO_{98}. Because 1,2,3,7,8-PeCDD was detected in only 3 of 10 samples, but OCDD and OCDF were detected in all samples, it is likely that the TEQ_{DF}-WHO_{98} emission factors would not be significantly different from the I-TEQ_{DF} emission factors.

Results of the sampling are presented in Table 8-14. The MDLs for all congeners were less than 150 ng/kg, and usually were less than 10 ng/kg. CDD/CDFs were detected in all samples. The ranges of TEQ concentrations (dry weight basis) for the two PVC-only facilities were 1.1 to 2.6 ng I-TEQ_{DF}/kg (ND = 0) and 2.8 to 4.4 ng I-TEQ_{DF}/kg (ND = 1/2 MDL). On an emission factor basis, the ranges were 1.7 to 46 μg I-TEQ_{DF}/1,000 metric tons of PVC produced (ND = 0) and 4.3 to 78 μg I-TEQ_{DF}/1,000 metric ton of PVC produced (ND = 1/2 DL). The range of TEQ concentrations for the samples from the EDC/VCM or EDC/VCM/PVC sites were 88 to 6,850 ng I-TEQ_{DF}/kg (ND = 0) and 93 to 6,850 ng I-TEQ_{DF}/kg (ND = 1/2 DL). On an emission factor basis, the

ranges were 28 to 4,000 μg I-TEQ$_{DF}$/1,000 metric tons of EDC (ND = 0) and 29 to 4,000 μg I-TEQ$_{DF}$/1,000 metric tons of EDC (ND = 1/2 DL).

The annual amounts of I-TEQ$_{DF}$ generated in 1995 in each of the three facility categories were estimated by The Vinyl Institute as follows. First, total annual contributions at each sampled site were estimated by multiplying the I-TEQ$_{DF}$ from the sample by the annual production of wastewater solids at that site. These annual site contributions of I-TEQ$_{DF}$ were then summed for each of the three facility types and multiplied by the ratio of each category's total annual production of PVC or EDC to the sum of the annual production of the sampled sites in that category.

The Vinyl Institute (1998) combined these emission factors with 1995 industry production statistics (i.e., 5,212 thousand metric tons of PVC and 11,115 thousand metric tons of EDC) to yield estimated amounts of I-TEQ$_{DF}$ in wastewater treatment plant solids. For PVC-only facilities, estimated amounts are 0.069 g I-TEQ$_{DF}$ per year (ND = 0) and 0.12 g I-TEQ$_{DF}$ per year (ND = 1/2 DL), assuming an annual PVC production of 5,212 thousand metric tons. For EDC/VCM/PVC fixed bed facilities, the estimated amounts of TEQ are 1.0 g I-TEQ$_{DF}$ per year (ND = 0 or ND = 1/2 DL), assuming an EDC annual production volume of 5,400 thousand metric tons. For EDC/VCM/PVC fluidized bed facilities, the estimated amount of TEQ is 11 g I-TEQ$_{DF}$ per year (ND = 0 or ND = 1/2 DL), assuming EDC annual production volume of 5,600 thousand metric tons. Thus, total amounts of TEQ in wastewater treatment plant solids are estimated to have been 12.1 g I-TEQ$_{DF}$ in 1995 (ND = 0 or ND = 1/2 DL).

Based on The Vinyl Institute survey data, Institute member companies dispose of wastewater solids by three methods: (1) RCRA hazardous waste landfilling (approximately 1 percent of industry total solids), (2) landfarming (approximately 6 percent), and (3) "secure" on-site landfilling (93 percent of industry total solids). Solids disposed of by methods 1 and 3 are assumed to be well controlled to prevent release into the general environment, whereas solids disposed of by landfarming are not as well controlled and could be released to the environment. Therefore, an estimated 0.73 g I-TEQ$_{DF}$ (i.e., 6 percent of 12.1 g I-TEQ$_{DF}$) can be considered as potentially released to the environment.

Stack Gas Emissions - By grouping similarities of design and service, The Vinyl Institute (1998) subcategorized thermal destruction units at EDC/VCM and/or PVC manufacturing units into three categories: (a) type A—vent gas incinerators at PVC-only

resin plants; (b) type B—vent gas thermal oxidizers at EDC/VCM plants; and (c) type C—liquid only and liquid/vent gas thermal oxidizers at EDC/VCM plants. Using an industrywide survey, The Vinyl Institute (1998) identified 22 type A units at 11 facilities, 23 type B units at 10 facilities, and 17 type C units at 10 facilities. The Vinyl Institute gathered test data from 5 of the 22 type A units (from three facilities representing 7 percent of total U.S. and Canadian EDC/VCM/PVC production in 1995), 14 of the 23 type B units (from 8 facilities), and 13 of the 17 type C units (from 7 facilities). The sampled types B and C units represent 70 percent of total U.S. and Canadian EDC/VCM/PVC production in 1995.

Annual I-TEQ_{DF} emission estimates were generated by The Vinyl Institute by combining estimated emissions from tested units (i.e., based on measured stack gas results and plant-specific activity data) with an estimate of emissions from untested units. The emissions from the untested units were estimated by multiplying the average emission factor for the tested units in the category (i.e., called the "most likely" estimate by The Vinyl Institute) or by multiplying the average emission factor of the three highest tested units in each class (i.e., the "upper bound" estimate) by the activity level for the untested units. It is not possible using the data presented in The Vinyl Institute (1998) to calculate emission factors for TEQ_{DF}-WHO_{98}.

The Vinyl Institute (1998) estimates of "most likely" and "upper-bound" emissions during 1995 for these three categories are as follows:

Category	"Most Likely" Emission Estimate (g I-TEQ_{DF}/yr)	"Upper Bound" Emission Estimate (g I-TEQ_{DF}/yr)
PVC-only incinerators	0.0014	0.0019
EDC/VCM liquid and liquid/vents	3.7	7.2
EDC/VCM vents for VCM only	6.9	21.6

The Vinyl Institute (1998) also estimated emissions that may result from incineration of EDC/VCM/PVC wastes processed by off-site third-party processing. Using the emission factors for liquid and liquid/vents developed in their study, The Vinyl Institute estimated that potential emissions to air from this source category would be 0.65 g I-

TEQ_{DF}/yr (most likely estimate) and 2.3 g I-TEQ_{DF}/yr (upper-bound estimate). Including these third-party release estimates with those developed above yields a most likely estimate of 11.2 g I-TEQ_{DF}/yr and an upper-bound estimate of 31 g I-TEQ_{DF}/yr.

Products - The Vinyl Institute (1998) presented results for 22 samples from 14 of the 24 U.S. and Canadian facilities manufacturing suspension and mass PVC resins (i.e., 13 pipe resins, 3 bottle resins, and 6 packaging resins). The results are summarized in Table 8-15. The 14 sampled sites represent approximately 74 percent of estimated 1995 U.S. and Canadian suspension and mass PVC resin production. CDD/CDFs were detected in only one sample (0.043 ng I-TEQ_{DF}/kg, assuming ND = 0). The overall mean TEQ concentrations were 0.002 ng I-TEQ_{DF}/kg (ND = 0) and 0.7 ng I-TEQ_{DF}/kg (ND = 1/2 MDL). The MDLs were 2 ng/kg or less for all congeners in all samples except for OCDD and OCDF, which had MDLs of 6 ng/kg or less.

The Vinyl Institute (1998) also presented results for six samples from four of the seven U.S. facilities manufacturing dispersion PVC resins. CDD/CDFs were detected in five of the samples. The results are summarized in Table 8-15. In terms of production, the four sampled sites represent approximately 61 percent of estimated 1995 U.S. dispersion PVC resin production. The results ranged from not detected to 0.008 ng I-TEQ_{DF}/kg (overall mean = 0.001 ng I-TEQ_{DF}/kg assuming ND = 0, and 0.4 ng I-TEQ_{DF}/kg, assuming ND = 1/2 MDL). The MDLs were 2 ng/kg or less for all congeners in all samples except OCDD and OCDF, which had MDLs of 4 ng/kg or less.

The Vinyl Institute (1998) also presented results for 5 samples from 5 of the 15 U.S. facilities manufacturing EDC. The results are summarized in Table 8-15. In terms of production, the five sampled sites represent approximately 71 percent of total U.S. estimated 1995 "sales" EDC production. CDD/CDFs were detected in only one sample (0.03 ng I-TEQ_{DF}/kg). The overall mean TEQ concentrations were 0.006 ng I-TEQ_{DF}/kg (ND = 0) and 0.21 ng I-TEQ_{DF}/kg (ND = 1/2 MDL). The MDLs for all congeners were 1 ng/kg or less.

Using 1995 U.S. production data (i.e., 4.846 million metric tons of suspension and mass PVC, 0.367 million metric tons of dispersion PVC resins, and 1.362 million metric tons of "sales" EDC) and the average TEQ observed for the samples analyzed, The Vinyl Institute estimated the total I-TEQ_{DF} contents of suspension/mass PVC resins, dispersion PVC resins, and "sales" EDC in 1995 to be 0.01 g, 0.004 g, and 0.008 g, respectively

(ND = 0) and 3.39 g, 0.15 g, and 0.29 g, respectively (ND = 1/2 MDL). Therefore, total I-TEQ_{DF} present in PVC in 1995 was estimated at between 0.02 g (ND = 0) and 3.83 g (ND = 1/2 MDL). It is not possible using the data presented in The Vinyl Institute (1998) to calculate emission factors for TEQ_{DF}-WHO_{98}. However, because neither 1,2,3,7,8-PeCDD nor OCDD were detected in any sample, the TEQ_{DF}-WHO_{98} emission factors would be very similar to the I-TEQ_{DF} emission factors.

8.3.5. Other Aliphatic Chlorine Compounds

Aliphatic chlorine compounds are used as monomers in the production of plastics, as solvents and cleaning agents, and as precursors for chemical synthesis (Hutzinger and Fiedler, 1991a). These compounds are produced in large quantities. In 1992, 14.6 million metric tons of halogenated hydrocarbons were produced (U.S. International Trade Commission, 1946–1994). The production of 1,2-dichloroethane and vinyl chloride accounted for 82 percent of this total production. Highly chlorinated CDDs and CDFs (i.e., hexa- to octachlorinated congeners) have been found in nanograde-quality samples of 1,2-dichloroethane (55 ng/kg of OCDF in one of five samples), tetrachloroethene (47 ng/kg of OCDD in one of four samples), epichlorohydrin (88 ng/kg of CDDs and 33 ng/kg of CDFs in one of three samples), and hexachlorobutadiene (360 to 425 ng/kg of OCDF in two samples) obtained in Germany from the company Promochem (Hutzinger and Fiedler, 1991a; Heindl and Hutzinger, 1987). No CDD/CDFs were detected in two samples of allyl chloride, three samples of 1,1,1-trichloroethane, and four samples of trichloroethylene (detection limit ranged from 5 to 20 ng/kg) (Heindl and Hutzinger, 1987). Because no more recent or additional data could be found in the literature to confirm these values for products manufactured or used in the United States, no national estimates of CDD/CDF emissions are made for the inventory.

EPA's Office of Water promulgated effluent limitations for facilities that manufacture chlorinated aliphatic chlorine compounds and discharge treated wastewater (40 CFR 414.70). These effluent limitations do not specifically address CDDs and CDFs. The following chlorinated aliphatic compounds are regulated: 68 μg/L for 1,2-dichloroethane and 22 μg/L for tetrachloroethylene. Similarly, EPA's Office of Solid Waste promulgated restrictions on land disposal of wastes generated during manufacture of

many chlorinated aliphatics (40 CFR 268); however, these restrictions do not specifically regulate CDD/CDFs.

8.3.6. Dyes, Pigments, and Printing Inks

Several researchers analyzed various dyes, pigments, and printing inks obtained in Canada and Germany for the presence of CDDs and CDFs (Williams et al., 1992; Hutzinger and Fiedler, 1991a; Santl et al., 1994c). The following paragraphs discuss the findings of those studies.

Dioxazine Dyes and Pigments - Williams et al. (1992) analyzed the CDD/CDF content in dioxazine dyes and pigments available in Canada. As shown in Table 8-16, OCDD and OCDF concentrations in the ng/kg range, and HpCDD, HxCDD, and PeCDD concentrations in the μg/kg range were found in Direct Blue 106 dye (3 samples), Direct Blue 108 dye (1 sample), and Violet 23 pigments (6 samples) (Williams et al., 1992). These dioxazine pigments are derived from chloranil, which has been found to contain high levels of CDD/CDFs and has been suggested as the source of contamination among these dyes (Christmann et al., 1989a; Williams et al., 1992; U.S. EPA, 1992b). In May 1990, EPA received test results showing that chloranil was heavily contaminated with dioxins; levels as high as 3,065 μg I-TEQ_{DF}/kg (2,903 μg TEQ_{DF}-WHO_{98}/kg) were measured in samples from four importers (mean value of 1,754 μg I-TEQ_{DF}/kg or 1,388 μg TEQ_{DF}-WHO_{98}/kg) (U.S. EPA, 1992b; Remmers et al., 1992). (See Section 8.3.7 for analytical results.)

In the early 1990s, EPA learned that I-TEQ_{DF} levels in chloranil could be reduced by more than two orders of magnitude (to less than 20 μg/kg) through manufacturing feedstock and process changes. EPA's Office of Pollution Prevention and Toxics (OPPT) subsequently began efforts to complete an industrywide switch from the use of contaminated chloranil to low-dioxin chloranil. Although chloranil is not manufactured in the United States, significant quantities are imported. As of May 1992, EPA had negotiated agreements with all chloranil importers and domestic dye/pigment manufacturers known to EPA that use chloranil in their products to switch to low-dioxin chloranil. In May 1993, when U.S. stocks of chloranil with high levels of CDD/CDFs had been depleted, EPA proposed a significant new use rule (SNUR) under Section 5 of TSCA that requires industry to notify EPA at least 90 days prior to the manufacture, import, or

processing, for any use, of chloranil containing CDD/CDFs at a concentration greater than 20 μg I-TEQ$_{DF}$/kg (Federal Register, 1993a; U.S. EPA, 1993c).

In 1983, approximately 36,500 kg of chloranil were imported (U.S. ITC, 1984). The U.S. International Trade Commission (ITC) has not published quantitative import data for chloranil since 1984. If it is assumed that this import volume reflects actual usage of chloranil in the United States during 1987, and the CDD/CDF contamination level was 1,754 μg I-TEQ$_{DF}$/kg (1,388 μg TEQ$_{DF}$-WHO$_{98}$/kg), then the maximum release into the environment via processing wastes and finished products was 64.0 g I-TEQ$_{DF}$. If it is assumed that the import volume in 1995 was also 36,500 kg, but that the imported chloranil contained 10 μg I-TEQ$_{DF}$/kg on average, then the total potential annual TEQ release associated with chloranil in 1995 was 0.36 g I-TEQ$_{DF}$ (50.6 g TEQ$_{DF}$-WHO$_{98}$).

Phthalocyanine Dyes and Printing Inks - Hutzinger and Fiedler (1991a) found CDD/CDFs (tetra-, penta-, and hexachlorinated congeners) in the μg/kg range in a sample of a Ni-phthalocyanine dye. No CDD/CDFs were detected (detection limit of 0.1 to 0.5 μg/kg) in two samples of Cu-phthalocyanine dyes and in one Co-phthalocyanine dye (Hutzinger and Fiedler, 1991a).

Santl et al. (1994) reported the results of analyses of four printing inks obtained from a supplier in Germany. Two of the inks are used for rotogravure printing, and two are used for offset printing. The results of the analyses are presented in Table 8-17. The I-TEQ$_{DF}$ content of the inks ranged from 15.0 to 88.6 ng/kg (17.7 to 87.2 ng/kg on a TEQ$_{DF}$-WHO$_{98}$ basis). Primarily non-2,3,7,8-substituted congeners were found. The identities of the dyes and pigments in these inks were not reported.

8.3.7. TSCA Dioxin/Furan Test Rule

Citing evidence that halogenated dioxins and furans may be formed as by-products during chemical manufacturing processes (Versar, 1985), EPA issued a rule under Section 4 of TSCA that requires chemical manufacturers and importers to test for the presence of chlorinated and brominated dioxins and furans in certain commercial organic chemicals (Federal Register, 1987c). The rule listed 12 manufactured or imported chemicals that required testing and 20 chemicals not currently manufactured or imported that would require testing if manufacture or importation resumed. These chemicals are listed in Table 8-18. The specific dioxin and furan congeners that require quantitation and

the target limits of quantitation (LOQ) that are specified in the rule are listed in Table 8-19. Under Section 8(a) of TSCA, the final rule also required that chemical manufacturers submit data on manufacturing processes and reaction conditions for chemicals produced using any of the 29 precursor chemicals listed in Table 8-20. The rule stated that subsequent to this data-gathering effort, testing may be proposed for additional chemicals if any of the manufacturing conditions used favored the production of dioxins and furans.

Sixteen sampling and analytical protocols and test data for 10 of the 12 chemicals that required testing were submitted to EPA (Holderman and Cramer, 1995). Data from 15 submissions were accepted; one submission is under review. Manufacture or import of two substances (tetrabromobisphenol-A-bis-2,3-dibromopropylether and tetrabromobisphenol-A-diacrylate) have stopped since the test rule was promulgated. [Note: All data and reports in the EPA TSCA docket are available for public review and inspection at EPA Headquarters in Washington, DC.]

Table 8-21 presents the results of analytical testing for CDDs and CDFs for the chemicals that have data available in the TSCA docket. Five of these 10 chemicals contained CDD/CDFs. Positive results were obtained for 2,3,5,6-tetrachloro-2,5-cyclohexadiene-1,4-dione (chloranil), pentabromodiphenyloxide, octabromodiphenyloxide, decabromodiphenyloxide, and 1,2-Bis(tribromophenoxy)-ethane. Table 8-22 presents the quantitative analytical results for the four submitted chloranil samples, as well as the results of an EPA analysis of a sample of carbazole violet, which is manufactured from chloranil.

Although testing conducted under this test rule for 2,4,6-tribromophenol indicated no halogenated dioxins or furans above the LOQs, Thoma and Hutzinger (1989) reported detecting BDDs and BDFs in a technical-grade sample of this substance. Total TBDD, TBDF, and PeBDF were found at 84 µg/kg, 12 µg/kg, and 1 µg/kg, respectively. No hexa-, hepta-, or octa-BDFs were detected. Thoma and Hutzinger (1989) also analyzed analytical-grade samples of two other brominated flame retardants, pentabromophenol and tetrabromophthalic anhydride; no BDDs or BDFs were detected (detection limits not reported).

8.3.8. Halogenated Pesticides and FIFRA Pesticides Data Call-In

In the late 1970s and early 1980s, attention began to focus on pesticides as potential sources of CDDs and CDFs in the environment. Up to that time, CDD and CDF levels were not regulated in end-use pesticide products. Certain pesticide active ingredients, particularly chlorinated phenols and their derivatives, were known or suspected, however, to be contaminated with CDDs and CDFs. During the 1980s and 1990s, EPA took several actions to investigate and control CDD/CDF contamination of pesticides.

Actions to Regulate 2,4,5-T and Silvex: In 1983, EPA cancelled the sale of Silvex and 2,4,5-T for all uses (Federal Register, 1983). Earlier, in 1979, EPA had ordered emergency suspension of the forestry, rights-of-way, and pasture uses of 2,4,5-T. Emergency suspensions of the forestry, rights-of-way, pasture, home and garden, commercial/ornamental turf, and aquatic weed control/ditch bank uses of Silvex were also ordered (Federal Register, 1979; Plimmer, 1980). The home and garden, commercial/ornamental turf, and aquatic weed control/ditch bank uses of 2,4,5-T had been suspended in 1970.

Actions to Regulate pentachlorophenol (PCP): In 1984, EPA issued a notice of intent to cancel registrations of pesticide products containing PCP (including its salts) for all wood preservative uses (Federal Register, 1984). This notice specified modifications to the terms and conditions of product registrations that were required in order to avoid cancellation of the products. In response to this notice, several trade associations and registrants requested administrative hearings to challenge EPA's determinations. After carefully considering the comments and alternatives suggested during the prehearing stage of the administrative proceedings, EPA concluded that certain changes to the 1984 notice were appropriate. These were finalized in 1986 (Federal Register, 1986) and included the following: (i) all wood preservative uses of PCP and its salts were classified as "restricted use" only by certified applicators; (ii) specific worker protection measures were required; (iii) limits were placed on the HxCDD content of PCP; and (iv) label restrictions for home and farm uses of PCP prohibiting its application indoors and to wood intended for interior use (with a few exceptions), as well as prohibiting application of these products in a manner that may result in direct exposure of domestic animals or livestock, or in the contamination of food, feed, or drinking and irrigation water.

EPA subsequently amended the wood preservative uses Notice to establish reliable and enforceable methods for implementing certified limits for HxCDD and 2,3,7,8-TCDD in registered wood-preservative pesticide products (Federal Register, 1987a). Levels of 2,3,7,8-TCDD were not allowed to exceed 1.0 ppb in any product, and after February 2, 1989, any manufacturing-use PCP released for shipment could not contain HxCDD levels that exceeded an average of 2 ppm over a monthly release or a batch level of 4 ppm (a gradually phased in requirement). On January 21, 1987, EPA prohibited the registration of PCP and its salts for most nonwood uses (Federal Register, 1987b). EPA deferred action on several uses (i.e., uses in pulp/paper mills, oil wells, and cooling towers) pending receipt of additional exposure, use, and ecological effects data. On January 8, 1993, EPA issued a press advisory stating that the EPA special review of these deferred nonwood uses was being terminated, because all of these uses either had been voluntarily cancelled by the registrants or had been cancelled by EPA for failure of the registrants to pay the required annual maintenance fees (U.S. EPA, 1993f).

Pentachlorophenol (PCP) was one of the most widely used biocides in the United States prior to the regulatory actions to cancel and restrict certain wood and nonwood preservative uses of PCP. PCP was registered for use as a herbicide, defoliant, mossicide, and as a mushroom house biocide. It also found use as a biocide in pulp-paper mills, oil wells, and cooling towers. These latter three uses were terminated on or before 1993 (U.S. EPA, 1993f). However, the major use (greater than 80 percent of consumption) of PCP was and continues to be wood preservation.

The production of PCP for wood preserving began on an experimental basis in the 1930s. In 1947, nearly 3,200 metric tons of PCP were reported to have been used in the United States by the commercial wood preserving industry. Use in this industry steadily increased through the mid-1970s (American Wood Preservers Institute, 1977). Although domestic consumption volumes are not available for all years, based on historical production/export data for PCP reported in Mannsville (1983), it is estimated that 90 to 95 percent of production volume have typically been consumed domestically rather than exported. A reasonable estimate of average annual domestic PCP consumption during the period 1970 to 1995 is about 400,000 metric tons. This estimate assumes an average annual consumption rate of 20,000 metric tons/yr during the 1970s, 15,000 metric tons/yr during the 1980s, and 10,000 metric tons/yr during the 1990s.

Table 8-7 presents a compilation of published data on the CDD/CDF content of technical grade PCP. The only samples that have been analyzed for all dioxin-like CDD/CDFs were manufactured in the mid to late 1980s. Figure 8-4 presents these data in graphical form. It is evident from the figures that the predominant congener groups are OCDD, OCDF, HpCDF, and HpCDD, and the dominant 2,3,7,8-substituted congeners are OCDD, 1,2,3,4,6,7,8-HpCDD, and OCDF. Waddell et al. (1995) tested analytical grade PCP (from Aldrich Chemical Co.) for CDD/CDF content and found the same congener profile; however, the CDD/CDF levels were three to four orders of magnitude lower. Table 8-8 presents a similar compilation of published data on the CDD/CDF content of PCP-Na. The table shows the same patterns of dominant congeners and congener groups reported for PCP.

Samples of technical PCP manufactured during the mid to late 1980s contained about 3 mg I-TEQ/kg, (1.7 mg TEQ_{DF}-WHO_{98}/kg) based on the data presented in Table 8-7. No published reports could be located that present the results of any congener-specific analyses of PCP manufactured since the late 1980s. However, monthly measurements of CDD/CDF congener group concentrations in technical PCP manufactured for use in the United States have been reported to EPA from 1987 to the present (KMG-Bernuth, 1997; Pentachlorophenol Task Force, 1997; U.S. EPA, 1999a). The average congener group concentrations reported to EPA for the years 1988 (i.e., 1 year after EPA regulations were imposed limiting HxCDD and 2,3,7,8-TCDD concentrations in PCP) to 1999 are presented in Table 8-7. In general, the average congener group concentrations during the period 1988-1999 are lower by factors of 2 to 4 than observed in the mid to late 1980s full congener analysis samples. If it is assumed that the toxic CDD/CDF congeners have also been reduced by similar factors, then the TEQ content of PCP manufactured since 1988 is about 1 mg I-TEQ/kg (0.6 mg TEQ_{DF}-WHO_{98}/kg).

An estimated 8,400 metric tons of PCP were used for wood preservation in the United States in 1994 (American Wood Preservers Institute, 1995); for purposes of this report, it is assumed that an identical amount was used in 1995. An estimated 12,000 metric tons were used in 1987 (WHO, 1991). Combining these activity level estimates with the TEQ concentration estimates presented above indicates that 8,400 g I-TEQ_{DF} (4,800 g TEQ_{DF}-WHO_{98}) and 36,000 g I-TEQ_{DF} (20,000 g TEQ_{DF}-WHO_{98}) were incorporated into PCP-treated wood products in 1995 and 1987, respectively. This estimate for 1987

is assigned a high confidence rating, indicating high confidence in both the activity level and TEQ concentration in PCP estimates. The estimate for 1995 is assigned a medium confidence estimate because of uncertainties about the actual TEQ content of PCP manufactured in 1995.

Although the estimates of the mass of TEQ in treated wood are fairly certain, no studies are available that provide measured CDD/CDF release rate data from which a reliable estimate can be made of the amount of CDD/CDFs that have or will volatilize or leach from treated wood. Several recent field studies, discussed in the following paragraphs demonstrate that CDD/CDFs do apparently leach into soil from PCP-treated wood, but the studies do not provide release rate data. No studies were located that provide any measured CDD/CDF volatilization rates from PCP-treated wood. Although CDD/CDFs have very low vapor pressures, they are not bound nor react with the wood in any way that would preclude volatilization. Several studies, discussed below, have attempted to estimate potential CDD/CDF volatilization releases using conservative assumptions or modeling approaches, but these estimates span many orders of magnitude.

Gurprasad et al. (1995) analyzed three PCP-treated utility poles and their surrounding surface soils for penta- through octa-CDD content. All three poles showed significant levels of HxCDD (0.29 to 0.47 mg/kg), HpCDD (4.69 to 6.63 mg/kg), and OCDD (27.9 to 42.1 mg/kg), but no PeCDD. Surface soils collected 2 cm from the poles also had detectable levels of HxCDD, HpCDD, and OCDD; however, no consistent pattern was found between the CDD concentrations in the poles and in the adjacent soils. The soil concentrations did, however, show the same relative congener group pattern observed in the wood. CDD concentrations in soils obtained 20 cm from the poles were an order of magnitude less than the soil concentrations measured at 2 cm. Soils 26 meters from the poles showed nondetected values or values close to the detection limit of 0.01 to 0.02 mg/kg.

In a study of the leaching of PCP from 31 utility poles, the Electric Power Research Institute (EPRI) (1995) found similar patterns of PCP distribution in soils surrounding poles as those found by Gurprasad et al. (1995) for CDDs. PCP concentrations decreased by as much as two orders of magnitude between 7.5 cm from the poles and 20 cm from the poles, with an average decrease of slightly more than one order of magnitude over this

distance. EPRI (1995) also found no obvious trend between PCP concentration in the wood (eight poles analyzed) and the age of the poles (4 to 11 years) or the PCP concentration in the surface soil. Based on their results and those of EPRI (1995), Gurprasad et al. (1995) concluded that CDDs probably leach from PCP-treated utility poles with the PCP/oil carrier and travel in the soil in a similar manner.

Wan (1995) and Wan and Van Oostdam (1995) measured CDD/CDF concentrations in waters and sediments from ditches surrounding utility poles and railroad ties and demonstrated that chlorophenol-treated wood could serve as a source of CDD/CDFs to the aquatic environment. Ten samples were collected at each of six utility pole sites and five railroad tie sites 1 to 2 days after major rainfall events and then were composited into one sample per site prior to analyses. Total CDDs (mean value of 76.7 mg/kg) and total CDFs (mean value of 18.7 mg/kg) detected in chlorophenol/creosote-treated utility poles were about 6 to 8 times greater, respectively, than the CDD and CDF concentrations detected in chlorophenol/creosote-treated railroad ties. Total CDDs found in water from railway ditches without utility poles (i.e., only treated railroad ties were present) were approximately 20 times higher than the background level found in farm ditch water. Total CDDs in railway ditches with utility poles were 4,300 times higher than the background levels. Water from railway ditches without utility poles contained total CDF levels 13 times higher than background, whereas water in ditches adjacent to poles were 8,500 times higher than background. Total CDDs in ditches adjacent to, and 4 m downstream of, utility poles were about 5,900 and 2,200 times, respectively, higher than background; total CDFs for the same sites were about 8,100 and 1,700 times, respectively, higher than background. Total CDDs found in ditch sediments of railway and ditch sediments adjacent to utility poles were about 5 and 700 times, respectively, higher than background; while total CDFs were about 9 and 1,800 times, respectively, higher than background. Both CDDs and CDFs were found in utility ditch sediments 4 m downstream of treated power poles, but at levels of 200 and 400 times, respectively, lower than those found adjacent to poles, indicating that they were transported from point sources of contamination. The corresponding values for CDFs were 5,400 and 8,000 times, respectively, higher in concentration.

Bremmer et al. (1994) estimated an annual release of 15 to 125 g of I-TEQ_{DF} from PCP-treated wood in The Netherlands. The lower estimate was based on three basic

assumptions: (1) the half-life of PCP in treated wood is 15 years (according to industry sources); (2) the half-life of CDD/CDFs in treated wood is 10 times that of PCP (i.e., 150 years) because of the lower vapor pressures of CDD/CDFs relative to PCP; and (3) the typical CDD/CDF concentration in PCP has been 3,000 μg/kg. The higher estimate was based on an assumed half-life of PCP in wood of 15 years and the results of an indoor air study by Papke et al. (1989) conducted at several kindergartens where PCP-treated wood had been used. Although Papke et al. (1989) found no clear correlation between indoor air concentrations of CDD/CDF and PCP across the range of CDD/CDF concentrations observed in the 20-plus samples (2.6 to 427 pg CDD/CDF/m^3), there did appear to be a positive correlation at the sites with more elevated CDD/CDF concentrations. Bremmer et al. (1994) reported that the average ratio of PCP to I-TEQ $_{DF}$ air concentrations at these elevated sites was found to be $1{:}5x10^{-6}$ (or about the same ratio as the concentration of I-TEQ $_{DF}$ in technical PCP). The results of the Papke et al. (1989) study imply that CDD/CDFs may be released from PCP-treated wood at the same rate as PCP, rather than at a rate 10 times slower.

Rappe (1995) used the emission factor approach developed by Bremmer et al. (1994) and an assumed U.S. usage volume of PCP over the past 50 years (0.5 million metric tons) to estimate that as much as 10.5 kg of I-TEQ$_{DF}$ could volatilize from PCP-treated wood in the United States annually. Eitzer and Hites (1987) derived a dramatically different estimate of CDD/CDF volatilization from PCP-treated wood in the United States, 3 kg of total CDD/CDF per year (or 66 g of I-TEQ$_{DF}$ per year assuming an I-TEQ$_{DF}$ content in PCP of 3 mg/kg). Eitzer and Hites (1987) based their estimate on: (1) an assumption that 0.1 percent of the PCP produced annually enters the atmosphere, and (2) that the CDD/CDF contaminants present in the PCP (assumed to be 130 mg/kg) are released to the atmosphere at the same rate as the PCP (i.e., 0.1 percent). The basis for the first assumption of Eitzer and Hites (1987) is not clear because U.S. EPA (1980), which was cited as the source of the 0.1 percent emission factor, does not appear to address volatilization of PCP from in-service treated wood. The report does, however, estimate that most PCP in treated wood leaches relatively rapidly from the wood, presumably to land, within a period of 12 years.

Eduljee and Dyke (1996) and Douben et al. (1995) estimate that 0.8 g of I-TEQ$_{DF}$ is released to the air annually from PCP-treated wood in the U.K. This estimate is based on

the assumed emission of 0.1 percent of the CDD/CDF present in PCP-treated wood during the first year of the service life of the wood that was assumed by Eitzer and Hites (1987). No emission is assumed for subsequent years of use of the treated wood.

The California Air Resources Board (Chinkin et al., 1987) generated estimates of CDD/CDF volatilization releases at wood treatment facilities from bundles of treated wood that remain on-site for 1 month prior to shipment. An "adapted" version of a model developed by McCord (1981) was used for estimating volatile releases from a constantly filling lagoon. The model is primarily driven by chemical-specific vapor pressures and air diffusivity coefficients. Chinkin et al. (1987) do not provide all model input parameter values used to generate the emission estimates. However, running the model with typical dimensions for treated poles yields an I-TEQ_{DF} emission rate on the order of 6E-12 g/yr-pole, an extremely low number (i.e., 170 billion poles would together emit 1 g TEQ/yr).

Actions to Identify Other Pesticides Containing CDD/CDFs: In addition to cancelling some pesticide registrations and establishing product standards, EPA's Office of Pesticide Programs (OPP) issued two Data Call-Ins (DCIs) in 1987. Pesticide manufacturers are required to register their products with EPA in order to market them commercially in the United States. Through the registration process, mandated by FIFRA, EPA can require that the manufacturer of each active ingredient generate a wide variety of scientific data through several mechanisms. The most common process is the five-phase reregistration process with which the manufacturers (i.e., registrants) of older pesticide products must comply. In most registration activities, registrants must generate data under a series of strict testing guidelines, 40 CFR 158--Pesticide Assessment Guidelines (U.S.EPA, 1988b). EPA can also require additional data from registrants, when necessary, through various mechanisms, including the DCI process.

The purpose of the first DCI, dated June and October 1987, "Data Call-In Notice for Product Chemistry Relating to Potential Formation of Halogenated Dibenzo-p-dioxin or Dibenzofuran Contaminants in Certain Active Ingredients," was to identify, using an analysis of raw materials and process chemistry, those pesticides that may contain halogenated dibenzo-p-dioxin and dibenzofuran contaminants. The 93 pesticides (76 pesticide active ingredients) to which the DCI applied, along with their corresponding Shaughnessey and Chemical Abstract code numbers, are presented in Table 8-23. [Note: The Shaughnessey code is an internal EPA tracking system--it is of interest because

chemicals with similar code numbers are similar in chemical nature (e.g., salts, esters, and acid forms of 2,4-D).] All registrants supporting registrations for these chemicals were subject to the requirements of the DCI, unless their product qualified for a Generic Data Exemption (i.e., a registrant exclusively used a FIFRA-registered pesticide product(s) as the source(s) of the active ingredient(s) identified in Table 8-23 in formulating their product(s)). Registrants whose products did not meet the Generic Data Exemption were required to submit the types of data listed below to enable EPA to assess the potential for formation of tetra- through hepta-halogenated dibenzo-p-dioxin or dibenzofuran contaminants during manufacture. Registrants, however, had the option to voluntarily cancel their product or "reformulate to remove an active ingredient," to avoid having to comply with the DCI.

- Product Identity and Disclosure of Ingredients: EPA required submittal of a Confidential Statement of Formula (CSF), based on the requirements specified in 40 CFR 158.108 and 40 CFR 158.120 - Subdivision D: Product Chemistry. Registrants who had previously submitted still-current CSFs were not required to resubmit this information.
- Description of Beginning Materials and Manufacturing Process: Under the requirements mandated by 40 CFR 158.120 - Subdivision D, EPA required submittal of a manufacturing process description for each step of the manufacturing process, including specification of the range of acceptable conditions of temperature, pressure, or pH at each step.
- Discussion of the Formation of Impurities: Under the requirements mandated by 40 CFR 158.120 - Subdivision D, EPA required submittal of a detailed discussion and assessment of the possible formation of halogenated dibenzo-p-dioxins and dibenzofurans.

The second DCI, dated June and October 1987, “Data Call-In for Analytical Chemistry Data on Polyhalogenated Dibenzo-p-Dioxins/Dibenzofurans (HDDs and HDFs),” was issued for 68 pesticides (16 pesticide active ingredients) suspected to be contaminated by CDD/CDFs. (See Table 8-24.) All registrants supporting registrations for these pesticides were subject to the requirements of this DCI, unless the product qualified

for various exemptions or waivers. Pesticides covered by the second DCI were strongly suspected by EPA to contain detectable levels of CDD/CDFs.

Under the second DCI, registrants whose products did not qualify for an exemption or waiver were required to generate and submit the following types of data in addition to the data requirements of the first DCI:

- Quantitative Method for Measuring CDDs or CDFs: Registrants were required to develop an analytical method for measuring the HDD/HDF content of their products. The DCI established a regimen for defining the precision of the analytical method. Target limits of quantitation were established in the DCI for specific CDD and CDF congeners. (See Table 8-25.)
- Certification of Limits of CDDs or CDFs: Registrants were required to submit a "Certification of Limits" in accordance with 40 CFR 158.110 and 40 CFR 158.120 - Subdivision D. Analytical results were required that met the guidelines described above.

Registrants could select one of two options to comply with the second DCI. The first option was to submit relevant existing data, develop new data, or share the cost to develop new data with other registrants. The second option was to alleviate the DCI requirements through several exemption processes, including a Generic Data Exemption, voluntary cancellation, reformulation to remove the active ingredient of concern, an assertion that the data requirements do not apply, or the application or award of a low-volume, minor-use waiver.

The data contained in CSFs, as well as any other data generated under 40 CFR 158.120 - Subdivision D, are typically considered Confidential Business Information (CBI) under the guidelines prescribed in FIFRA, because they usually contain information regarding proprietary manufacturing processes. In general, all analytical results submitted to EPA in response to both DCIs are considered CBI and cannot be released by EPA into the public domain. Summaries based on the trends identified in that data, as well as data made public by EPA, are summarized below.

The two DCIs included 161 pesticides. Of these, 92 are no longer supported by registrants. Following evaluation of the process chemistry submissions required under the

DCIs, OPP determined that formation of CDD/CDFs was not likely during the manufacture of 43 of the remaining 69 pesticides; thus, analysis of samples of these 43 pesticides was not required by OPP. Evaluation of process chemistry data is ongoing at OPP for an additional seven pesticides. Tables 8-23 and 8-24 indicate which pesticides are no longer supported, those for which OPP determined that CDD/CDF formation is unlikely, and those for which process chemistry data or analytical testing results are under review in OPP (U.S. EPA, 1995f).

OPP required that analysis of production samples be performed on the remaining 19 pesticides. (See Table 8-26.) The status of the analytical data generation/evaluation to date is summarized as follows: (1) no detection of CDD/CDFs above the LOQs in registrant submissions for 13 active ingredients, (2) detection of CDD/CDFs above the LOQs for 2,4-D acid (two submissions) and 2,4-D 2-ethyl hexyl acetate (one submission), and (3) ongoing data generation or evaluation for four pesticides.

Table 8-25 presents a summary of results obtained by EPA for CDDs and CDFs in eight technical 2,4-D herbicides; these data were extracted from program files in OPP. Because some of these files contained CBI, the data in this table were reviewed by OPP staff to ensure that no CBI was being disclosed (Funk, 1996). Figure 8-5 presents a congener profile for 2,4-D based on the average congener concentrations reported in Table 8-25.

Schecter et al. (1997) reported the results of analyses of samples of 2,4-D manufactured in Europe, Russia, and the United States. (See Table 8-27.) The total TEQ concentrations measured in the European and Russian samples are similar to those measured in the EPA DCI samples; however, the levels reported by Schecter et al. (1997) for U.S. samples are significantly lower.

As discussed in Section 12.2.1, an estimated 26,300 metric tons of 2,4-D were used in the United States in 1995, making it one of the top 10 pesticides in terms of quantity used (U.S. EPA, 1997e). An estimated 30,400 metric tons were used during 1987 (U.S. EPA, 1988c). On the basis of the average CDD/CDF congener concentrations in 2,4-D presented in Table 8-25 (not including OCDD and OCDF), the corresponding I-TEQ_{DF} concentration is 0.70 μg/kg (1.10 μg TEQ_{DF}-WHO_{98}/kg). Combining this TEQ concentration with the activity level estimates for 1995 and 1987 indicates that 18.4 g I-TEQ_{DF} (28.9 g TEQ_{DF}-WHO_{98}) may have entered the environment in 1995 and 21.3 g I-

TEQ_{DF} (33.4 g TEQ_{DF}-WHO_{98}) may have entered the environment in 1987. These release estimates are assigned a high confidence rating, indicating high confidence in both the production and emission factor estimates.

8.4. OTHER CHEMICAL MANUFACTURING AND PROCESSING SOURCES

8.4.1. Municipal Wastewater Treatment Plants

Sources - CDD/CDFs have been measured in nearly all sewage sludges tested, although the concentrations and, to some extent, the congener profiles and patterns differ widely. Potential sources of the CDD/CDFs include microbial formation (discussed in Chapter 9), runoff to sewers from lands or urban surfaces contaminated by product uses or deposition of previous emissions to air (discussed in Section 12.2.1), household wastewater, industrial wastewater, chlorination operations within the wastewater treatment facility, or a combination of all the above (Rappe, 1992a; Rappe et al., 1994; Horstmann et al., 1992; Sewart et al., 1995; Cramer et al., 1995; Horstmann and McLachlan, 1995).

The major source(s) for a given Publicly Owned Treatment Works (POTW) is likely to be site-specific, particularly in industrialized areas. For example, Rieger and Ballschmiter (1992) traced the origin of CDDs and CDFs found in municipal sewage sludge in Ulm, Germany, to metal manufacturing and urban sources. The characteristics of both sources were similar and suggested generation via thermal processing. However, in a series of recent studies, Horstmann et al. (1992, 1993a, 1993b) and Horstmann and McLachlan (1994a, 1994b, 1995) demonstrated that wastewater generated by laundering and bathing could be the major source at many, if not all, POTWs that serve primarily residential populations. Although runoff from streets during precipitation events, particularly from streets with high traffic density, was reported by these researchers as contributing measurably, the total contribution of TEQ from household wastewater was eight times greater than that from surface runoff at the study city.

Horstmann et al. (1992) provided initial evidence that household wastewater could be a significant source. Horstmann et al. (1993a) measured CDD/CDF levels in the effluent from four different loads of laundry from two different domestic washing machines. The concentrations of total CDD/CDF in the four samples ranged from 3,900 to 7,100 pg/L and were very similar in congener profile, with OCDD being the dominant

congener followed by the hepta- and hexa-CDDs. Because of the similar concentrations and congener profiles found, Horstmann et al. (1993a) concluded that the presence of CDD/CDF in washing machine wastewater is widespread. A simple mass balance performed using the results showed that the CDD/CDFs found in the four washing machine wastewater samples could account for 27 to 94 percent of the total CDD/CDF measured in the sludge of the local wastewater treatment plant (Horstmann and McLachlan, 1994a).

Horstmann et al. (1993a) also performed additional experiments that showed that detergents, commonly used bleaching agents, and the washing cycle process itself were not responsible for the observed CDD/CDFs. To determine if the textile fabric or fabric finishing processes could account for the observed CDD/CDFs, Horstmann et al. (1993b), Horstmann and McLachlan (1994a, 1994b), and Klasmeier and McLachlan (1995) analyzed the CDD/CDF content of eight different raw (unfinished) cotton cloths containing fiber from different countries and five different white synthetic materials (acetate, viscose, bleached polyester, polyamide, and polyacrylic), as well as more than 100 new textile finished products. Low concentrations were found in most products (i.e., less than 50 ng/kg of total CDD/CDF), but a small percentage contained high concentrations up to 290 μg/kg of total CDD/CDF. On the basis of the concentrations and patterns found, the authors concluded that neither unfinished new fabrics nor common cotton finishing processes can explain the CDD/CDF levels found in wastewater. Rather, the use of CDD/CDF-containing textile dyes and pigments and the use in some developing countries of pentachlorophenol to treat unfinished cotton appear to be the sources of the detected CDDs/CDFs.

Horstmann and McLachlan (1994a, 1994b, 1995) reported the results of additional experiments that demonstrated that the small percentage of clothing items with high CDD/CDF levels could be responsible for the quantity of CDD/CDFs observed in household wastewater and sewage sludge. They demonstrated that the CDD/CDFs can be gradually removed from the fabric during washing, can be transferred to the skin, subsequently transferred back to other textiles, and then washed out, or can be transferred to other textiles during washing and then removed during subsequent washings.

Releases to Water - The presence of CDD/CDFs in sewage sludge suggests that CDD/CDFs may also be present in the wastewater effluent discharges of POTWs;

however, few studies reporting the results of effluent analyses for CDD/CDFs have been published.

Rappe et al. (1989a) tested the effluent from two Swedish POTWs for all 2,3,7,8-substituted CDD/CDF congeners. OCDD was detected in the effluents from both facilities at concentrations ranging from 14 to 39 pg/L. Rappe et al. detected 1,2,3,4,6,7,8-HpCDD and 1,2,3,4,6,7,8-HpCDF in the effluent of one facility at concentrations of 2.8 and 2.0 pg/L, respectively. No 2,3,7,8-substituted tetra-, penta-, and hexa-CDDs and CDFs were detected (detection limits of 0.2 to 20 pg/L).

Ho and Clement (1990) reported the results of sampling during the late 1980s of 37 POTWs in Ontario, Canada, for each of the five CDD/CDF congener groups with four to eight chlorines. The sampled facilities included 27 secondary treatment facilities, 7 primary treatment facilities, 1 tertiary plant, and 2 lagoons. The facilities accounted for about 73 percent of the sewage discharged by POTWs in Ontario. No CDDs/CDFs were detected (detection limit in low ng/L range) in the effluents from the lagoons and the tertiary treatment facility. Only OCDD and TCDF were detected in the effluents from the primary treatment facilities (two and one effluent samples, respectively). HpCDD, OCDD, TCDF, and OCDF were detected in the effluents from the secondary treatment facilities (detected in four or fewer samples at levels ranging from 0.1 to 11 ng/L).

Gobran et al. (1995) analyzed the raw sewage and final effluent of an Ontario, Canada, wastewater treatment plant for CDD/CDF congeners over a 5-day period. Although HpCDD, OCDD, HpCDF, and OCDF were detected in the raw sewage (12 to 2,300 pg/L), no CDD/CDFs were detected in the final effluent at congener-specific detection limits ranging from 3 to 20 pg/L.

The California Regional Water Quality Control Board (CRWQCB, 1996) reported the results of effluent testing at nine POTWs in the San Francisco area. A total of 30 samples were collected during 1992-1995; 1 to 6 samples were analyzed for each POTW. Table 8-28 summarizes the sampling results. With the exception of OCDD, most 2,3,7,8-substituted CDD/CDF congeners were seldom detected.

The CRWQCB (1996) data were collected to provide representative effluent concentrations for the San Francisco area; these data cannot be considered to be representative of CDD/CDF effluent concentrations at the 16,000-plus POTWs nationwide. Therefore, the data can only be used to generate a preliminary estimate of the potential

mass of CDD/CDF TEQ that may be released annually by U.S. POTWs. Approximately 122 billion liters of wastewater are treated daily by POTWs in the United States (U.S. EPA, 1997c). Multiplying this value by 365 days/year and by the "overall mean" TEQ concentrations listed in Table 8-28 (i.e., 0.29 pg I-TEQ_{DF}/L and 0.27 pg TEQ_{DF}-WHO_{98}/L) yields annual TEQ release estimates of 13 g of I-TEQ_{DF} or 12 g of TEQ_{DF}-WHO_{98}.

Sewage Sludge Land Disposal - EPA conducted the National Sewage Sludge Survey in 1988 and 1989 to obtain national data on sewage sludge quality and management. As part of this survey, EPA analyzed sludges from 174 POTWs that employed at least secondary wastewater treatment for more than 400 analytes, including CDD/CDFs. Although sludges from only 16 percent of the POTWs had detectable levels of 2,3,7,8-TCDD, all sludges had detectable levels of at least one CDD/CDF congener (U.S. EPA, 1996a). I-TEQ_{DF} concentrations as high as 1,820 ng/kg dry weight were measured. The congener-specific results of the survey are presented in Table 8-29. If all nondetected values found in the study are assumed to be zero, then the mean and median I-TEQ_{DF} concentrations of the sludges from the 174 POTWs are 50 and 11.2 ng/kg (dry weight basis), respectively. If the nondetected values are set equal to the detection limit, then the mean and median I-TEQ_{DF} concentrations are 86 and 50.4 ng/kg, respectively (U.S. EPA, 1996a; Rubin and White, 1992).

Green et al. (1995) and Cramer et al. (1995) reported the results of analyses of 99 samples of sewage sludge collected from wastewater treatment plants across the United States during the summer of 1994. These data are summarized in Table 8-30. To calculate average results in units of TEQ, Green et al. (1995) averaged results from all samples collected from the same facility to ensure that results were not biased toward the concentrations found at facilities from which more than one sample were collected. Also, eight samples were excluded from the calculation of the overall TEQ averages because it was unclear as to whether they were duplicate samples from other POTWs. POTW average TEQ concentrations were calculated for 74 POTWs. If all nondetected values are assumed to be zero, then the overall study mean and median I-TEQ_{DF} concentrations were 47.7 and 33.4 ng I-TEQ_{DF}/kg (dry weight basis), respectively (standard deviation of 44.7 ng I-TEQ_{DF}/kg). The corresponding mean and median TEQ_{DF}-WHO_{98} concentrations were 36.3 and 25.5 ng TEQ_{DF}-WHO_{98}/kg, respectively (standard deviation of 38.6 ng TEQ_{DF}-WHO_{98}/kg). The mean and median results reported by Green et al. (1995) and Cramer et

al. (1995) are very similar in terms of total TEQ to those reported by EPA for samples collected 5 years earlier (U.S. EPA, 1996a; Rubin and White, 1992). The predominant congeners in both data sets are the octa- and hepta-CDDs and -CDFs. Although not present at high concentrations, 2,3,7,8-TCDF was commonly detected.

The CDD/CDF concentrations and congener group patterns observed in these two U.S. surveys are similar to the results reported for sewage sludges in several other Western countries. Stuart et al. (1993) reported mean CDD/CDF concentrations of 23.3 ng I-TEQ_{DF}/kg (dry weight) for three sludges from rural areas, 42.3 ng I-TEQ_{DF}/kg for six sludges from light industry/domestic areas, and 52.8 ng I-TEQ_{DF}/kg for six sludges from industrial/domestic areas collected during 1991-1992 in England and Wales. Näf et al. (1990) reported concentrations ranging from 31 to 40 ng I-TEQ_{DF}/kg (dry weight) in primary and digested sludges collected from the POTW in Stockholm, Sweden, during 1989. Gobran et al. (1995) reported an average concentration of 15.7 ng I-TEQ_{DF}/kg in anaerobically digested sludges from an industrial/domestic POTW in Ontario, Canada. In all three studies, the congener group concentrations increased with increasing degrees of chlorination, with OCDD the dominant congener. Figure 8-6 presents congener profiles, using the mean concentrations reported by Green et al. (1995).

Approximately 5.4 million dry metric tons of sewage sludge are estimated by EPA to be generated annually in the United States according to the results of the 1988/1989 EPA National Sewage Sludge Survey (Federal Register, 1993b). Table 8-31 lists the volume, by use and disposal practices, of sludge disposed of annually. More recent comprehensive survey data are not available to characterize sludge generation and disposal practices during 1995. For this reason, and because the mean I-TEQ_{DF} concentration values reported in the 1988/1989 survey (U.S. EPA, 1996a) and the 1995 survey (Green et al., 1995; Cramer et al., 1995) were very similar, the estimated amounts of TEQs that may have been present in sewage sludge and been released to the environment in 1987 and 1995 were assumed to be the same. These values, presented in Table 8-31, were estimated using the average (i.e., 49 ng I-TEQ_{DF}/kg) of the mean I-TEQ_{DF} concentration values (nondetected values set at detection limits) reported by EPA (1996a) (i.e., 50 ng I-TEQ_{DF}/kg) and by Green et al. (1995) and Cramer et al. (1995) (i.e., 47.7 ng I-TEQ_{DF}/kg). Multiplying this mean total TEQ concentration by the sludge volumes generated yields an annual potential total release of 204 g I-TEQ_{DF} or 151 g TEQ_{DF}-WHO_{98}

for nonincinerated sludges. Of this 204 g I-TEQ_{DF}, 3.5 g enter commerce as a product for distribution and marketing. The remainder is applied to land (103 g) or is landfilled (97 g). In units of TEQ_{DF}-WHO_{98}, the comparable estimates are 2.6 g to commerce, 76.6 g applied to land, and 71.7 g landfilled.

These release estimates are assigned a high confidence rating for both the production and emission factor estimates. The high rating was based on the judgment that the 174 facilities tested by EPA (U.S. EPA, 1996a) and the 74 facilities tested by Green et al. (1995) and Cramer et al. (1995) were reasonably representative of the variability in POTW technologies and sewage characteristics nationwide.

8.4.2. Drinking Water Treatment Plants

There is no strong evidence that chlorination of water for drinking purposes results in the formation of CDD/CDFs. Few surveys of CDD/CDF content in finished drinking water have been conducted. The few that have been published only rarely report the presence of any CDD/CDF even at low pg/L detection limits, and in those cases, the CDD/CDFs were also present in the untreated water.

Rappe et al. (1989b) reported the formation of CDFs (tetra- through octa-chlorinated CDFs) when tap water and double-distilled water were chlorinated using chlorine gas. The CDF levels found in the single samples of tap water and double-distilled water were 35 and 7 pg I-TEQ_{DF}/L, respectively. No CDDs were detected at detection limits ranging from 1 to 5 pg/L. However, the water samples were chlorinated at a dosage rate of 300 mg of chlorine per liter of water, which is considerably higher (by a factor of one to two orders of magnitude) than the range of dosage rates typically used to disinfect drinking water. Rappe et al. (1989b) hypothesized that the CDFs or their precursors are present in chlorine gas. Rappe et al. (1990a) analyzed a 1,500-liter sample of drinking water from a municipal drinking water treatment plant in Sweden. Although the untreated water was not analyzed, a sludge sample from the same facility was. The large sample volume enabled detection limits on the order of 0.001 pg/L. The TEQ content of the water and sludge was 0.0029 pg I-TEQ_{DF}/L and 1.4 ng/kg, respectively. The congener patterns of the drinking water and sludge sample were very similar, suggesting that the CDD/CDFs detected in the finished water were present in the untreated water.

8.4.3. Soaps and Detergents

As discussed in Section 8.4.1, CDD/CDFs were detected in nearly all sewage sludges tested, whether obtained from industrialized areas or rural areas. Because of the ubiquitous presence of CDD/CDFs in sewage sludge, several studies have been conducted to determine the source(s). A logical category of products to test, because of their widespread use are detergents, particularly those that contain or release chlorine during use (i.e., hypochlorite-containing and dichloroisocyanuric acid-containing detergents). The results of studies conducted to date, which are summarized below, indicate that CDD/CDFs are not formed during use of chlorine-free detergents, chlorine-containing or chlorine-releasing detergents, and chlorine bleach during household bleaching operations.

Sweden's Office of Nature Conservancy (1991) reported that the results of a preliminary study conducted at one household indicated that CDD/CDFs may be formed during use of dichloroisocyanurate-containing dishwasher detergents. A more extensive main study was then conducted using standardized food, dishes, cutlery, etc., and multiple runs. Testing of laundry washing and fabric bleaching, and actual testing of the CDD/CDF content of detergents, was also performed. The study examined (1) hypochlorite- and dichloroisocyanurate-containing dish-washing machine detergents; (2) sodium hypochlorite-based bleach (4.4 percent NaOCl) in various combinations with and without laundry detergent; and (3) sodium hypochlorite-based bleach, used at a high enough concentration to effect bleaching of a pair of imported blue jeans. CDD/CDFs were not detected in either the chlorine-free detergent or the detergent with hypochlorite; 0.6 pg TEQ/g was detected in the detergent containing dichloroisocyanurate. The results of all dish and laundry washing machine tests showed very low levels of CDD/CDFs, often nondetected values. There was no significant difference between the controls and test samples. In fact, the control samples contained higher TEQ content than some of the experimental samples. The drain water from the dish washing-machine tests contained <1.0 to <3.0 pg I-TEQ_{DF}/L (the water-only control sample contained <2.8 pg I-TEQ_{DF}/L). The CDD/CDF content of the laundry drain water samples ranged from <1.1 to <4.6 pg I-TEQ_{DF}/L (the water-only control sample contained <4.4 pg I-TEQ_{DF}/L).

Thus, under the test conditions examined by Sweden's Office of Nature Conservancy (1991), CDD/CDFs are not formed during dish washing and laundry washing nor during bleaching with hypochlorite-containing bleach. No definitive reason could be

found to explain the difference in results between the preliminary study and the main study for dish washing with dichloroisocyanurate-containing detergents. The authors of the study suggested that differences in the foods used and the prewashing procedures employed in the two studies were the likely causes of the variation in the results.

Rappe et al. (1990c) analyzed a sample of a Swedish commercial soft soap, as well as a sample of tall oil and a sample of tall resin, for CDD/CDF content. Tall oil and tall resin, by-products of the pulping industry, are the starting materials for the production of soft, liquid soap. Crude tall oil, collected after the Kraft pulping process, is distilled under reduced pressure at temperatures of up to 280-290°C, yielding tall oil and tall resin. The measured TEQ content of the liquid soap was 0.447 ng I-TEQ_{DF}/L (0.647 ng TEQ_{DF}-WHO_{98}/L). PeCDDs were the dominant congener group followed by HpCDDs, HxCDDs, PeCDFs, and OCDD with some tetra-CDFs and -CDDs also present. The TEQ content of the tall oil (9.4 ng I-TEQ_{DF}/kg, or 12.0 ng TEQ_{DF}-WHO_{98}/kg) and tall resin (200 ng I-TEF_{DF}/kg, 196 ng TEQ_{DF}-WHO_{98}/kg) was significantly higher than the level found in the liquid soap. The tall oil contained primarily tetra- and penta-CDDs and -CDFs, while the tall resin contained primarily HpCDDs, HxCDDs, and OCDD. Rappe et al. (1990c) compared the congener patterns of the three samples and noted that although the absolute values for the tetra- and penta-CDDs and -CDFs differed between the tall oil, tall resin and liquid soap samples, the same congeners were present in the samples. The congener patterns for the more chlorinated congeners were very similar. Table 8-32 presents the results reported by Rappe et al. (1990c).

In 1987, 118 million liters of liquid household soaps were shipped in the United States (U.S. DOC, 1990b); shipment quantity data are not available for liquid household soap in the 1992 U.S. Economic Census (U.S. DOC, 1996). Because only one sample of liquid soap has been analyzed for CDD/CDF content (Rappe et al., 1990c), only a very preliminary estimate of the annual release of CDD/CDF TEQ from liquid soap can be made. If it is assumed that an average 118 million liters of liquid soap contain 0.447 ng I-TEQ_{DF}/L (0.647 ng TEQ_{DF}-WHO_{98}/L), then the resulting estimate is 0.05 g I-TEQ_{DF}/yr (0.08 g TEQ_{DF}-WHO_{98}/yr).

8.4.4. Textile Manufacturing and Dry Cleaning

As discussed in Section 8.4.1, CDD/CDFs have been detected in nearly all sewage sludges tested, whether obtained from industrialized areas or rural areas. To determine if the textile fabric or fabric finishing processes could account for the observed CDD/CDFs, several studies were conducted in Germany. These studies, summarized in the following paragraphs, indicate that some finished textile products do contain detectable levels of CDD/CDFs and that these CDD/CDFs can be released from the textile during laundering or dry cleaning; however, textile finishing processes are typically not sources of CDD/CDF formation. Rather, the use of CDD/CDF-containing dyes and pigments and the use in some countries of pentachlorophenol to treat unfinished cotton appear to be the sources of the detected CDD/CDFs.

Horstmann et al. (1993b) analyzed the CDD/CDF content of eight different raw (unfinished) cotton cloths containing fiber from different countries and five different white synthetic materials (acetate, viscose, bleached polyester, polyamide, and polyacrylic). The maximum concentrations found in the textile fabrics were 30 ng/kg in the cotton products and 45 ng/kg in the synthetic materials. Also, a cotton finishing scheme was developed that subjected one of the cotton materials to a series of 16 typical cotton finishing processes; one sample was analyzed following each step. The fabric finishing processes showing the greatest effect on CDD/CDF concentration were the application of an indanthrene dye and the "wash and wear" finishing process, which together resulted in a CDD/CDF concentration of about 100 ng/kg. On the basis of the concentrations found, the authors concluded that neither unfinished new fabrics nor common cotton finishing processes can explain the CDD/CDF levels found in laundry wastewater.

Fuchs et al. (1990) reported that dry-cleaning solvent redistillation residues that were collected from 12 commercial and industrial dry-cleaning operations contained considerable amounts of CDD/CDFs. The reported I-TEQ_{DF} content ranged from 131 to 2,834 ng/kg, with the dominant congeners always OCDD and the HpCDDs. Towara et al. (1992) demonstrated that neither the use of chlorine-free solvents nor variation of the dry-cleaning process parameters lowered the CDD/CDF content of the residues.

Umlauf et al. (1993) conducted a study to characterize the mass balance of CDD/CDFs in the dry-cleaning process. The soiled clothes (containing 16 pg total CDD/CDF per kg) accounted for 99.996 percent of the CDD/CDF input. Input of CDD/CDF

from indoor air containing 0.194 pg/m^3 accounted for the remainder (i.e., 0.004 percent). The dry-cleaning process removed 82.435 percent of the CDD/CDF in the soiled clothing. Most of the input CDD/CDF (82.264 percent) was found in the solvent distillation residues. Air emissions (at 0.041 pg/m^3) accounted for 0.0008 percent of the total input, which was less than the input from indoor air. The fluff (at a concentration of 36 ng/kg) accounted for 0.1697 percent, and water effluent (at a concentration of 0.07 pg/L) accounted for 0.0000054 percent.

Horstmann and McLachlan (1994a, 1994b, 1995) analyzed 35 new textile samples (primarily cotton products) obtained in Germany for CDD/CDFs. Low levels were found in most cases (total CDD/CDF less than 50 ng/kg). The dominant congeners found were OCDD and the HpCDDs. However, several colored T-shirts from a number of clothing producers had extremely high levels, with concentrations up to 290,000 ng/kg. Because the concentrations in identical T-shirts purchased at the same store varied by up to a factor of 20, the authors concluded that the source of CDD/CDFs is not a textile finishing process, because a process source would have resulted in a more consistent level of contamination. Klasmeier and McLachlan (1995) subsequently analyzed 68 new textile products obtained in Germany for OCDD and OCDF. Most samples had nondetectable levels (42 samples $<$60 ng/kg). Only four samples had levels exceeding 500 ng/kg.

Horstmann and McLachlan (1994a, 1994b) reported finding two different congener group patterns in the more contaminated of the 35 textile products. One pattern agreed with the congener pattern for PCP reported by Hagenmaier and Brunner (1987), while the other pattern was similar to that reported by Remmers et al. (1992) for chloranil-based dyes. The authors hypothesize that the use of PCP to preserve cotton, particularly when it is randomly strewn on bales of cotton as a preservative during sea transport, is the likely source of the high levels occasionally observed. Although the use of PCP for nonwood uses was prohibited in the United States in 1987 (see Section 8.3.8), PCP is still used in developing countries, especially to preserve cotton during sea transport (Horstmann and McLachlan, 1994a).

Horstmann and McLachlan (1994a, 1994b) conducted additional experiments that demonstrated that the small percentage of clothing items with high CDD/CDF levels could be responsible for the quantity of CDD/CDFs observed in household wastewater. They demonstrated that the CDD/CDFs can be gradually removed from the fabric during

washing, can be transferred to the skin and subsequently transferred back to other textiles and then washed out, or can be transferred to other textiles during washing and then removed during subsequent washings.

Table 8-1. CDD/CDF Concentrations in Pulp and Paper Mill Bleached Pulp, Wastewater Sludge, and Effluent (circa 1988)

Congener/Congener Group	Bleached Pulp			Wastewater Sludge			Wastewater Effluent		
	Median (ng/kg)	Range (ng/kg)	No. of Detects (10 samples)	Median (ng/kg)	Range (ng/kg)	No. of Detects (9 samples)	Median (pg/L)	Range (pg/L)	No. of Detects (9 samples)
2,3,7,8-TCDD	6.4	0.4 to 124	10	63	ND (6.3) to 180	8	42	ND (11) to 98	8
1,2,3,7,8-PeCDD	ND (0.3)	ND (0.1) to 1.4	2	ND (2.5)	ND (1.4) to 28	1	ND (9.6)	ND (2.8) to ND (25)	0
1,2,3,4,7,8-HxCDD	ND (0.4)	ND (0.2) to 0.4	1	ND (3.1)	ND (1.5) to 40	1	ND (12)	ND (6.6) to ND (12)	0
1,2,3,6,7,8-HxCDD	ND (0.5)	ND (0.2) to 1.6	2	ND (3.2)	ND (1.7) to 95	1	ND (12)	ND (6.6) to ND (24)	0
1,2,3,7,8,9-HxCDD	ND (0.5)	ND (0.2) to 0.5	1	ND (3.9)	ND (1.7) to 80	1	ND (12)	ND (6.6) to ND (23)	0
1,2,3,4,6,7,8-HpCDD	3.3	2.3 to 8.4	10	37	18 to 490	9	170	77 to 270	9
OCDD	46	28 to 81	10	698	263 to 1,780	9	3,000	1,000 to 4,600	9
2,3,7,8-TCDF	18	1.4 to 716	10	233	13 to 1,150	9	120	12 to 840	9
1,2,3,7,8-PeCDF	ND (0.7)	ND (0.1) to 3.9	4	6.2	ND (1.2) to 22	6	ND (7.2)	ND (2.2) to 36	2
2,3,4,7,8-PeCDF	ND (0.2)	ND (0.1) to 4.7	3	4.7	ND (0.9) to 38	6	ND (6.3)	ND (2.2) to 33	2
1,2,3,4,7,8-HxCDF	ND (0.3)	ND (0.2) to ND (0.6)	0	ND (2.5)	ND (0.9) to 31	2	ND (8.4)	ND (4.8) to ND (15)	0
1,2,3,6,7,8-HxCDF	ND (0.3)	ND (0.1) to ND (0.4)	0	ND (1.4)	ND (0.9) to 33	1	ND (7.1)	ND (4.8) to ND (15)	0
1,2,3,7,8,9-HxCDF	ND (0.3)	ND (0.1) to ND (0.4)	0	ND (1.7)	ND (0.9) to ND (4.0)	0	ND (6.2)	ND (2.5) to ND (15)	0
2,3,4,6,7,8-HxCDF	ND (0.3)	ND (0.2) to ND (0.4)	0	ND (1.7)	ND (0.9) to 34	1	ND (8.2)	ND (4.8) to ND (15)	0
1,2,3,4,6,7,8-HpCDF	ND (0.6)	ND (0.1) to 0.8	3	6.6	ND (3.6) to 70	7	ND (23)	ND (13) to 44	3
1,2,3,4,7,8,9-HpCDF	ND (0.6)	ND (0.1) to ND (2.1)	0	ND (1.6)	ND (1.2) to 10	1	ND (22)	ND (6.4) to ND (41)	0
OCDF	2.2	ND(2.8) to 4.3	8	22	ND (54) to 168	8	190	ND (180) to 230	8
Total 2,3,7,8-CDD[a,b]	55.7			798			3,212		
Total 2,3,7,8-CDF[a,b]	18			272.5			310		
Total I-TEQ_{DF} (ND = zero)[b]	8.28			90.12			58.89		
Total I-TEQ_{DF} (ND = ½ DL)[b]	8.56			91.72			66.57		
Total TEQ_{DF}-WHO_{98} (ND = zero)[b]	8.24		89.47				56.02		
Total TEQ_{DF}-WHO_{98} (ND = ½ DL)[b]	8.59		91.7				66.09		
Total CDD/CDF[b]	120			1,695			4,013		

ND = Not detected; value in parentheses is the detection limit.
ng/kg = nanograms per kilogram
pg/L = picograms per liter

[a] Calculated assuming nondetected values are zero.
[b] Sum of median values.

Source: U.S. EPA (1990a).

Table 8-2. CDD/CDF Concentrations in Pulp and Paper Mill Bleached Pulp, Wastewater Sludge, and Effluent (circa 1996)

Congener/Congener Group	Bleached Pulp				Wastewater Sludge				Wastewater Effluent			
	Mean ND = 0 (ng/kg)	Median (ng/kg)	Range (ng/kg)	No. of Detects/ No. of Samples	Mean ND = 0 (ng/kg)	Median (ng/kg)	Range (ng/kg)	No. of Detects/ No. of Samples	Mean ND = 0 (pg/L)	Median (ng/kg)	Range (pg/L)	No. of Detects/ No. of Samples
2,3,7,8-TCDD	0.3	ND(1)	ND(1) to 5	1/18	0.8	ND(1)	ND(1) to 4	4/12	1.2	ND(11)	ND(10) to 21	1/18
1,2,3,7,8-PeCDD	0	ND(5)	ND(3) to ND(7)	0/18	0	ND(5)	ND(4) to ND(52)	0/12	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,4,7,8-HxCDD	0	ND(5)	ND(3) to ND(7)	0/18	0.5	ND(5)	ND(4) to 7	1/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,6,7,8-HxCDD	0	ND(5)	ND(3) to ND(7)	0/18	2.3	ND(5)	ND(4) to 18	2/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,7,8,9-HxCDD	0	ND(5)	ND(3) to ND(7)	0/18	1.6	ND(5)	ND(4) to 14	2/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,4,6,7,8-HpCDD	0	ND(5)	ND(3) to ND(7)	0/18	41.4	7	ND(4) to 330	9/13	3.2	ND(53)	ND(50) to 58	1/18
OCDD	2.4	ND(10)	ND(10) to 15	3/16	445	150	21 to 2,900	10/10	99.0	ND(110)	ND(100) to 370	6/14
2,3,7,8-TCDF	10.3	ND(1)	ND(1) to 170	7/18	6.2	3	ND(1) to 31	9/12	2.3	ND(11)	ND(10) to 23	2/18
1,2,3,7,8-PeCDF	0	ND(5)	ND(3) to ND(7)	0/18	0	ND(5)	ND(4) to ND(52)	0/13	0	ND(53)	ND(50) to ND(55)	0/18
2,3,4,7,8-PeCDF	0.4	ND(5)	ND(3) to 7	1/18	0.5	ND(5)	ND(4) to 7	1/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,4,7,8-HxCDF	0	ND(5)	ND(3) to ND(7)	0/18	0	ND(5)	ND(4) to ND(52)	0/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,6,7,8-HxCDF	0	ND(5)	ND(3) to ND(7)	0/18	0	ND(5)	ND(4) to ND(52)	0/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,7,8,9-HxCDF	0	ND(5)	ND(3) to ND(7)	0/18	0	ND(5)	ND(4) to ND(52)	0/13	0	ND(53)	ND(50) to ND(55)	0/18
2,3,4,6,7,8-HxCDF	0	ND(5)	ND(3) to ND(7)	0/18	0.5	ND(5)	ND(4) to 6	1/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,4,6,7,8-HpCDF	0	ND(5)	ND(3) to ND(7)	0/18	1.2	ND(5)	ND(4) to 10	2/13	0	ND(53)	ND(50) to ND(55)	0/18
1,2,3,4,7,8,9-HpCDF	0	ND(5)	ND(3) to ND(7)	0/18	0	ND(5)	ND(4) to ND(52)	0/13	0	ND(53)	ND(50) to ND(55)	0/18
OCDF	0	ND(10)	ND(6) to ND(14)	0/18	0	ND(10)	ND(9) to ND(100)	0/13	0	ND(106)	ND(104) to ND(110)	0/18
Total 2,3,7,8-CDD[a]	2.7				492				103			
Total 2,3,7,8-CDF[a]	10.7				8.4				2.3			
Total I-TEQ_{DF} (ND = zero)[a]	1.53				3.0				1.5			
Total I-TEQ_{DF} (ND = ½ DL)[a]	6.4				12.9				53.6			
Total TEQ_{DF}-WHO_{98} (ND = zero)[a]	1.5				2.6				1.4			
Total TEQ_{DF}-WHO_{98} (ND = ½ DL)[a]	7.6				15.2				66.5			

ND = Not detected; value in parentheses is the detection limit.
ng/kg = nanograms per kilogram
pg/L = picograms per liter

[a] Sum of mean values.

Source: Gillespie (1997).

Table 8-3. Summary of Bleached Chemical Pulp and Paper Mill Discharges of 2,3,7,8-TCDD and 2,3,7,8-TCDF

Matrix	Congener	EPA 1988 Discharge[a] (g/year)	NCASI 1992 Discharge[b] (g/year)	EPA 1993 Discharge[c] (g/year)	NCASI 1993 Discharge[b] (g/year)	NCASI 1994 Discharge[b] (g/year)	EPA 1995 Discharge[e] (g/year)
Effluent	2,3,7,8-TCDD	201	22	71	19	14.6	16
	2,3,7,8-TCDF	1,550	99	341	76	49.0	120
	TEQ	356	32	105	27	19.5	28
Sludge[d]	2,3,7,8-TCDD	210	33	NR	24	18.9	NR
	2,3,7,8-TCDF	1,320	118	NR	114	95.2	NR
	TEQ	343	45	177	35	28.4	50
Pulp	2,3,7,8-TCDD	262	24	NR	22	16.2	NR
	2,3,7,8-TCDF	2,430	124	NR	106	78.8	NR
	TEQ	505	36	149	33	24.1	40

NR = Not reported.
g/year = grams per year

[a] The total discharge rate of congener or TEQ (based only on 2,3,7,8-TCDD and 2,3,7,8-TCDF concentration) was summed across all 104 mills. 104-Mill Study (U.S. EPA, 1990a).

[b] The total discharge rate of congener or TEQ (based only on 2,3,7,8-TCDD and 2,3,7,8-TCDF concentration) was summed across all 104 mills. The daily discharge rates reported in NCASI (1993), Gillespie (1994), and Gillespie (1995) were multiplied by a factor of 350 days/yr to obtain estimates of annual discharge rates. NCASI 1992 Survey (NCASI, 1993), 1993 Update (Gillespie, 1994), and 1994 Update (Gillespie, 1995).

[c] The discharges in effluent and sludge were estimated in U.S. EPA (1993d; 1997f) for January 1, 1993. The TEQ discharge in pulp was estimated by multiplying the 1988 discharge estimate by the ratio of the 1993 and 1988 effluent discharge estimates (i.e., the estimate of the reduction in 1988 discharges achieved by pollution prevention measures taken by the industry between 1988 and 1993).

[d] Approximately 20.5 percent of the sludge generated in 1990 were incinerated. The remaining 79.5 percent were predominantly landfilled (56.5 percent) or placed in surface impoundments (18.1 percent); 4.1 percent were land-applied directly or as compost, and 0.3 percent were distributed/marketed (U.S. EPA, 1993e).

[e] The discharges in effluent and sludge were estimated in U.S. EPA (1997f) for mid-1995. The TEQ discharge in pulp was estimated by multiplying the 1988 discharge estimate by the ratio of the 1995 and 1988 effluent discharge estimates (i.e., the estimate of the reduction in 1988 discharges achieved by pollution prevention measures taken by industry between 1988 and 1995).

Table 8-4. CDD/CDF Concentrations in Graphite Electrode Sludge from Chlorine Production

Congener/Congener Group	Sludge 1 (μg/kg)	Sludge 2 (μg/kg)	Sludge 3 (μg/kg)	Sludge 4 (μg/kg)
2,3,7,8-TCDD	ND (0.006)	ND (0.009)	ND (0.009)	ND
1,2,3,7,8-PeCDD	ND (0.007)	ND (0.009)	ND (0.009)	ND (0.033)
1,2,3,4,7,8-HxCDD	ND (0.018)	ND (0.026)	ND (0.029)	ND (0.49)
1,2,3,6,7,8-HxCDD	ND (0.012)	ND (0.016)	ND (0.019)	ND (0.053)
1,2,3,7,8,9-HxCDD	ND (0.016)	ND (0.022)	ND (0.025)	ND (1.2)
1,2,3,4,6,7,8-HpCDD	0.095	0.21	0.25	0.055
OCDD	0.92	2.0	2.2	0.65
2,3,7,8-TCDF	26	56	57	52
1,2,3,7,8-PeCDF	25	55	56	55
2,3,4,7,8-PeCDF	12	25	24	27
1,2,3,4,7,8-HxCDF	32	71	73	44
1,2,3,6,7,8-HxCDF	7	16	15	12
1,2,3,7,8,9-HxCDF	1.3	2.8	2.6	1.7
2,3,4,6,7,8-HxCDF	0.87	1.9	2.0	1.3
1,2,3,4,6,7,8-HpCDF	9.1	19	19	15
1,2,3,4,7,8,9-HpCDF	8.1	19	20	14
OCDF	31	76	71	81
Total 2,3,7,8-CDD*	1.02	2.21	2.45	0.70
Total 2,3,7,8-CDF*	152.37	341.7	339.6	303.0
Total I-TEQ_{DF}*	14.2	30.5	30.2	27.7
Total TEQ_{DF}-WHO_{98}*	14.1	30.4	30.2	27.6
Total TCDD	ND (0.006)	ND (0.009)	ND (0.009)	NR
Total PeCDD	ND (0.070)	ND (0.009)	ND (0.009)	NR
Total HxCDD	ND (0.046)	ND (0.064)	ND (0.074)	NR
Total HpCDD	0.22	0.48	0.56	NR
Total OCDD	0.92	2	2.2	0.65
Total TCDF	64	150	140	NR
Total PeCDF	75	240	240	NR
Total HxCDF	68	140	140	NR
Total HpCDF	24	53	54	NR
Total OCDF	31	76	71	81
Total CDD/CDF*	263.14	661.48	647.76	NR

ND = Not detected value in parentheses is the reported detection limit.
NR = Not reported.
μg/kg = micrograms per kilogram

* Calculated assuming not detected values were zero.

Sources: Rappe et al. (1991), Rappe (1993).

Table 8-5. CDD/CDF Concentrations in Metal Chlorides

Congener Group	$FeCl_3$ (μg/kg)	$AlCl_3$ (μg/kg)	$AlCl_3$ (μg/kg)	$CuCl_2$ (μg/kg)	CuCl (μg/kg)	$TiCl_4$ (μg/kg)	$SiCl_4$ (μg/kg)
Total TCDD	NR	NR	NR	NR	NR	NR	NR
Total PeCDD	NR	NR	NR	NR	NR	NR	NR
Total HxCDD	NR	NR	NR	NR	NR	NR	NR
Total HpCDD	ND	ND	ND	0.03	ND	ND	ND
Total OCDD	ND	ND	0.1	0.6	0.03	ND	ND
Total TCDF	NR	NR	NR	NR	NR	NR	NR
Total PeCDF	NR	NR	NR	NR	NR	NR	NR
Total HxCDF	NR	NR	NR	NR	NR	NR	NR
Total HpCDF	12	ND	ND	0.1	0.08	ND	ND
Total OCDF	42	ND	34	0.5	0.2	ND	ND

NR = Not reported.
ND = Not detected; detection limit of 0.02 μg/kg.
μg/kg = micrograms per kilogram

Source: Hutzinger and Fiedler (1991a).

Table 8-6. CDD/CDF Concentrations in Mono- through Tetra-Chlorophenols

Congener/ Congener Group	2-CP (Ref. A) (mg/kg)	2,4-DCP (Ref. A) (mg/kg)	2,6-DCP (Ref. A) (mg/kg)	2,4,5-TrCP (Na salt) (Ref. A) (mg/kg)	2,4,5-TrCP (Ref. A) (mg/kg)	2,4,6-TrCP (Ref. A) (mg/kg)	2,4,6-TrCP (Na salt) (Ref. B & C) (mg/kg)	2,3,4,6-TeCP (Ref. A) (mg/kg)	2,3,4,6-TeCP (Na salt) (Ref. B & C) (mg/kg)
Total TCDD	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02) - 14	ND (0.02) - 6.5	ND (0.02) - 49	<0.02	ND (0.02)	0.7
Total PeCDD	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02) - 1.5	ND (0.02)	<0.03	ND (0.02)	5.2
Total HxCDD	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	<0.03	ND (0.02) - 15	9.5
Total HpCDD	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	<0.1	ND (0.02) - 5.1	5.6
Total OCDD	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	ND (0.02)	<0.1	ND (0.02) - 0.17	0.7
Total TCDF	+	ND	ND	ND	ND	+	1.5	+	0.5
Total PeCDF	ND	ND	ND	ND	ND	+	17.5	+	10
Total HxCDF	ND	ND	ND	ND	ND	+	36	+	70
Total HpCDF	ND	ND	ND	ND	ND	ND	4.8	+	70
Total OCDF	ND	ND	ND	ND	ND	ND	--	+	10
Total CDD/CDF	--	--	--	--	--	--	--	--	--

ND = Not detected; value in parentheses is the detection limit, if reported.
\+ = Detected but not quantified.
-- = Not reported.
mg/kg = milligrams per kilogram

Ref. A: Firestone et al. (1972); because of poor recoveries, authors stated that actual CDD/CDF levels may be considerably higher than those reported.
Ref. B: Rappe et al. (1978a); common Scandinavian commercial chlorophenols.
Ref. C: Rappe et al. (1978b); common Scandinavian commercial chlorophenols.

Table 8-7. CDD/CDF Concentrations in Historical and Current Technical Pentachlorophenol Products

Congener/ Congener Group	PCP (Ref. B) (1973) (μg/kg)	PCP (Ref. C) (1978) (μg/kg)	PCP (Ref. A) (1979) (μg/kg)	PCP (Ref. D) (1984) (μg/kg)	PCP (Ref. I) (1985) (μg/kg)	PCB (Ref. I) (1986) (μg/kg)	PCP (Ref. E) (1987) (μg/kg)	PCP (Ref. F) (1987) (μg/kg)	PCP (Ref. I) (1985-88) (μg/kg)	PCP (Ref. G) (1991) (μg/kg)	PCP (Ref. H) (1988-99) (μg/kg)	PCP (Ref. J) (1988-99) (μg/kg)	PCP (Ref. K) (unknown) (μg/kg)
2,3,7,8-TCDD	--	--	--	ND (10)	ND (0.05)	ND (0.05)	ND (0.03)	ND (0.05)	ND (0.05)	ND	--	ND (0.5)	ND (10)
1,2,3,7,8-PeCDD	--	--	--	ND (10)	ND (1)	ND (1)	1	2	ND (1)	ND	--	--	ND (10)
1,2,3,4,7,8-HxCDD	--	--	--	--	6	8	ND (1)	ND (1)	8	--	--	--	ND (10)
1,2,3,6,7,8-HxCDD	--	--	--	2,200	2,565	1,532	831	1,480	600	--	--	--	860
1,2,3,7,8,9-HxCDD	--	--	--	100	44	28	28	53	13	--	--	--	20
1,2,3,4,6,7,8-HpCDD	--	--	--	100,000	210,000	106,000	78,000	99,900	89,000	--	--	--	36,400
OCDD	--	--	--	610,000	1,475,000	930,000	733,000	790,000	2,723,000	1,100,000	--	--	296,810
2,3,7,8-TCDF	--	--	--	ND (10)	ND (0.5)	ND (0.5)	ND (0.1)	ND (0.1)	ND (0.5)	ND	--	--	ND (10)
1,2,3,7,8-PeCDF	--	--	--	--	ND (1)	ND (1)	0.5	0.2	ND (1)	ND	--	--	ND (10)
2,3,4,7,8-PeCDF	--	--	--	--	ND (1)	ND (1)	1.5	0.9	ND (1)	ND	--	--	ND (10)
1,2,3,4,7,8-HxCDF	--	--	--	--	49	34	125	163	67	--	--	--	200
1,2,3,6,7,8-HxCDF	--	--	--	--	5	4	ND (1)	ND (1)	2	--	--	--	ND (20)
1,2,3,7,8,9-HxCDF	--	--	--	--	5	ND (1)	32	146	ND (1)	--	--	--	ND (20)
2,3,4,6,7,8-HxCDF	--	--	--	--	ND (1)	ND (1)	ND (1)	ND (1)	ND (1)	--	--	--	ND (20)
1,2,3,4,6,7,8-HpCDF	--	--	--	--	34,000	29,000	11,280	19,940	22,000	--	--	--	2,000
1,2,3,4,7,8,9-HpCDF	--	--	--	--	4,100	6,200	637	980	3,400	--	--	--	140
OCDF	--	130,000	--	130,000	222,000	233,000	118,000	137,000	237,000	170,000	--	--	19,940
Total 2,3,7,8-CDD*	--	--	--	712,300	1,687,615	1,037,568	811,860	891,435	2,812,621	--	--	--	334,090
Total 2,3,7,8-CDF*	--	--	--	--	260,159	268,238	130,076	158,230	262,469	--	--	--	22,280
Total I-TEQ_{DF}*	--	--	--	1,970	4,445	2,736	1,853	2,321	4,173	≥1,270	--	--	810
Total TEQ_{DF}-WHO_{98}*	--	--	--	1,304	2,918	1,689	1,088	1,488	1,509	>127	--	--	525
Total TCDD	ND(20)	--	--	ND (10)	ND	ND	1.9	0.4	ND	ND (10)	ND (1)	ND	--
Total PeCDD	ND(30)	--	--	ND (10)	ND	ND	6.5	15.2	ND	ND (10)	ND (10)	3	--
Total HxCDD	5,500	--	10,100	4,500	4,694	2,925	1,700	3,300	912	8,900	1,440	1,490	--
Total HpCDD	98,000	--	296,000	135,000	283,000	134,000	154,000	198,000	117,000	130,000	55,560	48,430	--
Total OCDD	220,000	--	1,386,000	610,000	1,475,000	930,000	733,000	790,000	2,723,000	1,100,000	--	191,700	--
Total TCDF	40	900	--	ND (10)	6	ND	0.8	0.4	ND	ND (10)	ND (10)	48	--
Total PeCDF	250	4,000	1,400	--	10	3	141	343	200	ND (10)	ND (10)	520	--
Total HxCDF	22,000	32,000	9,900	--	1,982	1,407	4,300	13,900	1,486	14,000	3,070	13,650	--
Total HpCDF	150,000	120,000	88,000	62,000	125,000	146,000	74,000	127,000	99,000	36,000	36,530	76,090	--
Total OCDF	160,000	130,000	43,000	130,000	222,000	233,000	118,000	137,000	237,000	170,000	--	136,310	--
Total CDD/CDF*	655,800	1,280,000	1,834,400	941,500	2,111,692	1,447,335	1,085,000	1,270,000	3,178,598	1,459,000	--	468,240	--

ND = Not detected; value in parentheses is the detection limit.
-- = Not reported.
μg/kg = micrograms per kilogram

* Calculated assuming not detected values are zero.

Table 8-7. CDD/CDF Concentrations in Historical and Current Technical Pentachlorophenol Products (continued)

Sources:

Ref. A: U.S. Department of Health and Human Services (1989); composite of technical-grade materials produced in 1979 by Monsanto Industrial Chemical Co. (St. Louis, MO), Reichhold Chemicals, Inc. (White Plains, NY), and Vulcan Materials Co. (Birmingham, AL).
Ref. B: Buser and Bosshardt (1976); mean of 10 samples of "high" CDD/CDF content PCP received from Swiss commercial sources in 1973.
Ref. C: Rappe et al. (1978b); sample of U.S. origin, "presumably prepared by alkaline hydrolysis of hexachlorobenzene."
Ref. D: Cull et al. (1984); mean of four "recent" production batches from each of two manufacturers of technical PCP using three different analytical methods; ANOVA showed no statistically significant difference in CDD/CDF concentrations between the eight samples (samples obtained in the United Kingdom).
Ref. E: Hagenmaier and Brunner (1987); sample of Witophen P (Dynamit Nobel - Lot no. 7777) (obtained in Germany).
Ref. F: Hagenmaier and Brunner (1987); sample of PCP produced by Rhone Poulenc (obtained in Germany).
Ref. G: Harrad et al. (1991); PCP-based herbicide formulation from NY State Dept. Environmental Conservation.
Ref. H: Pentachlorophenol Task Force (1997); average of monthly batch samples for the period Jan. 1987 to Aug. 1996.
Ref. I: Pentachlorophenol Task Force (1997); samples of "penta" manufactured in 1985, 1986, and 1988.
Ref. J: KMG-Bermuth, Inc. (1997); average of monthly batch samples for the period Feb. 1987 to Dec. 1996 (excluding the following months, for which data were not available: Feb. 1993, Jan. 1992, Dec. 1991, Sept. 1991, Dec. 1988, and Sept. 1988).
Ref. K: Schecter et al. (1997); sample found stored in a barn in Vermont.

Table 8-8. Historical CDD/CDF Concentrations in Pentachlorophenol-Na

Congener/Congener Group	PCP-Na (Ref. A) (1969) (μg/kg)	PCP-Na (Ref. B) (1973) (μg/kg)	PCP-Na (Ref. C) (1973) (μg/kg)	PCP-Na (Ref. D) (1987) (μg/kg)	PCP-Na (Ref. E) (1987) (μg/kg)	PCP-Na (Ref. F) (1992) (μg/kg)	PCP-Na (Ref. G) (1980s) (μg/kg)
2,3,7,8-TCDD	--	--	--	0.23	0.51	0.076	ND (1.4)
1,2,3,7,8-PeCDD	--	--	--	18.2	3.2	18.7	28.3
1,2,3,4,7,8-HxCDD	--	--	--	28.3	13.3	96	ND (6.1)
1,2,3,6,7,8-HxCDD	--	--	--	2,034	53.0	4,410	4,050
1,2,3,7,8,9-HxCDD	--	--	--	282	19.0	328	ND (1.4)
1,2,3,4,6,7,8-HpCDD	--	--	--	9,100	3,800	175,400	33,800
OCDD	3,600	--	--	41,600	32,400	879,000	81,000
2,3,7,8-TCDF	--	--	--	1.8	0.79	ND (1.0)	149
1,2,3,7,8-PeCDF	--	--	--	8.2	1.9	ND (4.0)	319
2,3,4,7,8-PeCDF	--	--	--	6.6	1.1	ND (4.0)	324
1,2,3,4,7,8-HxCDF	--	--	--	48	4.6	27.6	ND (2.8)
1,2,3,6,7,8-HxCDF	--	--	--	69	1.3	21.9	225
1,2,3,7,8,9-HxCDF	--	--	--	ND (1)	1.3	9.8	480
2,3,4,6,7,8-HxCDF	--	--	--	87	4.6	103	ND (385)
1,2,3,4,6,7,8-HpCDF	--	--	--	699	197	9,650	6,190
1,2,3,4,7,8,9-HpCDF	--	--	--	675	36	2,080	154
OCDF	--	--	--	37,200	4,250	114,600	36,000
Total 2,3,7,8-CDD*	--	--	--	53,063	35,289	1,059,253	118,878
Total 2,3,7,8-CDF*	--	--	--	38,795	4,499	126,492	43,841
Total I-TEQ_{DF}*	--	--	--	452	79.5	3,374	1,201
Total TEQ_{DF}-WHO_{98}*	--	--	--	406	58.5	2,566	1,096
Total TCDD	--	140	50	27	52	3.6	1.9
Total PeCDD	--	40	ND (30)	213	31	142.7	140
Total HxCDD	17,000	140	3,400	3,900	230	9,694	14,000
Total HpCDD	9,600	1,600	38,000	18,500	5,800	260,200	100,000
Total OCDD	3,600	4,000	110,000	41,600	32,400	879,000	81,000
Total TCDF	--	ND (20)	ND (20)	82	12	10.1	1200
Total PeCDF	--	60	40	137	27	88.4	6400
Total HxCDF	--	1,400	11,000	3,000	90	9,082.3	49,000
Total HpCDF	--	4,300	47,000	13,200	860	75,930	91,000
Total OCDF	--	4,300	26,500	37,200	4,250	114,600	36,000
Total CDD/CDF*	--	15,980	235,990	117,859	43,752	1,348,751	378,742

ND = Not detected; value in parentheses is the detection limit.
-- = Not reported.
μg/kg = micrograms per kilogram

* Calculated assuming not-detected values are zero.

Sources:
Ref. A: Firestone et al. (1972); mean of two samples of PCP-Na obtained in the United States between 1967 and 1969.
Ref. B: Buser and Bosshardt (1976); mean of five samples of "low" CDD/CDF content PCP-Na received from Swiss commercial sources.
Ref. C: Buser and Bosshardt (1976); sample of "high" CDD/CDF content PCP-Na received from a Swiss commercial source.
Ref. D: Hagenmaier and Brunner (1987); sample of Dowicide-G purchased from Fluka; sample obtained in Germany.
Ref. E: Hagenmaier and Brunner (1987); sample of Preventol PN (Bayer AG); sample obtained in Germany.
Ref. F: Santl et al. (1994c); 1992 sample of PCP-Na from Prolabo, France.
Ref. G: Palmer et al. (1988); sample of a PCP-Na formulation collected from a closed sawmill in California in the late 1980s.

Table 8-9. Summary of Specific Dioxin-Containing Wastes That Must Comply with Land Disposal Retrictions

EPA Hazardous Waste Number	Waste Description	Land Disposal Restriction Effective Date	Regulated Waste Constituent	Treatment Standard[a] (ppb)	
				Wastewaters (μg/L)	Nonwastewaters (μg/kg)
F020	Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production or manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tri- or tetrachlorophenol, or of intermediates used to produce their pesticide derivatives. (This listing does not include wastes from the production of hexachlorophene from highly purified 2,4,5-trichlorophenol.)	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
F021	Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production or manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of pentachlorophenol, or of intermediates used to produce its derivatives.	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
F022	Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tetra-, penta-, or hexachlorobenzenes under alkaline conditions.	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
F023	Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production of materials on equipment previously used for the production or manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tri- and tetrachlorophenols. (This listing does not include wastes from equipment used only for the production or use of hexachlorophene from highly purified 2,4,5-trichlorophenol.)	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
F026	Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production of materials on equipment previously used for the manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tetra-, penta-, or hexachlorobenzene under alkaline conditions.	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
F027	Discarded unused formulations containing tri-, tetra-, or pentachlorophenol or discarded unused formulations containing compounds derived from these chlorophenols. (This listing does not include formulations containing hexachlorophene synthesized from prepurified 2,4,5-trichlorophenol as the sole component.)	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1

Table 8-9. Summary of Specific Dioxin-Containing Wastes That Must Comply with Land Disposal Retrictions (continued)

EPA Hazardous Waste Number	Waste Description	Land Disposal Restriction Effective Date	Regulated Waste Constituent	Treatment Standard[a] (ppb)	
				Wastewaters (μg/L)	Nonwastewaters (μg/kg)
F028	Residues resulting from the incineration or thermal treatment of soil contaminated with EPA Hazardous Waste Nos. F020-F023, F026, and F027	November 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
F039	Leachate (liquids that have percolated through land disposed wastes) resulting from the disposal of more than one restricted waste classified as hazardous under subpart D of 40 CFR 268. (Leachate resulting from the disposal of one or more of the following EPA Hazardous Wastes and no other Hazardous Wastes retains its EPA Hazardous Waste Number(s): F020, F021, F022, F026, F027, and/or F028.)	August 8, 1990 (wastewater) May 8, 1992 (non-wastewater)	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
K043	2,6-dichlorophenol waste from the production of 2,4-D.	June 8, 1989	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1
K099	Untreated wastewater from the production of 2,4-D.	August 8, 1988	TCDDs PeCDDs HxCDDs TCDFs PeCDFs HxCDFs	0.063 0.063 0.063 0.063 0.035 0.063	1 1 1 1 1 1

[a] Treatment standards (i.e., maximum allowable concentration in waste extract) are based on incineration to 99.9999 percent destruction and removal efficiency.

μg/L = micrograms per liter
μg/kg = micrograms per kilogram

Source: 40 CFR 268

Table 8-10. CDD/CDF Concentrations in Chlorobenzenes

Congener/ Congener Group	MCBz (Ref. A) (μg/kg)	1,2-DCBz (for synthesis) (Ref. A) (μg/kg)	1,2,4-TrCBz ("pure") (Ref. B) (μg/kg)	Mixed TrCBz (47%) (Ref. A) (μg/kg)	1,2,4,5-TeCBz (99%) (Ref. A) (μg/kg)	PeCBz (98%) (Ref. A) (μg/kg)	HCBz (97%) (Ref. A) (μg/kg)	HCBz (Ref. B) (μg/kg)
Total TCDD	ND (0.02)	0.3	ND (0.1)	0.027	ND (0.02)	ND (0.02)	ND (20)	--
Total PeCDD	ND (0.02)	ND (0.02)	ND (0.1)	0.140	0.2	ND (0.02)	ND (20)	--
Total HxCDD	ND (0.02)	ND (0.02)	ND (0.1)	0.259	0.5	0.02	ND (20)	--
Total HpCDD	ND (0.02)	ND (0.02)	ND (0.1)	0.253	0.8	0.02	470	--
Total OCDD	ND (0.02)	ND (0.02)	ND (0.1)	0.081	0.4	0.05	6,700	50 - 212,000
Total TCDF	ND (0.02)	ND (0.02)	ND (0.1)	0.736	0.03	0.02	ND (20)	--
Total PeCDF	ND (0.02)	0.5	ND (0.1)	0.272	0.2	ND (0.02)	ND (20)	--
Total HxCDF	ND (0.02)	ND (0.02)	ND (0.1)	0.091	0.8	ND (0.02)	ND (20)	--
Total HpCDF	ND (0.02)	ND (0.02)	ND (0.1)	0.030	1.5	0.1	455	--
Total OCDF	ND (0.02)	ND (0.02)	ND (0.1)	0.016	2.1	0.1	2,830	350 - 58,300
Total CDD/CDF	--	--	--	1.904	--	--	--	--

ND = Not detected; value in parentheses is the detection limit, if reported.
-- = Not reported.
μg/kg = micrograms per kilogram

Ref. A: Hutzinger and Fiedler (1991a); unpublished results of tests performed at the Univ. of Bayreuth, Germany, and by Dr. H. Hagenmaier.
Ref. B: Villanueva et al. (1974); range of three samples of commercially available HCBz.

Table 8-11. Concentrations of CDD/CDF Congener Groups in Unused Commercial PCB Mixtures

PCB Mixture	Year of Manufacture	CDF Congener Group Concentrations (mg/kg)						CDD Congener Group Concentrations (mg/kg)						Reference Number
		TCDF	PeCDF	HxCDF	HpCDF	OCDF	Total CDF	TCDD	PeCDD	HxCDD	HpCDD	OCDD	Total CDD	
Aroclor 1016	1972	ND	ND	ND	--	--	ND	--	--	--	--	--	--	A
Aroclor 1242	--	0.07	0.03	0.003	--	--	0.15	--	--	--	--	--	--	B, C
Aroclor 1242	--	2.3	2.2	ND	--	--	4.5	--	--	--	--	--	--	B, C
Aroclor 1242	--	0.25	0.7	0.81	--	--	1.9	--	--	--	--	--	--	B
Clophen A-30	--	6.377	2.402	0.805	0.108	0.016	9.708	0.0007	ND	0.001	0.006	0.031	0.039	E
Clophen A-30	--	0.713	0.137	0.005	0.001	ND	0.855	ND	ND	ND	0.005	0.025	0.030	D
Aroclor 1248	1969	0.5	1.2	0.3	--	--	2.0	--	--	--	--	--	--	B
Clophen A-40	--	1.289	0.771	0.144	0.020	0.011	2.235	ND	ND	ND	0.012	0.030	0.042	D
Kanechlor 400	--	--	--	--	--	--	20.0	--	--	--	--	--	--	B, C
Aroclor 1254	1969	0.1	0.2	1.4	--	--	1.7	--	--	--	--	--	--	A
Aroclor 1254	1970	0.2	0.4	0.9	--	--	1.5	--	--	--	--	--	--	A
Aroclor 1254	--	0.02	0.2	0.6	--	--	0.8	--	--	--	--	--	--	B, C
Aroclor 1254	--	0.05	0.1	0.02	--	--	0.2	--	--	--	--	--	--	B
Clophen A-50	--	5.402	2.154	2.214	0.479	0.069	10.318	ND	ND	ND	0.011	0.027	0.038	D
Aroclor 1260	--	0.3	1.0	1.10	1.35	--	3.8	--	--	--	--	--	--	B, C
Aroclor 1260	1969	0.1	0.4	0.5	--	--	1.0	--	--	--	--	--	--	A
Aroclor 1260	--	0.8	0.9	0.5	--	--	2.2	--	--	--	--	--	--	B, C
Aroclor 1260	--	0.2	0.3	0.3	--	--	0.8	--	--	--	--	--	--	A
Clophen A-60	--	15.786	11.655	4.456	1.517	0.639	34.052	0.0004	0.002	0.002	0.003	0.015	0.022	E
Clophen A-60	--	16.340	21.164	7.630	2.522	1.024	48.681	ND	ND	ND	0.014	0.032	0.046	D
Clophen A-60	--	1.4	5.0	2.2	--	--	8.6	--	--	--	--	--	--	A
Phenoclor DP-6	--	0.7	10.0	2.9	--	--	13.6	--	--	--	--	--	--	A
Clophen T-64	--	0.3	1.73	2.45	0.82	--	5.4	--	--	--	--	--	--	B
Prodelec 3010	--	1.08	0.35	0.07	--	--	2.0	--	--	--	--	--	--	B

ND = Not detected.
-- = Not reported.
mg/kg = milligram per kilogram

Ref. A: Bowes et al. (1975a).
Ref. B: Erickson (1986).
Ref. C: ATSDR (1993).

Table 8-12. 2,3,7,8-Substituted Congener Concentrations in Unused PCB Mixtures

Congener	Congener Concentrations in Clophens (μg/kg)						Congener Concentrations in Aroclors (μg/kg)									
	A-30 (Ref. A)	A-30 (Ref. B)	A-40 (Ref. B)	A-50 (Ref. B)	A-60 (Ref. A)	A-60 (Ref. B)	1016 (Ref. C)	1242 (Ref. C)	1248 (Ref. D)	1254 (Ref. C)	1254 (Ref. C)	1254 (Ref. C)	1254 (Ref. D)	1260 (Ref. C)	1260 (Ref. C)	1260 (Ref. C)
2,3,7,8-TCDD	ND	ND	ND	ND	ND	ND	--	--	--	--	--	--	--	--	--	--
1,2,3,7,8-PeCDD	ND	ND	ND	ND	0.1	ND	--	--	--	--	--	--	--	--	--	--
1,2,3,4,7,8-HxCDD	ND	ND	ND	ND	0.2	ND	--	--	--	--	--	--	--	--	--	--
1,2,3,6,7,8-HxCDD	0.8	ND	ND	ND	ND	ND	--	--	--	--	--	--	--	--	--	--
1,2,3,7,8,9-HxCDD	ND	ND	ND	ND	ND	ND	--	--	--	--	--	--	--	--	--	--
1,2,3,4,6,7,8-HpCDD	5.6	2.4	4.4	5.3	2.5	6.8	--	--	--	--	--	--	--	--	--	--
OCDD	31.1	24.7	30.3	26.9	14.9	32.3	--	--	--	--	--	--	--	--	--	--
2,3,7,8-TCDF	1032.6	36.9	250.2	1005.7	2287.7	3077.2	0.10	40.1	330	28.0	20.9	55.8	110	63.5	6.88	29.0
1,2,3,7,8-PeCDF	135.8	14.9	52.7	155.2	465.2	1750.8	--	--	--	--	--	--	--	--	--	--
2,3,4,7,8-PeCDF	509.2	13.1	171.3	407.5	1921.9	2917.0	1.75	40.8	830	110	179	105	120	135	58.2	112
1,2,3,4,7,8-HxCDF	301.4	1.9	48.4	647.5	1604.2	2324.1	--	--	--	--	--	--	--	--	--	--
1,2,3,6,7,8-HxCDF	65.3	0.8	19.6	227.5	157.6	351.3	--	--	--	--	--	--	--	--	--	--
1,2,3,7,8,9-HxCDF	ND	ND	0.7	8.3	42.8	19.0	0.08	0.26	--	28.8	28.7	19.4	--	5.1	9.7	10.7
2,3,4,6,7,8-HxCDF	50.6	0.1	6.8	62.5	369.5	408.3	--	--	--	--	--	--	--	--	--	--
1,2,3,4,6,7,8-HpCDF	43.7	0.6	7.0	205.5	480.6	1126.1	--	--	--	--	--	--	--	--	--	--
1,2,3,4,7,8,9-HpCDF	22.5	ND	2.8	72.2	321.7	304.0	--	--	--	--	--	--	--	--	--	--
OCDF	15.7	ND	11.4	69.2	639.2	1024.3	--	--	--	--	--	--	--	--	--	--
Total TCDD	0.7	ND	ND	ND	0.4	ND	--	--	--	--	--	--	--	--	--	--
Total PeCDD	ND	ND	ND	ND	2.0	ND	--	--	--	--	--	--	--	--	--	--
Total HxCDD	1.2	ND	ND	ND	1.8	ND	--	--	--	--	--	--	--	--	--	--
Total HpCDD	5.6	5.4	11.6	11.0	3.0	13.5	--	--	--	--	--	--	--	--	--	--
Total OCDD	31.1	24.7	30.3	26.9	14.9	32.3	--	--	--	--	--	--	--	--	--	--
Total TCDF	6376.6	713	1289.4	5402.3	15785.7	16340	--	--	--	--	--	--	--	--	--	--
Total PeCDF	2402.4	136.5	770.8	2153.7	11654.6	21164	--	--	--	--	--	--	--	--	--	--
Total HxCDF	804.8	5.1	143.6	2213.8	4455.8	7630.2	--	--	--	--	--	--	--	--	--	--
Total HpCDF	108.3	0.8	19.5	478.8	1517.0	2522.3	--	--	--	--	--	--	--	--	--	--
Total OCDF	15.7	ND	11.4	69.2	639.2	1024.3	--	--	--	--	--	--	--	--	--	--
Total CDD/CDF*	9746.4	885.5	2276.6	10355.7	34074.4	48726.5	--	--	--	--	--	--	--	--	--	--
Total I-TEQ_{DF}*	407.2	11.3	121.0	409.6	1439.2	2179	--	--	--	--	--	--	--	--	--	--
Total TEQ_{DF}-WHO_{98}*	407.2	11.3	121.0	409.5	1439	2178	--	--	--	--	--	--	--	--	--	--

ND = Not detected.
-- = Not reported.
μg/kg = micrograms per kilogram.
* Calculated assuming not-detected values are zero.

Ref. A: Malisch (1994).
Ref. B: Hagenmaier (1987).
Ref. C: Brown et al. (1988).
Ref. D: Bowes (1975b).

Table 8-13. Reported CDD/CDF Concentrations in Wastes from PVC Manufacture

Congener/Congener Group	F024 Waste (μg/kg)	K019 Waste (μg/kg)	K020 Waste (μg/kg)
2,3,7,8-TCDD	0.37	260	0.06
1,2,3,7,8-PeCDD	0.14	890	0.05
1,2,3,4,7,8-HxCDD	.30	260	0.08
1,2,3,6,7,8-HxCDD	0.14	330	0.06
1,2,3,7,8,9-HxCDD	0.11	620	0.07
1,2,3,4,6,7,8-HpCDD	4.20	920	0.89
OCDD	15.00	1,060	3.00
2,3,7,8-TCDF	0.91	680	0.44
1,2,3,7,8-PeCDF	9.5	975	1.80
2,3,4,7,8-PeCDF	1.6	1,050	0.58
1,2,3,4,7,8-HxCDF	110	10,100	11.0
1,2,3,6,7,8-HxCDF	24.0	9,760	2.4
1,2,3,7,8,9-HxCDF	9.5	21,800	1.3
2,3,4,6,7,8-HxCDF	3.1	930	0.89
1,2,3,4,6,7,8-HpCDF	250	13,400	38.0
1,2,3,4,7,8,9-HpCDF	51.0	1,340	6.0
OCDF	390	43,500	650
Total 2,3,7,8-CDD	20.3	4,340	4.21
Total 2,3,7,8-CDF	849.6	103,535	712.4
Total I-TEQ_{DF}	20.0	5,928	3.2
Total TEQ_{DF}-WHO_{98}	19.7	6,333	2.6
Total TCDD	3.1	1,230	1.9
Total PeCDD	3.6	3,540	1.7
Total HxCDD	1.3	3,950	NR
Total HpCDD	5.0	1,270	1.7
Total OCDD	15.0	1,060	3.0
Total TCDF	15.0	20,600	6.0
Total PeCDF	65.0	45,300	11.0
Total HxCDF	300	63,700	27.0
Total HpCDF	450	16,600	58.0
Total OCDF	390	43,500	650
Total CDD/CDF	1,248	200,750	760.3

NR = Congener group concentration reported in source is not consistent with reported congener concentrations.
μg/kg = micrograms per kilogram

Source: Stringer et al. (1995).

Table 8-14. CDD/CDF Measurements in Treated Wastewater and Wastewater Solids from U.S. EDC/VCM/PVC Manufacturers

Congener and Congener Groups	Treated Wastewater PVC-only Facilities			Treated Wastewater EDC/VCM/PVC Facilities			Wastewater Solids EDC/VCM/PVC Facilities			Wastewater Solids PVC-only Facilities		
	No. Detects/ No. Samples	Concentration Range[a] (ng/L)		No. Detects/ No. Samples	Concentration Range[a] (ng/L)		No. Detects/ No. Samples	Concentration Range[b,c] (ng/kg)		No. Detects/ No. Samples	Concentration Range[b,c] (ng/kg)	
		Min.	Max.		Min.	Max.		Min.	Max.		Min.	Max.
2,3,7,8-TCDD	0/6	ND	ND	0/4	ND	ND	4/8	ND	109	1/2	ND	2.0
1,2,3,7,8-PeCDD	0/6	ND	ND	0/4	ND	ND	3/8	ND	320	0/2	ND	ND
1,2,3,4,7,8-HxCDD	0/6	ND	ND	0/4	ND	ND	4/8	ND	455	1/2	ND	3.2
1,2,3,6,7,8-HxCDD	0/6	ND	ND	0/4	ND	ND	7/8	ND	520	1/2	ND	2.3
1,2,3,7,8,9-HxCDD	0/6	ND	ND	0/4	ND	ND	6/8	ND	645	1/2	ND	2.4
1,2,3,4,6,7,8-HpCDD	2/6	ND	26	1/4	ND	14	8/8	74	3,230	2/2	28	35
OCDD	1/6	ND	260	1/4	ND	130	8/8	390	9,700	2/2	200	640
2,3,7,8-TCDF	0/6	ND	ND	0/4	ND	ND	8/8	18	460	0/2	ND	ND
1,2,3,7,8-PeCDF	0/6	ND	ND	0/4	ND	ND	8/8	36	1,500	0/2	ND	ND
2,3,4,7,8-PeCDF	0/6	ND	ND	0/4	ND	ND	8/8	50	1,750	0/2	ND	ND
1,2,3,4,7,8-HxCDF	1/6	ND	5.8	0/4	ND	ND	8/8	180	7,550	1/2	ND	3.6
1,2,3,6,7,8-HxCDF	1/6	ND	3.8	0/4	ND	ND	8/8	74	3,650	1/2	ND	2.4
1,2,3,7,8,9-HxCDF	0/6	ND	ND	0/4	ND	ND	8/8	78	2,800	1/2	ND	3.8
2,3,4,6,7,8-HxCDF	1/6	ND	6.1	1/4	ND	6.5	7/8	ND	425	0/2	ND	ND
1,2,3,4,6,7,8-HpCDF	1/6	ND	26	3/4	ND	78	8/8	570	20,600	1/2	9.7	12
1,2,3,4,7,8,9-HpCDF	1/6	ND	6.2	2/4	ND	20	7/8	ND	12,000	1/2	ND	2.0
OCDF	2/6	ND	33	4/4	ND	900	8/8	1,800	4,200,000	2/2	39	43
Mean I-TEQ$_{DF}$ (ND = zero)		0.42			0.88			1,680			1.90	
Mean I-TEQ$_{DF}$ (ND = 1/2 DL)			4.4			4.7			1,680			3.6
Total TCDD	0/6	ND	ND	0/4	ND	ND	6/8	ND	730	1/2	ND	6.3
Total PeCDD	0/6	ND	ND	0/4	ND	ND	5/8	ND	1,630	1/2	ND	3.3
Total HxCDD	0/6	ND	ND	0/4	ND	ND	7/8	ND	3,915	1/2	ND	14
Total HpCDD	2/6	ND	48	1/4	ND	22	8/8	74	5,300	2/2	58	64
Total OCDD	1/6	ND	260	1/4	ND	130	8/8	390	9,700	2/2	200	640
Total TCDF	0/6	ND	ND	0/4	ND	ND	8/8	210	9,800	1/2	ND	4.8
Total PeCDF	0/6	ND	ND	0/4	ND	ND	8/8	380	18,000	1/2	ND	4.0
Total HxCDF	1/6	ND	30	1/4	ND	14	8/8	750	31,000	2/2	1.5	11
Total HpCDF	1/6	ND	49	3/4	ND	140	8/8	880	39,400	2/2	11	18
Total OCDF	2/6	ND	33	4/4	ND	900	8/8	1,800	4,200,000	2/2	39	43

ND = Not detected.

a Method detection limits (MDLs) for individual samples were less than 10 pg/L for all congeners and congener groups except OCDD and OCDF, which had MDLs less than 50 pg/L.

b Dry weight basis.

c MDLs for all congeners were less than 150 ng/kg, and usually were less than 10 ng/kg.

Table 8-15. CDD/CDF Measurements in Products from U.S. EDC/VCM/PVC Manufacturers

Congener and Congener Groups	Suspension and Mass PVC Resins			Dispersion PVC Resins			"Sales" Ethylene Dichloride (EDC)[d]		
	No. Detects/ No. Samples[b]	Range of Concentrations[a] (ng/kg)		No. Detects/ No. Samples	Range of Concentrations[c] (ng/kg)		No. Detects/ No. Samples	Range of Concentrations[e] (ng/kg)	
		Min.	Max.		Min.	Max.		Min.	Max.
2,3,7,8-TCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,7,8-PeCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,4,7,8-HxCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,6,7,8-HxCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,7,8,9-HxCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,4,6,7,8-HpCDD	1/22	nd	0.64	1/6	nd	0.8	0/5	nd	nd
OCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
2,3,7,8-TCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,7,8-PeCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
2,3,4,7,8-PeCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,4,7,8-HxCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,6,7,8-HxCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
1,2,3,7,8,9-HxCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
2,3,4,6,7,8-HxCDF	1/22	nd	0.37	0/6	nd	nd	0/5	nd	nd
1,2,3,4,6,7,8-HpCDF	0/22	nd	nd	0/6	nd	nd	1/5	nd	1.1
1,2,3,4,7,8,9-HpCDF	0/22	nd	nd	0/6	nd	nd	1/5	nd	0.40
OCDF	0/22	nd	nd	2/6	nd	0.38	1/5	nd	11
Mean I-TEQ_{DF} (ND = zero)		0.002			0.001			0.0006	
Mean I-TEQ_{DF} (ND = 1/2 DL)			0.7			0.4			0.21
Total TCDD	0/22	nd	nd	1/6	nd	0.24	0/5	nd	nd
Total PeCDD	0/22	nd	nd	1/6	nd	0.32	0/5	nd	nd
Total HxCDD	0/22	nd	nd	5/6	nd	0.97	0/5	nd	nd
Total HpCDD	1/22	nd	0.64	1/6	nd	1.3	0/5	nd	nd
Total OCDD	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
Total TCDF	0/22	nd	nd	0/6	nd	nd	0/5	nd	nd
Total PeCDF	0/22	nd	nd	1/6	nd	0.3	0/5	nd	nd
Total HxCDF	1/22	nd	0.37	0/6	nd	nd	0/5	nd	nd
Total HpCDF	0/22	nd	nd	0/6	nd	nd	1/5	nd	2.02
Total OCDF	0/22	nd	nd	2/6	nd	0.38	1/5	nd	11

nd = Not detected.

ng/kg = nanograms per kilogram

a Method detection limits (MDLs) for individual samples were less than 2 ng/kg for all congeners and congener groups except OCDD and OCDF, which had MDLs less than 6 ng/kg.

b Two of these 22 samples were duplicate samples from two sites. The results were averaged and treated as one sample for each site.

c MDLs for individual samples were less than 2 ng/kg for all congeners and congener groups except OCDD and OCDF, which had MDLs less than 4 ng/kg.

d "Sales" EDC is defined as EDC sold commercially for non-VCM uses or exported from the United States.

e MDLs were less than 1 ng/kg for all congeners in all samples.

Source: The Vinyl Institute (1998).

Table 8-16. CDD/CDF Concentrations in Dioxazine Dyes and Pigments (Canada)

Congener/Congener Group	Blue 106 (μg/kg)			Blue 108 (μg/kg)	Violet 23 (μg/kg)					
2,3,7,8-TCDD	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,7,8-PeCDD	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,4,7,8-HxCDD	--	--	--	--	--	--	--	--	--	--
1,2,3,6,7,8-HxCDD	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,7,8,9-HxCDD	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,4,6,7,8-HpCDD	31	6	9	ND (0.3)	9	1	16	10	2	4
OCDD	41,953	28,523	18,066	23	7,180	806	11,022	7,929	1,627	1,420
2,3,7,8-TCDF	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,7,8-PeCDF	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	0.5	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
2,3,4,7,8-PeCDF	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,4,7,8-HxCDF	12	2	2	ND (0.3)	76	4	39	31	9	7
1,2,3,6,7,8-HxCDF	*	*	*	*	*	*	*	*	*	*
1,2,3,7,8,9-HxCDF	--	--	--	--	--	--	--	--	--	--
2,3,4,6,7,8-HxCDF	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
1,2,3,4,6,7,8-HpCDF	50	10	14	9	13	10	11	4	1	12
1,2,3,4,7,8,9-HpCDF	--	--	--	--	--	--	--	--	--	--
OCDF	12,463	1,447	1,006	11	941	125	3,749	1,556	147	425
Total 2,3,7,8-CDD	41,984	28,529	18,075	23	7,189	807	11,038	7,939	1,629	1,424
Total 2,3,7,8-CDF	12,525	1,459	1,022	20	1,031	139	3,799	1,591	157	444
Total I-TEQ_{DF} **	56.4	30.3	19.5	0.1	16.0	1.4	18.9	12.7	2.7	2.7
Total TEQ_{DF}-WHO_{98} **	7.45	3.4	2.3	0.1	8.7	0.6	5.6	4.2	1.1	1.0
Total TCDD	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
Total PeCDD	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
Total HxCDD	ND (0.3)	ND (0.3)	ND (0.3)	1	21	2	7	ND (0.3)	ND (0.3)	1
Total HpCDD	34	8	12	ND (0.3)	30	5	36	11	2	6
Total OCDD	41,953	28,523	18,066	23	7,180	806	11,022	7,929	1,627	1,420
Total TCDF	ND (0.3)	0.3	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	0.4	ND (0.3)
Total PeCDF	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	0.5	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)	ND (0.3)
Total HxCDF	12	2	2	ND (0.3)	76	5	39	31	9	7
Total HpCDF	71	32	26	12	26	14	29	13	2	21
Total OCDF	12,463	1,447	1,006	11	941	125	3,749	1,556	147	425
Total CDD/CDF**	54,533	30,012	19,112	47	8,275	957	14,882	9,540	1,787	1,880

ND = Not detected; value in parenthesis is the detection limit.
-- = Not reported.
μg/kg = micrograms per kilogram
* = Results listed for 1,2,3,4,7,8-HxCDF include concentrations for 1,2,3,6,7,8-HxCDF.
** = Calculations assume nondetected values are equal to zero.

Table 8-17. CDD/CDF Concentrations in Printing Inks (Germany)

Congener/Congener Group	Rotogravure (2-color) (ng/kg)	Rotogravure (4-color) (ng/kg)	Offset (4-color) (ng/kg)	Offset (4-color) (ng/kg)
2,3,7,8-TCDD	ND (1)	ND (1.5)	ND (2)	ND (2)
1,2,3,7,8-PeCDD	8	ND (4)	15	6
1,2,3,4,7,8-HxCDD	19	ND (5)	16	11
1,2,3,6,7,8-HxCDD	325	310	82	21
1,2,3,7,8,9-HxCDD	155	105	42	14
1,2,3,4,6,7,8-HpCDD	2,770	1,630	540	240
OCDD	5,810	2,350	890	230
2,3,7,8-TCDF	2.5	14	7	7
1,2,3,7,8-PeCDF	ND (2)	ND (4)	ND (4)	ND (3)
2,3,4,7,8-PeCDF	ND (2)	ND (4)	ND (4)	ND (3)
1,2,3,4,7,8-HxCDF	4	7	27	35
1,2,3,6,7,8-HxCDF	ND (3)	ND (5)	ND (5)	ND (5)
1,2,3,7,8,9-HxCDF	ND (3)	ND (5)	ND (5)	ND (5)
2,3,4,6,7,8-HxCDF	ND (3)	ND (5)	ND (5)	ND (5)
1,2,3,4,6,7,8-HpCDF	40	14	315	42
1,2,3,4,7,8,9-HpCDF	ND (4)	ND (7)	11	ND (6)
OCDF	129	ND (10)	960	165
Total 2,3,7,8-CDD	9,087	4,395	1,585	522
Total 2,3,7,8-CDF	175.5	35	1320	249
Total I-TEQ_{DF} *	88.6	62.4	35.4	15.0
Total TEQ_{DF}-WHO_{98}	87.2	60.3	41.2	17.7
Total TCDD	4	ND (2)	77	38
Total PeCDD	58	145	35	25
Total HxCDD	2,679	2,485	660	246
Total HpCDD	5,630	3,460	1,100	445
Total OCDD	5,810	2,350	890	230
Total TCDF	5.5	28	90	35
Total PeCDF	13	ND (4)	340	110
Total HxCDF	29	45	95	94
Total HpCDF	64	14	566	63
Total OCDF	129	ND (10)	960	165
Total CDD/CDF	14,422	8,527	4,813	1,451

ND = Not detected; value in parenthesis is the detection limit.
-- = Not reported.
ng/kg = nanograms per kilogram.
* Calculations assume not-detected values are zero.

Source: Santl et al. (1994c).

Table 8-18. Chemicals Requiring TSCA Section 4 Testing under the Dioxin/Furan Rule

Currently Manufactured or Imported as of June 5, 1987[a]	
CAS No.	Chemical Name
79-94-7	Tetrabromobisphenol-A
118-75-2	2,3,5,6-Tetrachloro-2,5-cyclohexadiene-1,4-dione
118-79-6	2,4,6-Tribromophenol
120-83-2	2,4-Dichlorophenol
1163-19-5	Decabromodiphenyloxide
4162-45-2	Tetrabromobisphenol-A-bisethoxylate
21850-44-2	Tetrabromobisphenol-A-bis-2,3-dibromopropylether [a]
25327-89-3	Allyl ether of tetrabromobisphenol-A
32534-81-9	Pentabromodiphenyloxide
32536-52-0	Octabromodiphenyloxide
37853-59-1	1,2-Bis(tribromophenoxy)-ethane
55205-38-4	Tetrabromobisphenol-A-diacrylate [a]
Not Currently Manufactured or Imported as of June 5, 1987[b]	
CAS No.	Chemical Name
79-95-8	Tetrachlorobisphenol-A
87-10-5	3,4',5-Tribromosalicylanide
87-65-0	2,6-Dichlorophenol
95-77-2	3,4-Dichlorophenol
95-95-4	2,4,5-Trichlorophenol
99-28-5	2,6-Dibromo-4-nitrophenol
120-36-5	2[2,4-(Dichlorophenoxy)]-propanoic acid
320-72-9	3,5-Dichlorosalicyclic acid
488-47-1	Tetrabromocatechol
576-24-9	2,3-Dichlorophenol
583-78-8	2,5-Dichlorophenol
608-71-9	Pentabromophenol
615-58-7	2,4-Dibromophenol
933-75-5	2,3,6-Trichlorophenol
1940-42-7	4-Bromo-2,5-dichlorophenol
2577-72-2	3,5-Dibromosalicylanide
3772-94-9	Pentachlorophenyl laurate
37853-61-5	Bismethylether of tetrabromobisphenol-A
-	Alkylamine tetrachlorophenate
-	Tetrabromobisphenol-B

[a] Tetrabromobisphenol-A-bis-2,3-dibromopropylether and tetrabromobisphenol-A-diacrylate are no longer manufactured in or imported into the United States (Cash, 1993).

[b] As of August 5, 1995, neither manufacture nor importation of any of these chemicals had resumed in the United States (Holderman, 1995).

Table 8-19. Congeners and Limits of Quantitation (LOQ) for Which Quantitation is Required under the Dioxin/Furan Test Rule and Pesticide Data Call-In

Chlorinated Dioxins and Furans	Brominated Dioxins and Furans	LOQ (μg/kg)
2,3,7,8-TCDD	2,3,7,8-TBDD	0.1
1,2,3,7,8-PeCDD	1,2,3,7,8-PeBDD	0.5
1,2,3,4,7,8-HxCDD	1,2,3,4,7,8-HxBDD	2.5
1,2,3,6,7,8-HxCDD	1,2,3,6,7,8-HxBDD	2.5
1,2,3,7,8,9-HxCDD	1,2,3,7,8,9-HxBDD	2.5
1,2,3,4,6,7,8-HpCDD	1,2,3,4,6,7,8-HpBDD	100
2,3,7,8-TCDF	2,3,7,8-TBDF	1
1,2,3,7,8-PeCDF	1,2,3,7,8-PeBDF	5
2,3,4,7,8-PeCDF	2,3,4,7,8-PeBDF	5
1,2,3,4,7,8-HxCDF	1,2,3,4,7,8-HxBDF	25
1,2,3,6,7,8-HxCDF	1,2,3,6,7,8-HxBDF	25
1,2,3,7,8,9-HxCDF	1,2,3,7,8,9-HxBDF	25
2,3,4,6,7,8-HxCDF	2,3,4,6,7,8-HxBDF	25
1,2,3,4,6,7,8-HpCDF	1,2,3,4,6,7,8-HpBDF	1,000
1,2,3,4,7,8,9-HpCDF	1,2,3,4,7,8,9-HpBDF	1,000

μg/kg = microgram per kilogram

Table 8-20. Precursor Chemicals Subject to Reporting Requirements under TSCA Section 8(a)

CAS No.	Chemical Name
85-22-3	Pentabromoethylbenzene
87-61-6	1,2,3-Trichlorobenzene
87-84-3	1,2,3,4,5-Pentabromo-6-chlorocyclohexane
89-61-2	1,4-Dichloro-2-nitrobenzene
89-64-5	4-Chloro-2-nitrophenol
89-69-0	2,4,5-Trichloronitrobenzene
92-04-6	2-Chloro-4-phenylphenol
97-74-6	4-Chloro-o-toloxy acetic acid
94-81-5	4-(2-Methyl-4-chlorophenoxy) butyric acid
95-50-1	o-Dichlorobenzene
95-56-7	o-Bromophenol
95-57-8	o-Chlorophenol
95-88-5	4-Chlororesorcinol
95-94-3	1,2,4,5-Tetrachlorobenzene
95-50-7	5-Chloro-2,4-dimethoxyaniline
99-30-9	2,6-Dichloro-4-nitroaniline
99-54-7	1,2-Dichloro-4-nitrobenzene
106-37-6	Dibromobenzene
106-46-7	p-Dichlorobenzene
108-70-3	1,3,5-Trichlorobenzene
108-86-1	Bromobenzene
108-90-7	Chlorobenzene
117-18-0	1,2,4,5-Tetrachloro-3-nitrobenzene
120-82-1	1,2,4-Trichlorobenzene
348-51-6	o-Chlorofluorobenzene
350-30-1	3-Chloro-4-fluoronitrobenzene
615-67-8	Chlorohydroquinone
626-39-1	1,3,5-Tribromobenzene
827-94-1	2,6-Dibromo-4-nitroaniline

Table 8-21. Results of Analytical Testing for Dioxins and Furans in the Chemicals Tested to Date under Section 4 of the Dioxin/Furan Test Rule

CAS Number	Chemical Name	No. of Chemical Companies That Submitted Data	No. of Positive Studies	Congeners Detected (detection range: μg/kg)
79-94-7	Tetrabromobisphenol-A	3	0	ND[a]
118-75-2	2,3,5,6-Tetrachloro-2,5-cyclohexadiene-1,4-dione (chloranil)	4	4	See Table 8-22
118-79-6	2,4,6-Tribromophenol	1	0	ND[a]
120-83-2	2,4-Dichlorophenol	1	0	ND[a]
1163-19-5	Decabromodiphenyl oxide	3	3	2,3,7,8-PeBDD (ND-0.1) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDD (ND-0.5) 1,2,3,7,8,9-HxBDD (ND-0.76) 1,2,3,7,8-PeBDF (ND-0.7) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDF (ND-0.8) 1,2,3,4,6,7,8-HpBDF (17-186)
25327-89-3	Allyl ether of tetrabromobisphenol-A	1	0	ND[a]
32536-52-0	Octabromodiphenyl oxide	3	3	2,3,7,8-TBDD (ND-0.71) 1,2,3,7,8-PeBDD (ND-0.1) 2,3,7,8-TBDF (ND-12.6) 1,2,3,7,8-PeBDF (ND-6.3) 2,3,4,7,8-PeBDF (ND-83.1) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDF (ND-67.8) 1,2,3,7,8,9-HxBDF (ND-56.0) 1,2,3,4,6,7,8-HpBDF (ND-330)
378-53-59-1	1,2-Bis(tribromo-phenoxy)-ethane	1	1	2,3,7,8-TBDF (ND-0.04) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDF (ND-0.03) 1,2,3,4,6,7,8-HpBDF (ND-0.33)
32534-81-9	Pentabromodiphenyl oxide	2	2	1,2,3,7,8-PeBDD (ND-5.9) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDD (ND-6.8) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDD (ND-6.8) 1,2,3,7,8,9-HxBDD (ND-0.02) 2,3,7,8-TBDF(ND-3.1) 1,2,3,7,8-PeBDF (0.7-10.2) 2,3,4,7,8-PeBDF (0.1-2.9) 1,2,3,4,7,8/1,2,3,6,7,8-HxBDF (15.6-61.2) 1,2,3,4,6,7,8-HpBDF (0.7-3.0)
4162-45-2	Tetrabromobisphenol-A-bisethoxylate	1	0	ND[a]

μg/kg = micrograms per kilogram

[a] No 2,3,7,8-substituted dioxins and furans detected above the Test Rule target limits of quantitation (LOQ). (See Table 8-18.)

Source: Holderman and Cramer (1995).

Table 8-22. CDDs and CDFs in Chloranil and Carbazole Violet Samples Analyzed Pursuant to the EPA Dioxin/Furan Test Rule

Congener	Concentration (µg/kg) in Chloranil				Concentration (µg/kg) in Carbazole Violet
	Importer 1	Importer 2	Importer 3	Importer 4	
2,3,7,8-TCDD	nd (1)	nd (1)	nd (2)	nd (2)	nd (0.8)
1,2,3,7,8-PeCDD	nd (2)	nd (2)	nd (5)	nd (6)	nd (0.5)
1,2,3,4,7,8-HxCDD	nd (3)	nd (10)	nd (5)	nd (3)	nd (1.2)
1,2,3,6,7,8-HxCDD	nd (3)	75	nd (5)	6	nd (1.2)
1,2,3,7,8,9-HxCDD	nd (1)	48	nd (5)	9	nd (1.2)
1,2,3,4,6,7,8-HpCDD	110	8,200	390	2,300	28
OCDD	240,000	180,000	760,000	71,000	1,600
2,3,7,8-TCDF	nd (1)	nd (2)	nd (1)	nd (2)	nd (1.6)
1,2,3,7,8-PeCDF	nd (1)	nd (1)	nd (3)	nd (5)	nd (0.9)
2,3,4,7,8-PeCDF	nd (1)	nd (1)	nd (3)	nd (5)	nd (0.9)
1,2,3,4,7,8-HxCDF	35	nd (860)	nd (4)	5,600	nd (20)
1,2,3,6,7,8-HxCDF	nd (5)	nd (860)	nd (4)	nd (600)	nd (20)
1,2,3,7,8,9-HxCDF	6	nd (680)	nd (4)	nd (600)	nd (20)
2,3,4,6,7,8-HxCDF	nd (5)	nd (680)	nd (4)	nd (600)	nd (20)
1,2,3,4,6,7,8-HpCDF	33	240,000	36	230,000	15,000
1,2,3,4,7,8,9-HpCDF	nd (15)	nd (100)	nd (15)	nd (400)	nd (20)
OCDF	18,000	200,000	50,000	110,000	59,000
TOTAL I-TEQ_{DF}*	263	2,874	814	3,065	211
TOTAL TEQ_{DF}-WHO_{98}*	31	2,532	85	2,903	156

nd = Not detected; minimum limit of detection shown in parentheses.
µg/kg = micrograms per kilogram.

* Calculated assuming not-detected values are zero.

Source: Remmers et al. (1992).

Table 8-23. Status of First Pesticide Data Call-In: Pesticides Suspected of Having the Potential to Become Contaminated with Dioxins if Synthesized under Conditions Favoring Dioxin Formation

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
000014	Dichlorodifluoromethane	75-71-8	Yes	--
008706	O-(4-Bromo-2,5-dichlorophenyl) O,O-dimethyl phosphorothioate	2104-96-3	Yes	--
009105	Dimethylamine 2,3,5-triiodobenzoate	17601-49-9	Yes	--
012001	Neburon	555-37-3	Yes	--
012101	Crufomate	299-86-5	Yes	--
019201	MCPB, 4-butyric acid [4-(2-Methyl-4-chlorophenoxy)butyric acid]	94-81-5	No	Yes
019202	MCPB, Na salt [Sodium 4-(2-methyl-4-chlorophenoxy)butyrate]	6062-26-6	No	No
019401	4-Chlorophenoxyacetic acid	122-88-3	No	Yes
025501	Chloroxuron	1982-47-4	Yes	--
027401	Dichlobenil	1194-65-6	No	Yes
028201	Propanil [3',4'-Dichloropropionanilide]	709-98-8	No	No
028601	Dichlofenthion [O-(2,4-Dichlorophenyl) O,O-diethyl phosphorothioate)]	97-17-6	Yes	--
029201	DDT [Dichloro diphenyl trichloroethane]	50-29-3	Yes	--
029601	Dichlone [2,3-dichloro-1,4-naphthoquinone]	117-80-6	Yes	--
029902	Ammonium chloramben [3-amino-2,5-dichlorobenzoic acid]	1076-46-6	Yes	--
029906	Sodium chloramben [3-amino-2,5-dichlorobenzoic acid]	1954-81-0	Yes	--
030602	Sodium 2-(2,4-dichlorophenoxy)ethyl sulfate	136-78-7	Yes	--
031301	DCNA [2,6-Dichloro-4-nitroaniline]	99-30-9	No	Yes
031503	Potassium 2-(2-methyl-4-chlorophenoxy)propionate	1929-86-8	Yes	--
031516	MCCP, DEA Salt [Diethanolamine 2-(2-methyl-4-chlorophenoxy)propionate]	1432-14-0	Yes	--
031563	MCPP, IOE [Isooctyl 2-(2-methyl-4-chlorophenoxy)propionate]	28473-03-2	No	No
034502	Dicapthon [O-(2-chloro-4-nitrophenyl) O,O-dimethyl phosphorothioate]	2463-84-5	Yes	--
035502	Monuron trichloroacetate [3-(4-chlorophenyl)-1,1-dimethylurea trichloroacetate]	140-41-0	Yes	--
035505	Diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea]	330-54-1	No	No

Table 8-23. Status of First Pesticide Data Call-In: Pesticides Suspected of Having the Potential to Become Contaminated with Dioxins if Synthesized under Conditions Favoring Dioxin Formation (continued)

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
035506	Linuron [3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea]	330-55-2	No	No
035901	Metobromuron [3-(p-bromophenyl)-1-methoxy-1-methylurea]	3060-89-7	Yes	--
053501	Methyl parathion [O,O-Dimethyl O-p-nitrophenyl phosphorothioate]	298-00-0	No	No
055001	Dichlorophene [Sodium 2,2'-methylenebis(4-chlorophenate)]	97-23-4	Yes	--
055005	Dichlorophene, sodium salt [Sodium 2,2'-methylenebis(4-chlorophenate)]	10254-48-5	Yes	--
055201	1,2,4,5-Tetrachloro-3-nitrobenzene	117-18-0	Yes	--
057501	Ethyl parathion [O,O-diethyl O-p-nitrophenyl phosphorothioate]	56-38-2	No	No
058102	Carbophenothion [S-(((p-chlorophenyl)thio)methyl) O,O-diethyl phosphorodithioate]	786-19-6	Yes	--
058301	Ronnel [O,O-dimethyl O-(2,4,5-trichlorophenyl) phosphorothioate]	229-84-3	Yes	--
058802	Mitin FF [Sodium 5-chloro-2-(4-chloro-2-(3-(3,4-dichlorophenyl)ureido)phenoxy) benzenesulfonate]	3567-25-7	No	No
059401	Orthodichlorobenzene	95-50-1	Yes	--
061501	Paradichlorobenzene	106-46-7	No	No
062201	Chlorophene [2-Benzyl-4-chlorophenol]	120-32-1	No	No
062202	Potassium 2-benzyl-4-chlorophenate	35471-49-9	No	In review
062203	Sodium 2-benzyl-4-chlorophenate	3184-65-4	No	In review
062204	2-Chlorophenol	95-57-8	Yes	--
062206	2-Chloro-4-phenylphenol	92-04-6	Yes	--
062207	Potassium 2-chloro-4-phenylphenate	18128-16-0	Yes	--
062208	4-Chloro-2-phenylphenol	not available	Yes	--
062209	4-Chloro-2-phenylphenol, potassium salt	53404-21-0	Yes	--
062210	6-Chloro-2-phenylphenol	85-97-2	Yes	--
062211	6-Chloro-2-phenylphenol, potassium salt	18128-17-1	Yes	--
062212	4-Chloro-2-phenylphenol, sodium salt	10605-10-4	Yes	--
062213	6-Chloro-2-phenylphenol, sodium salt	10605-11-5	Yes	--

Table 8-23. Status of First Pesticide Data Call-In: Pesticides Suspected of Having the Potential to Become Contaminated with Dioxins if Synthesized under Conditions Favoring Dioxin Formation (continued)

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
062214	4 and 6-Chloro-2-phenylphenol, diethanolamine salt	53537-63-6	Yes	--
062215	2-Chloro-4-phenylphenol, sodium salt	31366-97-9	Yes	--
064202	4-Chloro-2-cyclopentylphenol	13347-42-7	Yes	--
064208	Fentichlor [2,2'-Thiobis(4-chloro-6-methylphenol)]	4418-66-0	Yes	--
064209	Fentichlor [2,2'-Thiobis(4-chlorophenol)]	97-24-5	Yes	--
064214	4-Chloro-2-cyclopentylphenol, potassium salt of	35471-38-6	Yes	--
064218	4-Chloro-2-cyclopentylphenol, sodium salt	53404-20-9	Yes	-
067707	Chlorophacinone	3691-35-8	No	No
069105	ADBAC [Alkyl* dimethyl benzyl ammonium chloride *(50% C14, 40% C12, 10% C16)]	68424-85-1	No	No
069144	ADBAC [Alkyl* dimethyl 3,4-dichlorobenzyl ammonium chloride *(61% C12, 23% C14, 11% C16, 5% C18)]	not available	No	No
077401	Niclosamide [2-Aminoethanol salt of 2',5-dichloro-4'-nitrosalicylanilide]	1420-04-8	No	No
077406	5-Chlorosalicylanilide	4638-48-6	Yes	--
078780	2-Methyl-4-isothiazolin-3-one	Not available	Yes	--
079202	Tetradifon [4-chlorophenyl 2,4,5-trichlorophenyl sulfone]	116-29-0	Yes	--
079301	Chloranil [tetrachloro-p-benzoquinone]	118-75-2	Yes	--
080403	6-Chlorothymol	89-68-9	Yes	--
080811	Anilazine [2,4-Dichloro-6-(o-chloroanilino)-s-triazine]	101-05-3	Yes	--
081901	Chlorothalonil [tetrachloroisophthalonitrile]	1897-45-6	No	Yes
082602	Sodium 2,3,6-Trichlorophenylacetate	2439-00-1	Yes	--
084101	Chlorfenvinphos	470-90-6	Yes	--

Table 8-23. Status of First Pesticide Data Call-In: Pesticides Suspected of Having the Potential to Become Contaminated with Dioxins if Synthesized under Conditions Favoring Dioxin Formation (continued)

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
100601	Fenamiphos	Not available	No	No
101001	p-Chlorophenyl diiodomethyl sulfone	20018-12-6	Yes	--
101101	Metribuzin	21087-64-9	No	No
104301	Bifenox [methyl 5-(2,4-dichlorophenoxy)-2-nitrobenzoate]	42576-02-3	Yes	--
106001	Methazole [2-(3,4-dichlorophenyl)-4-methyl-1,2,4-oxadiazolidine-3,5-dione]	20354-26-1	Yes	--
108201	Diflubenzuron [N-(((4-chlorophenyl)amino)carbonyl)-2,6-difluorobenzamide]	35367-38-5	No	Yes
109001	Oxadiazon [2-tert-butyl-4-(2,4-dichloro-5-isopropoxyphenyl)- delta 2 -1,3,4-oxadiazoline-5-one]	19666-30-9	No	Yes
109301	Fenvalerate	51630-58-1	No	In review
109302	Fluvalinate [N-2-Chloro-4-trifluoromethyl)phenyl-DL-valine (+-)-cyano(3-phenoxy-phenyl)methyl ester]	69409-94-5	No	No
109801	Iprodione [3-(3,5-Dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide (9CA)]	36734-19-7	No	No
109901	Triadimefon [1-(4-Chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butanone]	43121-43-3	No	No
110902	Diclofop - methyl [methyl 2-(4-(2,4-dichlorophenoxy)phenoxy)propanoate]	51338-27-3	No	Yes
111401	Profenofos [O-(4-Bromo-2-chlorophenyl)-O-ethyl S-propyl phosphorothioate]	41198-08-7	No	In review
111601	Oxyfluorfen [2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene]	42874-03-3	No	In review
111901	Imazalil [1-(2-(2,4-Dichlorophenyl)-2-(2-propenyloxy)ethyl)-1H-imidazole]	35554-44-0	No	No
112802	Bromothalin [N-Methyl-2,4-dinitro-n-(2,4,6-tribromophenyl)-6-(trifuloromethyl)benzenamine]	63333-35-7	No	No
113201	Vinclozolin [3-(3,5-Dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedione (9CA)]	50471-44-8	No	No
119001	Fenridazon [Potassium 1-(p-chlorophenyl)-1,4-dihydro-6-methyl-4-oxo- pyridazine-3-carboxylate]	83588-43-6	No	In review
123901	Tridiphane [2-(3,5-Dichlorophenyl)-2-(2,2,2-trichloroethyl) oxirane]	58138-08-2	No	No
125601	Paclobutrazol	76738-62-0	No	No
128838	Linalool	78-70-6	No	In review
206600	Fenarimol [a-(2-chlorophenyl)-a-(4-chlorophenyl)-5-pyrimidinemethanol]	60168-88-9	No	No

Table 8-24. Status of Second Pesticide Data Call-In: Pesticides Suspected of Being Contaminated with Dioxins

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
029801	Dicamba [3,6-dichloro-o-anisic acid]	1918-00-9	No	Yes
029802	Dicamba dimethylamine [3,6-dichloro-o-anisic acid]	2300-66-5	No	Yes
029803	Diethanolamine dicamba [3,6-dichloro-2-anisic acid]	25059-78-3	Yes	--
030001	2,4-Dichlorophenoxyacetic acid	94-75-7	No	Yes
030002	Lithium 2,4-dichlorophenoxyacetate	3766-27-6	No	No
030003	Potassium 2,4-dichlorophenoxyacetate	14214-89-2	Yes	--
030004	Sodium 2,4-dichlorophenoxyacetate	2702-72-9	No	No
030005	Ammonium 2,4-dichlorophenoxyacetate	2307-55-3	Yes	--
030010	Alkanol* amine 2,4-dichlorophenoxyacetate *(salts of the ethanol and ispropanol series)	Not available	Yes	--
030011	Alkyl* amine 2,4-dichlorophenoxyacetate *(100% C12)	2212-54-6	Yes	--
030013	Alkyl* amine 2,4-dichlorophenoxyacetate *(100% C14)	28685-18-9	Yes	--
030014	Alkyl* amine 2,4-dichlorophenoxyacetate *(as in fatty acids of tall oil)	Not available	Yes	--
030016	Diethanolamine 2,4-dichlorophenoxyacetate	5742-19-8	No	No
030017	Diethylamine 2,4-dichlorophenoxyacetate	20940-37-8	Yes	--
030019	Dimethylamine 2,4-dichlorophenoxyacetate	2008-39-1	No	No
030020	N,N-Dimethyloleylamine 2,4-dichlorophenoxyacetate	53535-36-7	Yes	--
030021	Ethanolamine 2,4-dichlorophenoxyacetate	3599-58-4	Yes	--
030023	Heptylamine 2,4-dichlorophenoxyacetate	37102-63-9	Yes	--
030024	Isopropanolamine 2,4-dichlorophenoxyacetate	6365-72-6	Yes	--
030025	Isopropylamine 2,4-dichlorophenoxyacetate	5742-17-6	No	No
030028	Morpholine 2,4-dichlorophenoxyacetate	6365-73-7	Yes	--
030029	N-Oleyl-1,3-propylenediamine 2,4-dichlorophenoxyacetate	2212-59-1	Yes	--
030030	Octylamine 2,4-dichlorophenoxyacetate	2212-53-5	Yes	--
030033	Triethanolamine 2,4-dichlorophenoxyacetate	2569-01-9	Yes	--
030034	Triethylamine 2,4-dichlorophenoxyacetate	2646-78-8	No	No

Table 8-24. Status of Second Pesticide Data Call-In: Pesticides Suspected of Being Contaminated with Dioxins (continued)

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
030035	Triisopropanolamine 2,4-dichlorophenoxyacetate	32341-80-3	No	No
030039	N,N-Dimethyl oleyl-linoleyl amine 2,4-dichlorophenoxyacetate	55256-32-1	Yes	--
030052	Butoxyethoxypropyl 2,4-dichlorophenoxyacetate	1928-57-0	Yes	--
030053	Butoxyethyl 2,4-dichlorophenoxyacetate	1929-73-3	No	No
030055	Butoxypropyl 2,4-dichlorophenoxyacetate	1928-45-6	Yes	--
030056	Butyl 2,4-dichlorophenoxyacetate	94-80-4	Yes	--
030062	Isobutyl 2,4-dichlorophenoxyacetate	1713-15-1	Yes	--
030063	Isooctyl(2-ethylhexyl) 2,4-dichlorophenoxyacetate	1928-43-4	No	Yes
030064	Isooctyl(2-ethyl-4-methylpentyl) 2,4-dichlorophenoxyacetate	25168-26-7	Yes	--
030065	Isooctyl(2-octyl) 2,4-dichlorophenoxyacetate	1917-97-1	Yes	--
030066	Isopropyl 2,4-dichlorophenoxyacetate	94-11-1	No	No
030072	Propylene glycol butyl ether 2,4-dichlorophenoxyacetate	1320-18-9	Yes	--
030801	4-(2,4-Dichlorophenoxy)butyric acid	94-82-6	No	Yes
030804	Sodium 4-(2,4-dichlorophenoxy)butyrate	10433-59-7	No	No
030819	Dimethylamine 4-(2,4-dichlorophenoxy)butyrate	2758-42-1	No	No
030853	Butoxyethanol 4-(2,4-dichlorophenoxy)butyrate	32357-46-3	Yes	--
030856	Butyl 4-(2,4-dichlorophenoxy)butyrate	6753-24-8	Yes	--
030863	Isooctyl 4-(2,4-dichlorophenoxy)butyrate	1320-15-6	Yes	--
031401	2-(2,4-Dichlorophenoxy)propionic acid	120-36-5	No	Yes
031419	Dimethylamine 2-(2,4-dichlorophenoxy)propionate	53404-32-3	No	No
031453	Butoxyethyl 2-(2,4-dichlorophenoxy)propionate	53404-31-2	No	No
031463	Isooctyl 2-(2,4-dichlorophenoxy)propionate	28631-35-8	No	No

Table 8-24. Status of Second Pesticide Data Call-In: Pesticides Suspected of Being Contaminated with Dioxins (continued)

Shaughnessey Code	Pesticide [Active Ingredient]	CAS Number	Support Withdrawn	Testing Required
031519	MCPP, DMA [Dimethylamine 2-(2-methyl-4-chlorophenoxy)propionate]	32351-70-5	No	No
035301	Bromoxynil [3,5-dibromo-4-hydroxybenzonitrile]	1689-84-5	No	Yes
044901	Hexachlorophene [2,2'-Methylenebis(3,4,6-trichlorophenol)]	70-30-4	Yes	--
044902	Hexachlorophene, Na salt [Monosodium 2,2'-methylenebis(3,4,6-trichlorophenate)]	5736-15-2	Yes	--
044904	Hexachlorophene, K salt [Potassium 2,2'-methylenebis(3,4,6-trichlorophenate)]	67923-62-0	Yes	--
054901	Irgasan [5-Chloro-2-(2,4-dichlorophenoxy)phenol]	3380-34-5	No	Yes
063004	Tetrachlorophenols	25167-83-3	Yes	--
063005	Tetrachlorophenols, sodium salt	25567-55-9	Yes	--
063006	Tetrachlorophenols, alkyl* amine salt*(as in fatty acids of coconut oil)	not available	Yes	--
063007	Tetrachlorophenols, potassium salt	53535-27-6	Yes	--
064203	Bithionolate sodium [Disodium 2,2'-thiobis(4,6-dichlorophenate)]	6385-58-6	Yes	--
064212	Phenachlor [2,4,6-Trichlorophenol]	88-06-2	Yes	--
064219	Potassium 2,4,6-trichlorophenate	2591-21-1	Yes	--
064220	2,4,6-Trichlorophenol, sodium salt	3784-03-0	Yes	--
064501	Phenothiazine	92-84-2	Yes	--
078701	Dacthal-DCPA [Dimethyl tetrachloroterephthalate]	1861-32-1	No	Yes
079401	Endosulfan [hexachlorohexahydromethano-2,4,3-benzodioxathiepin-3-oxide]	115-29-7	No	No
082501	Silvex [2-(2,4,5-trichlorophenoxy)propionic acid]	93-72-1	Yes	--
083701	Tetrachlorvinphos [2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate]	961-11-5	No	Yes
104101	Edolan [Sodium 1,4',5'-trichloro-2'-(2,4,5-trichlorophenoxy) methanesulfonanilide]	69462-14-2	Yes	--

Table 8-25. Summary of Results for CDDs and CDFs in Technical 2,4-D and 2,4-D Ester Herbicides

Congener	EPA LOQ[a] (μg/kg)	Total Number of Technicals	Number of Technicals Greater Than LOQ	Observed Maximum Concentration (μg/kg)	Average Concentration[b] (μg/kg)
2,3,7,8-TCDD	0.1	8	2	0.13	0.06
1,2,3,7,8-PeCDD	0.5	8	3	2.6	0.78
1,2,3,4,7,8-HxCDD	2.5	8	0	0.81	0.31
1,2,3,6,7,8-HxCDD	2.5	8	0	0.77	0.39
1,2,3,7,8,9-HxCDD	2.5	8	0	0.68	0.24
1,2,3,4,6,7,8-HpCDD	100	8	0	1.5	0.21
OCDD	--	--	--	--	--
2,3,7,8-TCDF	1	8	0	0.27	0.07
1,2,3,7,8-PeCDF	5	8	0	0.62	0.38
2,3,4,7,8-PeCDF	5	7	0	0.73	0.07
1,2,3,4,7,8-HxCDF	25	8	0	1.6	0.36
1,2,3,6,7,8-HxCDF	25	8	0	1.2	0.11
1,2,3,7,8,9-HxCDF	25	8	0	1.4	0.16
2,3,4,6,7,8-HxCDF	25	8	0	1.1	0.14
1,2,3,4,6,7,8-HpCDF	1000	8	0	8.3	2.17
1,2,3,4,7,8,9-HpCDF	1000	8	0	1.2	0.18
OCDF	--	--	--	--	--
				TOTAL[c]	5.60
				I-TEQ_{DF}	0.70
				TEQ_{DF}-WHO_{98}	1.10

[a] Limit of quantitation required by EPA in the Data Call-In.

[b] Average of the mean results for multiple analyses of four technical 2,4-D and/or 2,4-D ester products for which detectable CDD/CDF congener concentrations less than the LOQs were quantified; not-detected values were assumed to be zero.

[c] Total equals the sum of the individual congener averages.

μg/kg = micrograms per kilogram

-- = Analyses not performed.

Source: U.S. EPA Office of Pesticide Program file.

Table 8-26. Summary of Analytical Data Submitted to EPA in Response to Pesticide Data Call-Ins

Shaughnessey Code	Pesticide		Number of Positive Submissions[a] to Date
	Common Name	Chemical Name	
019201	MCPB, 4-butyric acid	4-(2-methyl-4-chlorophenoxy)butyric acid	0
019401	4-CPA	4-Chlorophenoxyacetic acid	0
027401	Dichlobenil	2,6-Dichlorobenzonitrile	0
029801	Dicamba	3,6-Dichloro-o-anisic acid	0
029802	Dicamba, dimethylamine	3,6-Dichloro-o-anisic acid, dimethylamine salt	0
030001	2,4-D	2,4-Dichlorophenoxy acetic acid	2
030063	2,4-D, 2EH	Isooctyl(2-ethylhexyl)2,4-dichlorophenoxyacetate	1
030801	2,4-DB	4-(2,4-Dichlorophenoxy)butyric acid	0
031301	DCNA	2,6-Dichloro-4-nitroaniline	Pending
031401	2,4-DP	2-(2,4-Dichlorophenoxy)propionic acid	0
031501	Mecoprop (MCPP)	2-(2-methyl-4-chlorophenoxy)propionic acid	0
035301	Bromoxynil	3,5-Dibromo-4-hydroxybenzonitrile	0
054901	Irgasan	5-Chloro-2-(2,4-dichlorophenoxy)phenol	0
078701	Dacthal (DCPA)	Dimethyl tetrachloroterephthalate	Pending
081901	Chlorothalonil	Tetrachloroisophthalonitrile	Pending
083701	Tetrachlorvinphos	2-Chloro-1-(2,4,5-trichlorophenyl)vinyl dimethyl phosphate	0
108201	Diflubenzuron	N-(((4-chlorophenyl)amino)carbonyl)-2,6-difluorobenzamide	0
109001	Oxadiazon	2-Tert-butyl-4(2,4-dichloro-5-isopropoxyphenyl)-delta2-1,3,4-oxadiazoline-5-one	Pending
110902	Dichlofop-methyl	Methyl-2-(4-(2,4-dichlorophenoxy)phenoxy) propanoate	0

[a] "Positive" is defined as the detection of any congener at a concentration equal to or exceeding the LOQs listed in Table 8-24.

Sources: U.S. EPA (1995a); personal communication with S. Funk (EPA/OPP/HED) on March 27, 1996.

Table 8-27. CDD/CDF Concentrations in Samples of 2,4-D and Pesticide Formulations Containing 2,4-D

Congener/Congener Group	Acbar Super (Gaza City*) (μg/kg)	Amco Super (Gaza City*) (μg/kg)	(Bethlehem)* (μg/kg)	Chimprom (Russia) (μg/kg)	Dragon Lawn Weed Killer (μg/kg)	KGRO (U.S.) (μg/kg)	Pro Care Premium (U.S.) (μg/kg)	Ortho Weed-B-Gone (U.S.) (μg/kg)	Sigma Co. (U.S.) (μg/kg)	American Brand Chemical Co. (U.S.) (μg/kg)
2,3,7,8-TCDD	ND (0.1)	ND (0.1)	ND (0.1)	ND (0.02)	ND (0.001)	--	--	--	--	--
1,2,3,7,8-PeCDD	0.1	ND (0.1)	1.2	0.03	0.0014	--	--	--	--	--
1,2,3,4,7,8-HxCDD	ND (0.1)	ND (0.1)	ND (0.1)	0.02	ND (0.001)	--	--	--	--	--
1,2,3,6,7,8-HxCDD	ND (0.1)	0.2	0.6	0.05	0.0024	--	--	--	--	--
1,2,3,7,8,9-HxCDD	ND (0.1)	ND (0.1)	0.4	ND (0.02)	0.0010	--	--	--	--	--
1,2,3,4,6,7,8-HpCDD	0.1	1.2	0.3	0.23	0.0017	--	--	--	--	--
OCDD	0.1	2.6	0.1	0.85	0.0063	--	--	--	--	--
2,3,7,8-TCDF	0.3	ND (0.1)	ND (0.1)	ND (0.1)	0.0036	--	--	--	--	--
1,2,3,7,8-/1,2,3,4,8-PeCDF	ND (0.1)	0.2	0.7	1.2	0.0010	--	--	--	--	--
2,3,4,7,8-PeCDF	ND (0.1)	ND (0.1)	0.1	0.06	0.0011	--	--	--	--	--
1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF	ND (0.1)	0.1	0.4	0.08	0.0013	--	--	--	--	--
	ND (0.1)	ND (0.1)	0.1	0.11	ND (0.001)	--	--	--	--	--
1,2,3,6,7,8-HxCDF	ND (0.1)	ND (0.1)	ND (0.1)	ND (0.02)	ND (0.001)	--	--	--	--	--
1,2,3,7,8,9-HxCDF	ND (0.1)	ND (0.1)	0.1	0.05	0.0011	--	--	--	--	--
2,3,4,6,7,8-HxCDF	0.1	0.8	0.1	0.24	0.0016	--	--	--	--	--
1,2,3,4,6,7,8-HpCDF	ND (0.1)	ND (0.1)	ND (0.1)	0.02	ND (0.001)	--	--	--	--	--
1,2,3,4,7,8,9-HpCDF	0.2	3.8	0.4	0.46	0.0039	--	--	--	--	--
OCDF										
Total 2,3,7,8-CDD (ND = 0)	0.3	4	2.6	1.18	0.0128	0.0144	0.0143	0.0091	0.127	0.0278
Total 2,3,7,8-CDF (ND = 0)	0.6	4.9	1.9	2.22	0.0136	0.1628	0.4253	0.1095	3.0507	0.0822
Total I-TEQ_{DF} (ND = 0)**	0.082	0.066	0.850	0.142	0.0023	0.0009	0.0012	0.0014	0.0013	0.0019
Total TEQ_{DF}-WHO_{98} (ND = 0)**	0.134	0.061	1.449	0.156	0.0030					
Total TCDD	--	--	--	--	--	--	--	--	--	--
Total PeCDD	--	--	--	--	--	--	--	--	--	--
Total HxCDD	--	--	--	--	--	--	--	--	--	--
Total HpCDD	--	--	--	--	--	--	--	--	--	--
Total OCDD	--	--	--	--	--	--	--	--	--	--
Total TCDF	--	--	--	--	--	--	--	--	--	--
Total PeCDF	--	--	--	--	--	--	--	--	--	--
Total HxCDF	--	--	--	--	--	--	--	--	--	--
Total HpCDF	--	--	--	--	--	--	--	--	--	--
Total OCDF	--	--	--	--	--	--	--	--	--	--
Total CDD/CDF	--	--	--	--	--	--	--	--	--	--

-- = Not reported.
μg/kg = micrograms per kilogram
* 2,4-D manufactured in Europe and packaged in Palestine.
** Calculated assuming not-detected values are zero.

Table 8-28. Mean CDD/CDF Measurements in Effluents from Nine U.S. POTWs

Congener/Congener Group	No. Detections/ No. Samples	Range of Detection Limits (pg/L)	Range of Detected Concentrations (POTW mean basis)		Overall Means*	
			Minimum Detected Conc. (pg/L)	Maximum Detected Conc. (pg/L)	Mean Conc. (ND = 0) (pg/L)	Mean Conc. (ND = 1/2DL) (pg/L)
2,3,7,8-TCDD	0/30	0.31 - 8.8	nd	nd	0.00	0.98
1,2,3,7,8-PeCDD	0/30	0.45 - 15	nd	nd	0.00	1.32
1,2,3,4,7,8-HxCDD	0/30	0.43 - 9.8	nd	nd	0.00	1.38
1,2,3,6,7,8-HxCDD	0/30	0.81 - 10	nd	nd	0.00	1.42
1,2,3,7,8,9-HxCDD	0/30	0.42 - 9.7	nd	nd	0.00	1.31
1,2,3,4,6,7,8-HpCDD	3/30	0.75 - 18	nd	5.0	1.06	3.61
OCDD	13/30	6.2 - 57	nd	99.75	29.51	37.95
2,3,7,8-TCDF	1/27	0.74 - 4.4	nd	1.3	0.14	0.98
1,2,3,7,8-PeCDF	1/30	0.64 - 9.4	nd	2.0	0.22	1.58
2,3,4,7,8-PeCDF	1/30	0.61 - 14	nd	2.8	0.31	1.68
1,2,3,4,7,8-HxCDF	1/30	0.25 - 6.8	nd	2.4	0.27	1.22
1,2,3,6,7,8-HxCDF	1/30	0.23 - 6.8	nd	1.5	0.17	0.97
1,2,3,7,8,9-HxCDF	1/30	0.57 - 10	nd	2.0	0.22	1.72
2,3,4,6,7,8-HxCDF	1/30	0.25 - 7.9	nd	nd	0.00	0.93
1,2,3,4,6,7,8-HpCDF	2/30	0.36 - 6.9	nd	4.6	0.68	1.83
1,2,3,4,7,8,9-HpCDF	0/30	0.19 - 11	nd	nd	0.00	1.18
OCDF	1/30	0.86 - 28	nd	3.2	0.36	3.40
Total 2,3,7,8-CDD			nd	99.75	30.57	47.98
Total 2,3,7,8-CDF			nd	16.6	2.37	15.49
Total I-TEQ_{DF}			nd	2.42	0.29	3.66
Total TEQ_{DF}-WHO_{98}			nd	2.33	0.27	4.28
Total TCDD	4/27	1.2 - 8.8	nd	9.7	1.23	2.61
Total PeCDD	0/27	0.62 - 200	nd	nd	0.00	6.27
Total HxCDD	1/30	0.84 - 11	nd	1.7	0.19	1.93
Total HpCDD	3/30	0.75 - 18	nd	8.4	1.83	4.77
Total OCDD	13/30	6.2 - 57	nd	99.75	29.51	37.95
Total TCDF	2/30	0.39 - 6.8	nd	25.0	6.61	7.70
Total PeCDF	1/30	0.64 - 25	nd	20.0	2.22	4.72
Total HxCDF	1/30	0.93 - 17	nd	13.0	1.44	3.43
Total HpCDF	2/30	0.36 - 19	nd	4.6	0.68	2.41
Total OCDF	1/30	0.86 - 28	nd	3.2	0.36	3.40
Total CDD/CDF			nd	99.75	42.00	71.96

nd = Not detected.
pg/L = picograms per liter.

* The "overall means" are the means of the individual POTW mean concentrations rather than the means of the individual sample concentrations.

Source: California Regional Water Quality Control Board (1996).

Table 8-29. CDD/CDF Concentrations Measured in EPA's National Sewage Sludge Survey

Congener	Percent Detected	Maximum Concentration Detected (ng/kg)	Median Concentration (ng/kg)		Mean Concentration (ng/kg)	
			Nondetects Set to Det. Limit	Nondetects Set to Zero	Nondetects Set to Det. Limit	Nondetects Set to Zero
2,3,7,8-TCDD	16	116	6.86	0	NR	NR
1,2,3,7,8-PeCDD	18	736	9.84	0	NR	NR
1,2,3,4,7,8-HxCDD	25	737	22.5	0	NR	NR
1,2,3,6,7,8-HxCDD	49	737	27.3	0	NR	NR
1,2,3,7,8,9-HxCDD	39	737	28.0	0	NR	NR
1,2,3,4,6,7,8-HpCDD	98	52,500	335	335	NR	NR
OCDD	100	905,000	3,320	3,320	NR	NR
2,3,7,8-TCDF	65	337	17.0	3.90	NR	NR
1,2,3,7,8-PeCDF	22	736	9.60	0	NR	NR
2,3,4,7,8-PeCDF	26	736	10.4	0	NR	NR
1,2,3,4,7,8-HxCDF	43	1,500	28.0	0	NR	NR
1,2,3,6,7,8-HxCDF	35	737	18.0	0	NR	NR
1,2,3,7,8,9-HxCDF	16	1,260	18.0	0	NR	NR
2,3,4,6,7,8-HxCDF	27	737	18.0	0	NR	NR
1,2,3,4,6,7,8-HpCDF	71	7,100	57.0	36.0	NR	NR
1,2,3,4,7,8,9-HpCDF	26	842	23.0	0	NR	NR
OCDF	80	69,500	110	80.0	NR	NR
Total I-TEQ_{DF}		1,820	50.4	11.2	86*	50*
Total 2,3,7,8-CDD/CDF		NR	NR	NR	NR	NR

NR = Not reported.
ng/kg = nanograms per kilogram.
* Values presented by Rubin and White (1992) for 175 rather than 174 POTWs.

Source: U.S. EPA (1996a); for POTWs with multiple samples, the pollutant concentrations were averaged before the summary statistics presented in the table were calculated. All concentrations are in units of ng/kg dry weight.

Table 8-30. CDD/CDF Concentrations Measured in 99 Sludges Collected from U.S. POTWs During 1994

Congener	Percent Detected	Maximum Concentration Detected (ng/kg)	Median Concentration (ng/kg)		Mean Concentration (ng/kg)	
			Nondetects Set to Det. Limit	Nondetects Set to Zero	Nondetects Set to Det. Limit[a]	Nondetects Set to Zero[a]
2,3,7,8-TCDD	40	12.3	1.95	0	2.72 (2.40)	1.71 (2.86)
1,2,3,7,8-PeCDD	23	37.5	8.23	0	10.9 (7.80)	3.34 (7.43)
1,2,3,4,7,8-HxCDD	34	45.6	5.25	0	11.1 (8.13)	6.03 (10.2)
1,2,3,6,7,8-HxCDD	87	130	25.6	24.7	33.8 (27.6)	32.2 (28.8)
1,2,3,7,8,9-HxCDD	64	88.8	12.3	9.48	20.2 (17.7)	17.0 (19.8)
1,2,3,4,6,7,8-HpCDD	98	5,380	642	642	981 (977)	981 (977)
OCDD	99	65,500	6,630	6,630	11,890 (12,540)	11,890 (12,540)
2,3,7,8-TCDF	76	156	7.53	6.28	12.8 (19.6)	11.1 (20.2)
1,2,3,7,8-PeCDF	21	60.3	7.91	0	10.7 (11.3)	3.53 (9.36)
2,3,4,7,8-PeCDF	42	155	9.70	0	15.7 (19.8)	10.5 (21.6)
1,2,3,4,7,8-HxCDF	48	170	11.5	0	20.4 (25.3)	14.0 (25.9)
1,2,3,6,7,8-HxCDF	17	200	14.0	0	30.4 (53.6)	5.13 (21.9)
1,2,3,7,8,9-HxCDF	4	115	7.53	0	11.1 (13.6)	1.56 (11.7)
2,3,4,6,7,8-HxCDF	35	356	9.85	0	21.8 (40.4)	13.6 (41.0)
1,2,3,4,6,7,8-HpCDF	64	1,460	91.7	31.8	223 (271)	97.5 (207)
1,2,3,4,7,8,9-HpCDF	31	213	11.7	0	27.1 (34.8)	15.0 (33.4)
OCDF	93	11,200	286	281	786 (1,503)	775 (1,506)
Average I-TEQ_{DF} (facility basis)[b]		246	49.6	33.4	64.5 (50.1)	47.7 (44.7)
Total 2,3,7,8-CDD/CDF		73,520	7,916	7,881	14,110 (14,390)	13,880 (14,200)
Average TEQ_{DF}-WHO_{98} (facility basis)[b]			44.6	25.5	57.2 (44.4)	36.3 (38.6)

[a] Values in parentheses are standard deviations.

[b] For POTWs with multiple samples, the sample TEQ concentrations were averaged to POTW averages before calculation of the total TEQ mean and median values presented in the table. A total of 74 POTW average concentrations were used in the calculations. In addition, the following sample ID numbers were not included in the averaging because, according to Green et al. (1995), it was not possible to determine if they were duplicate or multiple samples from other POTWs: 87, 88, 89, 90, 91, 97, 98, and 106.

Source: Green et al. (1995); Cramer et al. (1995).

Table 8-31. Quantity of Sewage Sludge Disposed of Annually by Primary, Secondary, or Advanced Treatment POTWs and Potential Dioxin TEQ Releases

Use/Disposal Practice	Volume Disposed (thousands of dry metric tons/year)	Percent of Total Volume	Potential Dioxin Release[c] (g of TEQ/yr)	
			$I\text{-}TEQ_{DF}$	$TEQ_{DF}\text{-}WHO_{98}$
Land Application	1,714	32.0[e]	84.0	62.2
Distribution and Marketing	71	1.3	3.5	2.6
Surface Disposal Site/Other	396	7.4	19.4	14.4
Sewage Sludge Landfill	157	2.9	7.7	5.7
Co-disposal Landfills[a]	1,819	33.9	89.1	66.0
Sludge Incinerators and Co-incinerators[b]	865	16.1	(f)	(f)
Ocean Disposal	(336)[d]	(6.3)[d]	(0)[d]	(0)[d]
TOTAL	5,357	100.0	204.0	151.0

[a] Landfills used for disposal of sewage sludge and solid waste residuals.

[b] Co-incinerators treat sewage sludge in combination with other combustible waste materials.

[c] Potential dioxin TEQ release for nonincinerated sludges was estimated by multiplying the sludge volume generated (i.e., column 2) by the average of the mean $I\text{-}TEQ_{DF}$ concentrations in sludge reported by Rubin and White (1992) (i.e., 50 ng/kg dry weight) and Green et al. (1995) and Cramer et al. (1995) (i.e., 47.7 ng/kg). The calculations of $TEQ_{DF}\text{-}WHO_{98}$ used the mean concentration of 36.3 ng $TEQ_{DF}\text{-}WHO_{98}$/kg for the results reported by Green et al. (1995) and Cramer et al. (1995).

[d] The Ocean Dumping Ban Act of 1988 generally prohibited the dumping of sewage sludge into the ocean after December 31, 1991. Ocean dumping of sewage sludge ended in June 1992 (Federal Register, 1993b). The current method of disposal of the 336,000 metric tons of sewage sludge that were disposed of in the oceans in 1988 has not been determined.

[e] Includes 21.9 percent applied to agricultural land, 2.8 percent applied as compost, 0.6 percent applied to forestry land, 3.1 percent applied to "public contact" land, 1.2 percent applied to reclamation sites, and 2.4 percent applied in undefined settings.

[f] See Section 3.6.5 for estimates of CDD/CDF releases to air from sewage sludge incinerators.

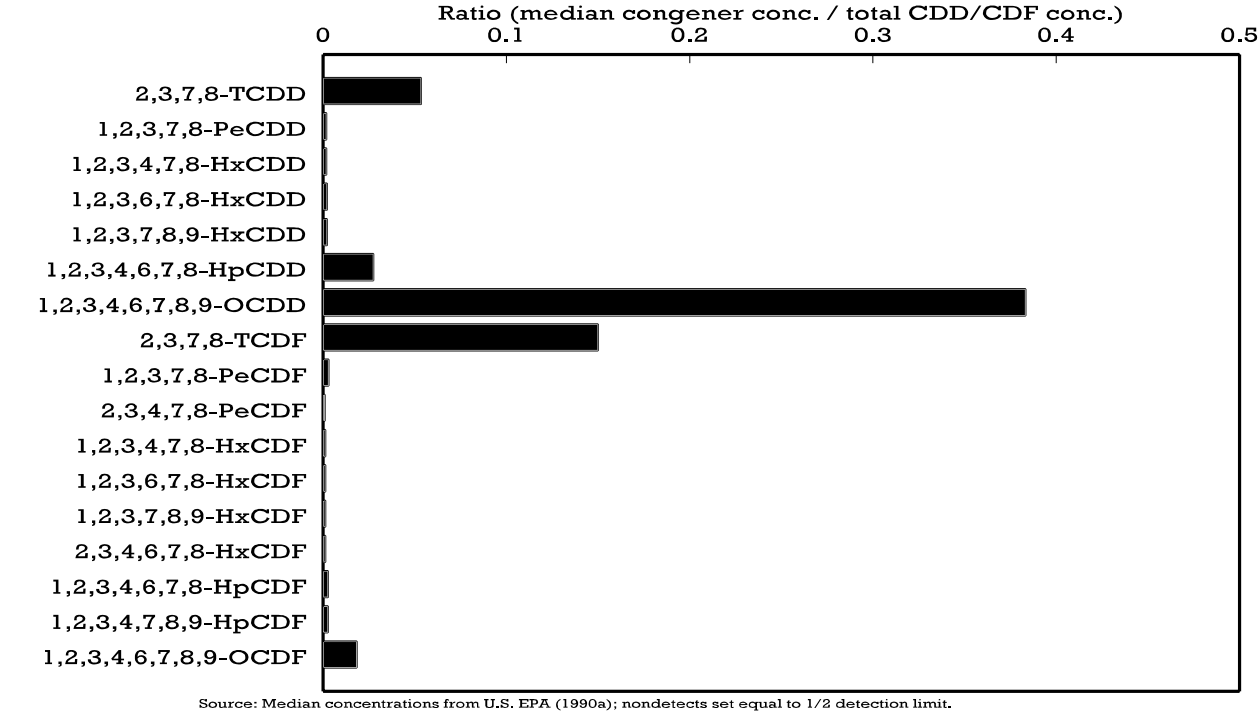
Table 8-32. CDD/CDF Concentrations in Swedish Liquid Soap, Tall Oil, and Tall Resin

Congener/Congener Group	Liquid Soap (ng/L)	Tall Oil (ng/kg)	Tall Resin (ng/kg)
2,3,7,8-TCDD	ND (0.009)	3.6	ND (1)
1,2,3,7,8-PeCDD	0.400	5.3	3.1
1,2,3,4,7,8-HxCDD	ND (0.020)	ND (2)	ND (4)
1,2,3,6,7,8-HxCDD	0.320	ND (2)	810
1,2,3,7,8,9-HxCDD	0.180	ND (2)	500
1,2,3,4,6,7,8-HpCDD	1.900	ND (1)	5,900
OCDD	1.000	5.3	6,000
2,3,7,8-TCDF	0.620	17	ND (2)
1,2,3,4,8-/1,2,3,7,8-PeCDF	0.290	4.2	ND (0.4)
2,3,4,7,8-PeCDF	0.200	1.9	ND (0.5)
1,2,3,4,7,8/9-HxCDF	0.013	1.4	24
1,2,3,6,7,8-HxCDF	ND (0.004)	0.7	--
1,2,3,7,8,9-HxCDF	ND (0.004)	ND (0.7)	ND (1)
2,3,4,6,7,8-HxCDF	ND (0.004)	ND (0.5)	ND (0.7)
1,2,3,4,6,7,8-HpCDF	ND (0.005)	ND (0.8)	10
1,2,3,4,7,8,9-HpCDF	ND (0.010)	ND (2)	9.0
OCDF	NA	NA	NA
Total 2,3,7,8-CDD*	3.8	14.2	13213.1
Total 2,3,7,8-CDF*	1.123	25.2	43
Total I-TEQ_{DF}*	0.447	9.4	200
Total TEQ_{DF}-WHO_{98}*	0.647	12.0	196
Total TCDD	0.120	31	ND (1)
Total PeCDD	15.000	380	25
Total HxCDD	3.400	3.3	6,800
Total HpCDD	3.600	ND (1)	11,000
Total OCDD	1.000	5.3	6,000
Total TCDF	1.000	26	ND (2)
Total PeCDF	1.300	41	ND (0.5)
Total HxCDF	0.150	4.9	56
Total HpCDF	ND (0.010)	ND (2)	19
Total OCDF	NA	NA	NA
Total CDD/CDF*	25.57	491.5	23,900

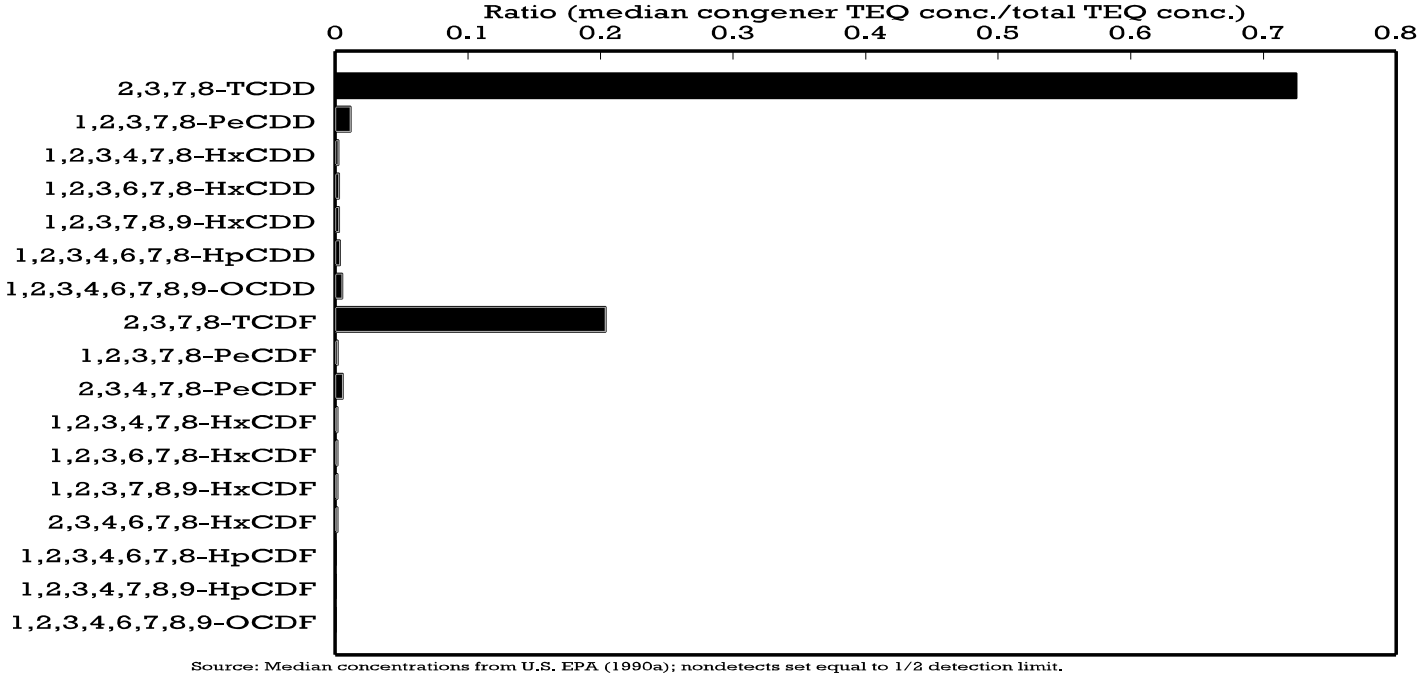
* Calculations assume not-detected values are zero.
ng/kg = nanograms per kilogram.
Ng/L = nanograms per liter.

ND = Not detected; value in parentheses is the detection limit.
NA = Not analyzed.
-- = Not reported.

Source: Rappe et al. (1990c).

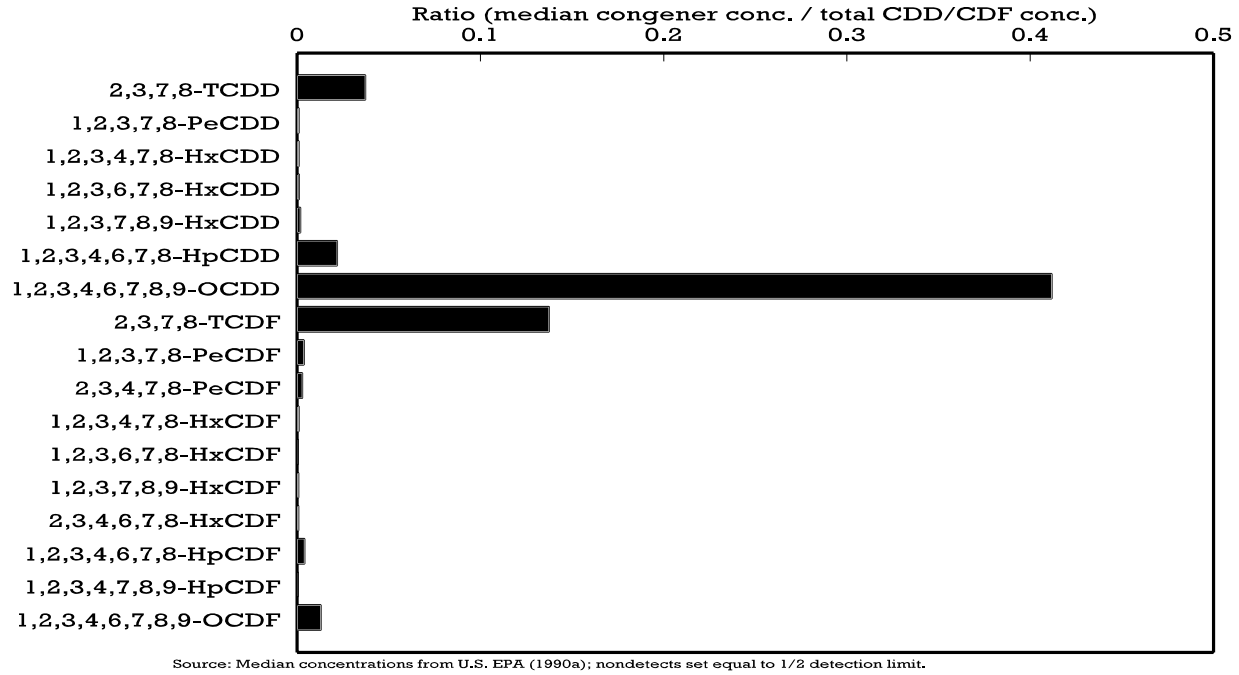


Source: Median concentrations from U.S. EPA (1990a); nondetects set equal to 1/2 detection limit.

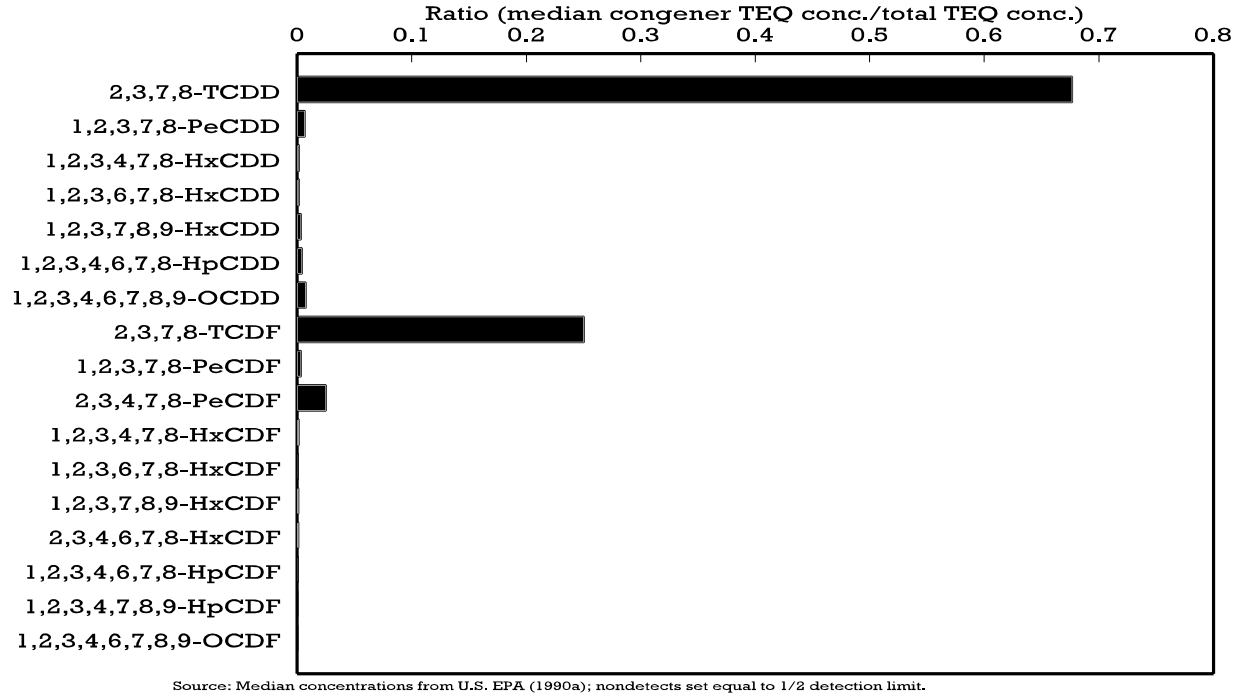


Source: Median concentrations from U.S. EPA (1990a); nondetects set equal to 1/2 detection limit.

Figure 8-1. 104 Mill Study Full Congener Analysis Results for Pulp

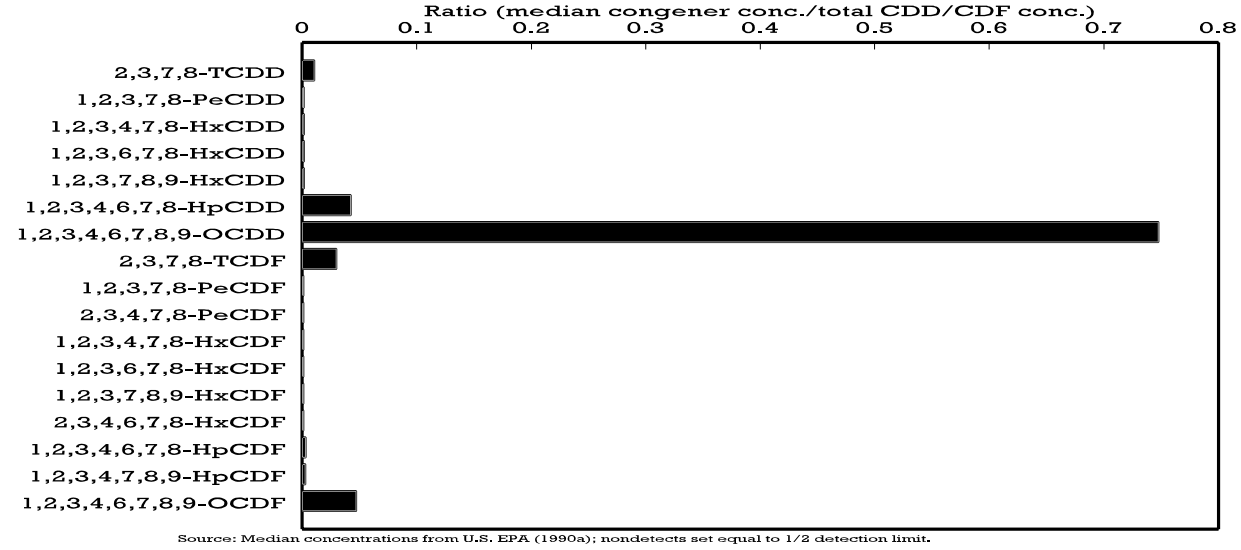


Source: Median concentrations from U.S. EPA (1990a); nondetects set equal to 1/2 detection limit.

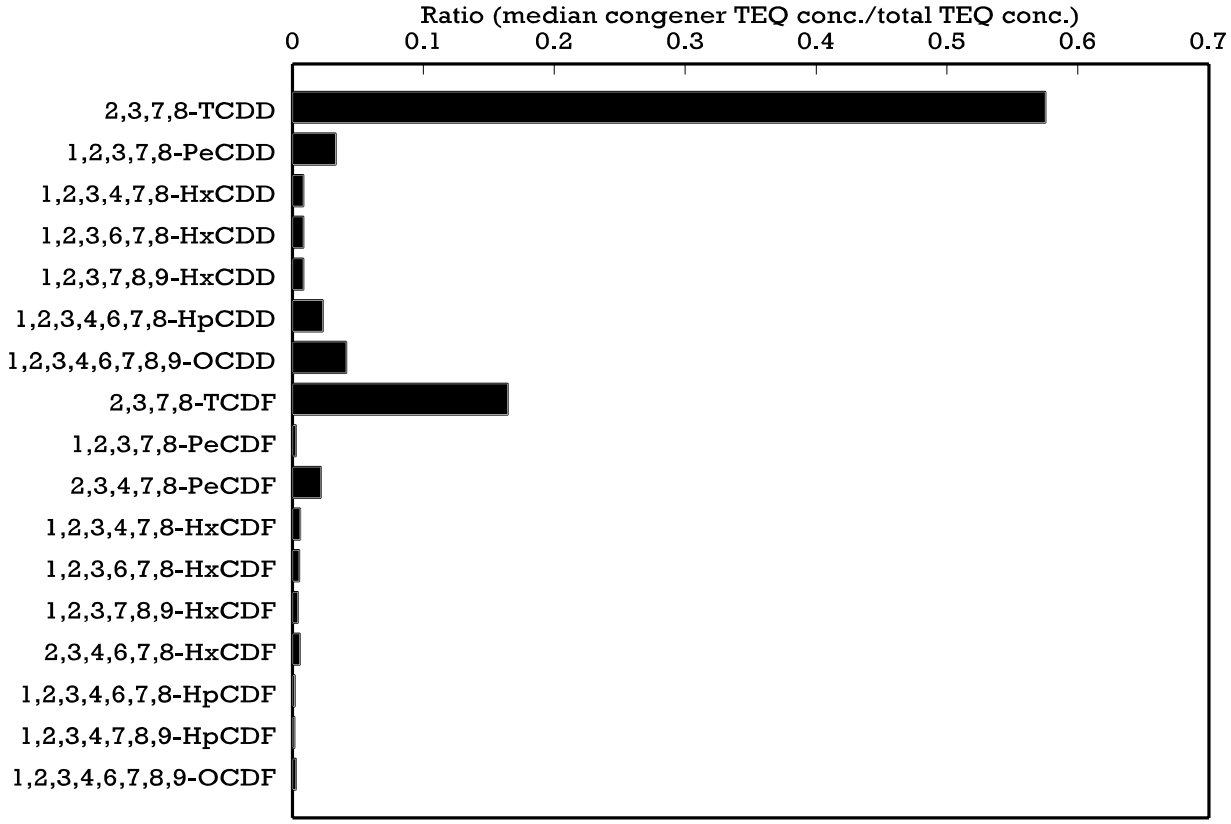


Source: Median concentrations from U.S. EPA (1990a); nondetects set equal to 1/2 detection limit.

Figure 8-2. 104 Mill Study Full Congener Analysis Results for Sludge

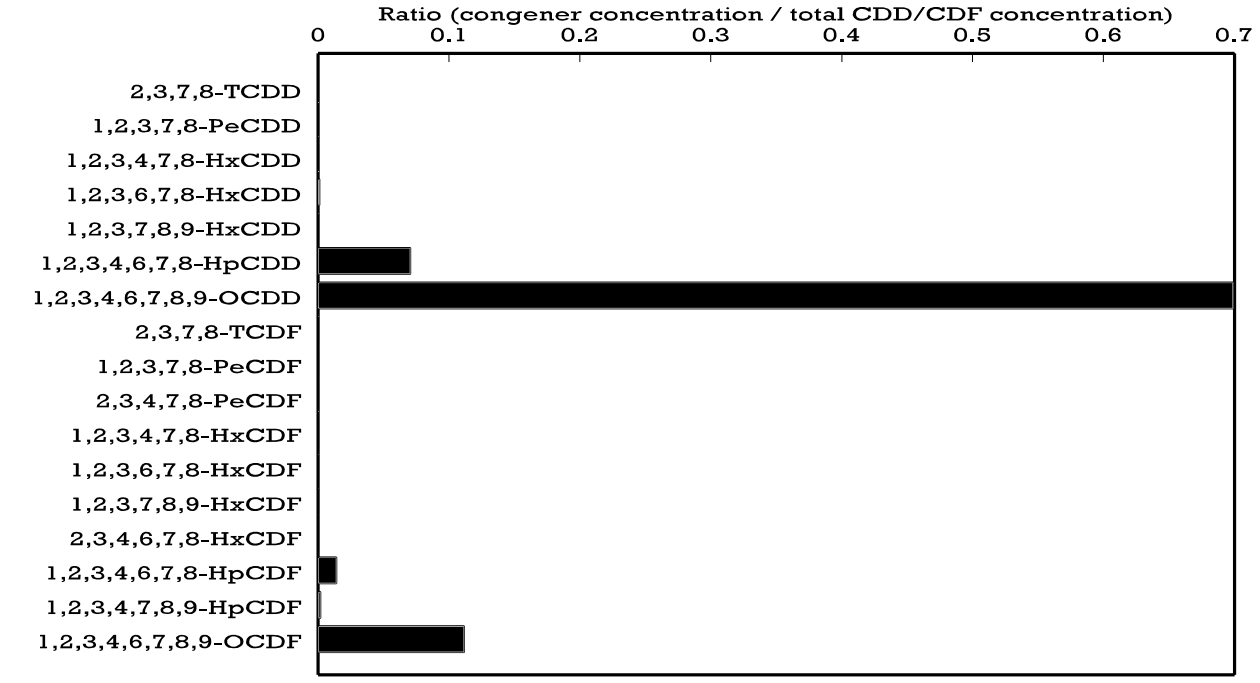


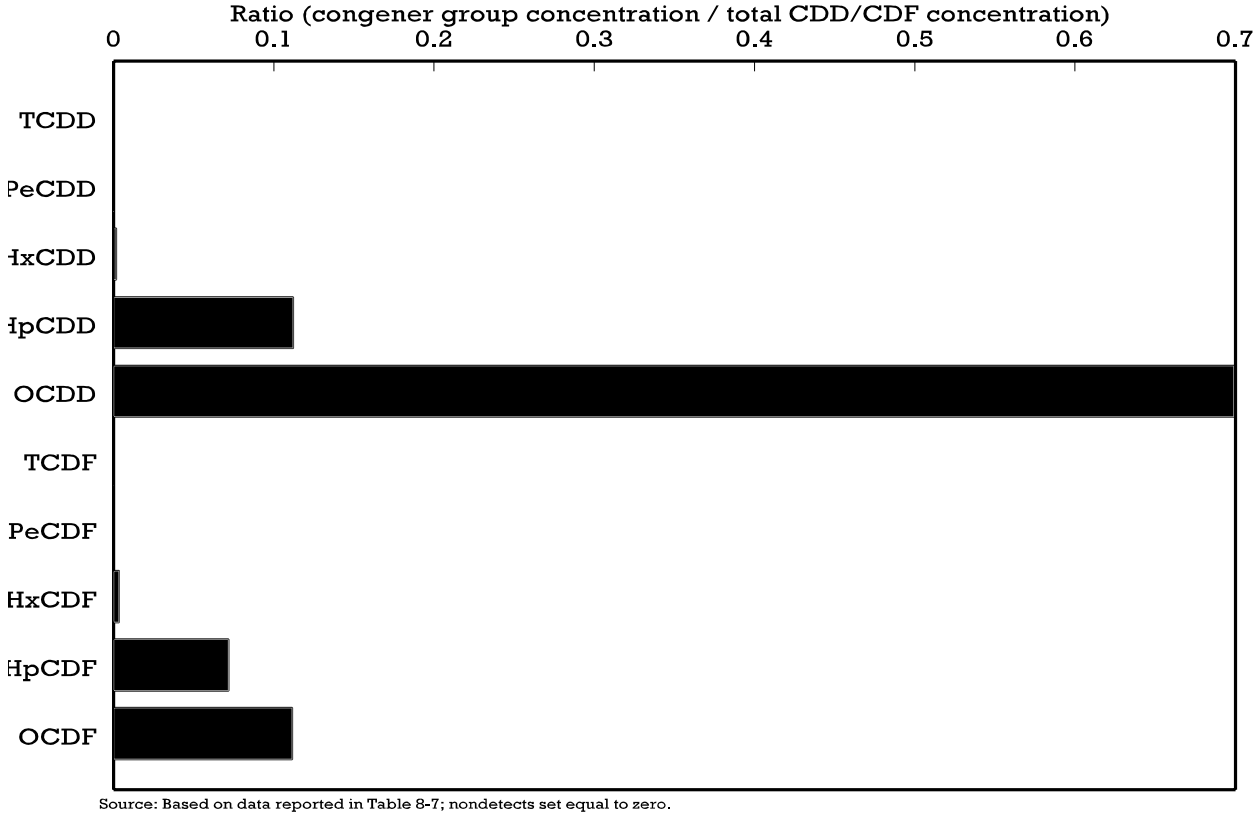
Source: Median concentrations from U.S. EPA (1990a); nondetects set equal to 1/2 detection limit.



Source: Median concentrations from U.S. EPA (1990a); nondetects set equal to 1/2 detection limit.

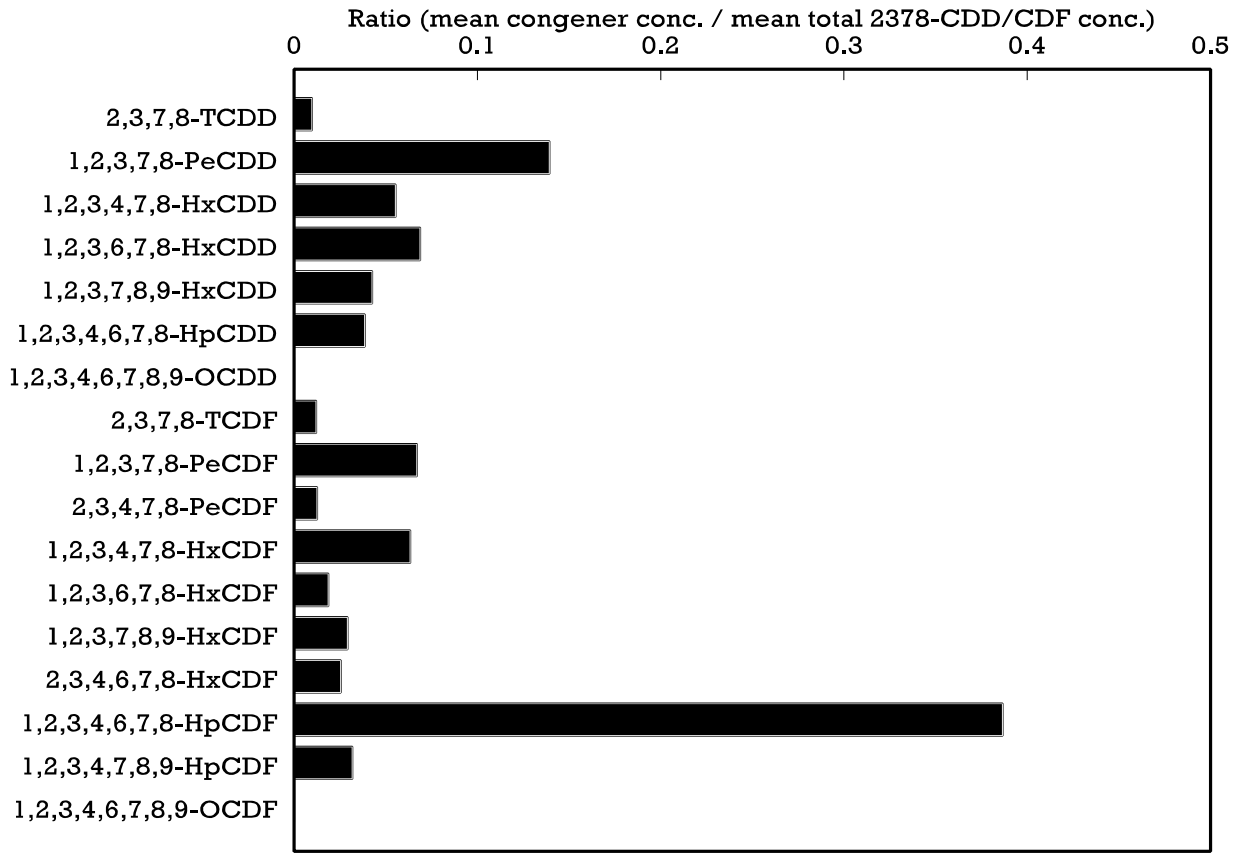
Figure 8-3. 104 Mill Study Full Congener Analysis Results for Effluent





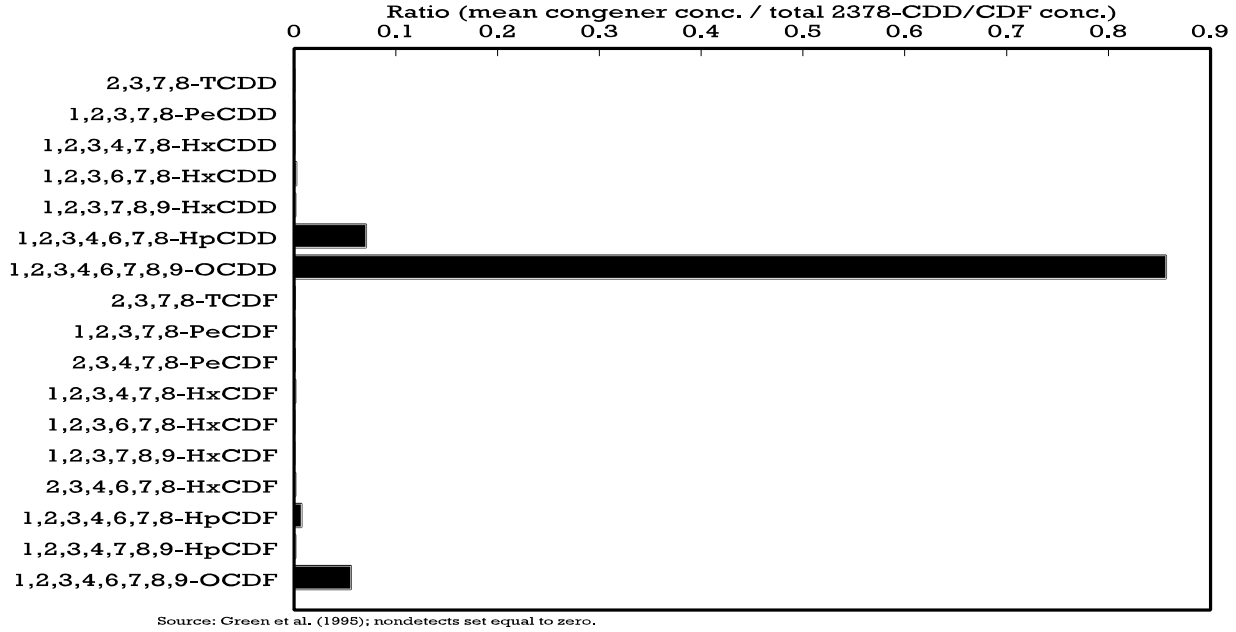
Source: Based on data reported in Table 8-7; nondetects set equal to zero.

Figure 8-4. Congener and Congener Group Profiles for Technical PCP

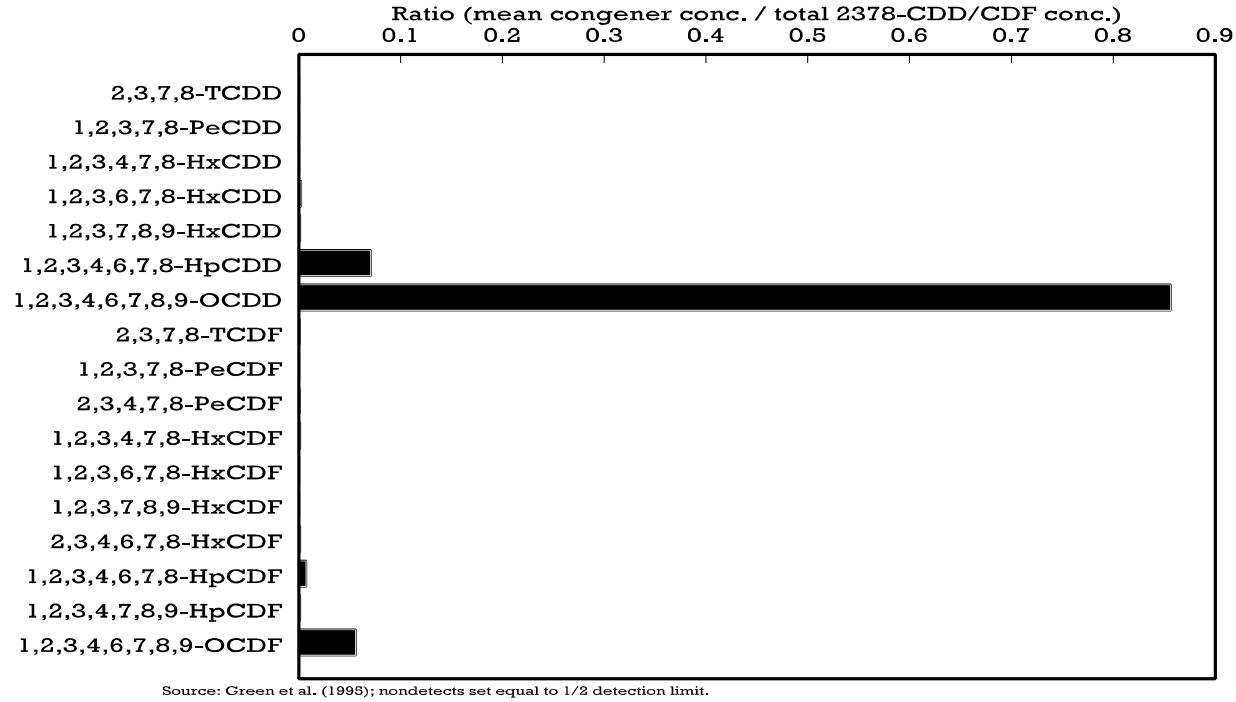


Source: Based on mean concentrations reported in Table 8-24; nondetects set equal to zero.

Figure 8-5. Congener Profile for 2,4-D (salts and esters)



Source: Green et al. (1995); nondetects set equal to zero.



Source: Green et al. (1995); nondetects set equal to 1/2 detection limit.

Figure 8-6. Congener Profiles for Sewage Sludge

9. BIOLOGICAL SOURCES OF CDD/CDF

Recent laboratory and field research studies demonstrate that biochemical formation of CDD/CDFs from chlorophenol precursors is possible. In addition, under certain conditions, some CDD/CDFs can be biodegraded to form less chlorinated (and possibly more toxic) CDD/CDFs. Both of these mechanisms are discussed in this chapter. However, the extent to which CDD/CDFs are formed by either mechanism in the environment is not known at present.

The origin of CDD/CDFs that were recently discovered in ball clay deposits is not yet determined, and natural occurrence is still considered a possibility. Chapter 13 discusses this topic in detail.

9.1. BIOTRANSFORMATION OF CHLOROPHENOLS

Biochemical formation of CDD/CDFs, particularly the higher chlorinated congeners, from chlorophenol precursors is possible, as indicated by laboratory studies with solutions of trichlorophenols and pentachlorophenol (PCP) in the presence of peroxidase enzymes and hydrogen peroxide (Svenson et al., 1989; Oberg et al., 1990; Wagner et al., 1990; Oberg and Rappe, 1992; Morimoto and Kenji, 1995) and with sewage sludge spiked with PCP (Oberg et al., 1992). However, the extent to which CDD/CDFs are formed in the environment via this mechanism cannot be estimated at this time.

In 1991, Lahl et al. (1991) reported finding CDD/CDFs in all 22 samples of various types of composts analyzed. The hepta- and octa-substituted CDDs and CDFs were typically the dominant congener groups found. The I-TEQ_{DF} content of the composts ranged from 0.8 to 35.7 ng I-TEQ_{DF}/kg. The CDD/CDFs found in compost may be primarily the result of atmospheric deposition onto plants that are subsequently composted but may also be caused by uptake of CDD/CDFs from air by the active compost (Krauss et al., 1994). Similarly, CDD/CDFs are frequently detected in sewage sludges. The CDD/CDFs found in sewage sludge may be primarily from the sources identified in Section 8.4.1.

Peroxidases are common enzymes in nature. For example, the initial degradation of the lignin polymer by white- and brown-rot fungi is peroxidase catalyzed (Wagner et al., 1990). The conversion efficiency of chlorinated phenols to CDD/CDFs that has been

observed is low. In the solution studies, Oberg and Rappe (1992) reported a conversion efficiency of PCP to OCDD of about 0.01 percent, Morimoto and Kenji (1995) reported a conversion efficiency of PCP to OCDD of 0.8 percent, and Wagner et al. (1990) reported a conversion efficiency of trichlorophenol to HpCDD of about 0.001 percent. Oberg et al. (1990) reported a conversion efficiency of trichlorophenols to CDD/CDFs of about 0.001 percent. In their sewage sludge study, Oberg et al. (1992) reported a conversion efficiency of PCP to total CDDs of 0.0002 to 0.0004 percent.

Several researchers recently conducted both laboratory and field studies in an attempt to better understand the extent of and factors affecting the fate or formation of CDD/CDFs in composts and sewage sludges. The findings of several of these studies are discussed in the following paragraphs. The findings are not always consistent, the congener profiles and patterns detected, and the extent, if any, of CDD/CDF "formation," may vary with the compost materials studied, differences in experimental or field composting design, and duration of the studies.

Harrad et al. (1991) analyzed finished composts and active compost windrows from a municipally operated yard-waste composting facility in Long Island, New York. Concentrations measured in 12 finished composts ranged from 14 to 41 ng I-TEQ_{DF}/kg (mean of 3 ng I-TEQ_{DF}/kg). The concentrations in the five active compost samples (1 to 30 days in age) ranged from 7.7 to 54 ng I-TEQ_{DF}/kg (mean of 21 ng I-TEQ_{DF}/kg). The authors observed that CDD/CDF concentrations measured in two soil samples from the immediate vicinity of the composting facility were significantly lower (1.0 and 1.3 ng I-TEQ_{DF}/kg) than the levels found in the composts, suggesting that the source(s) of CDD/CDFs in the composts was different than the source(s) affecting local soils. The authors also noted a strong similarity between the congener profiles observed in the composts and the congener profile of a PCP formulation (i.e., predominance of 1,2,4,6,8,9-HxCDF and 1,2,3,4,6,8,9-HpCDF in their respective congener groups), which indicated to the authors that leaching of CDD/CDFs from PCP-treated wood in the compost piles was the likely source of the observed CDD/CDFs. The levels of PCP in the 12 finished composts ranged from 7 to 190 μg/kg (mean of 33 μg/kg), and the PCP levels in the active compost samples ranged from 17 to 210 μg/kg (mean of 68 μg/kg). The PCP level in both soil samples was 1.5 μg/kg.

Goldfarb et al. (1992) and Malloy et al. (1993) reported the results of testing of composts at three municipal yard-waste composting facilities (5 to 91 ng I-TEQ_{DF}/kg; mean of 30 ng I-TEQDF/kg), two municipal solid waste composting facilities (19 to 96 ng I-TEQ_{DF}/kg; mean of 48 ng I-TEQ_{DF}/kg), and one municipal facility composting solid waste and dewatered sewage sludge (37 to 87 ng I-TEQ_{DF}/kg; mean of 56 ng I-TEQ_{DF}/kg). All facilities were located in the United States. Two general trends were observed. First, an increase in analyte levels was observed, with an increasing degree of chlorination for each compound type (i.e., CDDs, CDFs, chlorophenols, and chlorobenzenes). Second, an increase in concentration of each congener or homologue group, with a progression from yard waste to solid waste to solid waste/sewage sludge composts, was observed. As noted above, TEQ concentrations showed this same trend, which was primarily due to increasing levels of 1,2,3,4,6,7,8-HpCDD and OCDD. The mean PCP concentrations in the three compost types were 20 μg/kg (yard waste), 215 μg/kg (solid waste), and 615 μg/kg (solid waste/sewage sludge). Comparison of congener profiles by the authors indicated that the CDD/CDF residue in PCP-treated wood in the compost feedstock was a major but not exclusive contributor of the observed CDD/CDFs. The authors postulated that biological formation of HxCDDs, HpCDDs, and OCDD from chlorophenols (tri-, tetra-, and penta-) in the compost could be responsible for the elevated levels of these congener groups relative to their presence in PCP.

Oberg et al. (1993) measured the extent of CDD/CDF formation in three conventional garden composts; two were spiked with PCP, and one was spiked with hexachlorobenzene. The two PCP-spiked composts were monitored for periods of 55 days and 286 days, respectively. A significant increase in the concentrations of the higher chlorinated congeners, particularly the HpCDDs, OCDD, and, to a lesser extent, OCDF, were observed. Similar results were reported for the hexachlorobenzene-spiked compost, which was monitored for a period of 49 days. Oberg et al. (1993) state that for a "typical" composting event, a two- to threefold increase in TEQ content corresponds to an elevation by 0.2 to 0.5 ng I-TEQ_{DF}/kg dry weight.

Weber (1995) subjected sewage sludges from two German communities to anaerobic digestion in laboratory reactors for 60 days. The two sludges were spiked with 2,3,5-trichlorophenol (10 to 25 mg/kg), a mixture of 2,3,5-trichlorophenol and dichlorophenols (2.5 to 25 mg/kg), or a mixture of di-, tri-, and tetrachlorobenzenes (4 to

40 mg/kg). In nearly all of the digestion experiments, the addition of these precursors did not lead to any significant changes in CDD/CDF concentrations. The initial CDD/CDF concentrations in the two sludges were 9 and 20 ng I-TEQ_{DF}/kg. The only exceptions were increased 2,3,7,8-TCDF concentrations in the mixed chlorophenol experiments and decreased 2,3,7,8-TCDF concentrations in the mixed chlorobenzene experiments. However, the same increases or decreases for this congener were also observed in the controls (i.e., no precursors added).

Researchers at the U.S. Department of Agriculture (USDA) (Fries et al., 1997) reported that dairy cows that were fed PCP-treated wood excreted OCDD in amounts almost four times what they ingested. Feil and Tiernan (1997) reported that rats fed technical PCP had liver concentrations of HxCDD, HpCDD, HpCDF, OCDD, and OCDF two to three orders of magnitude higher than rats fed purified PCP. These results suggest the in vivo formation of CDD/CDFs from pre-dioxins (i.e., chlorinated phenoxy phenols present as contaminants in the PCP). A followup USDA study (Huwe et al., 1998) investigated the metabolic conversion of a pre-dioxin (monochloro-2-phenoxyphenol) to OCDD in a feeding study with rats. The results of the study demonstrate the formation of OCDD from the pre-dioxin, although the conversion was estimated to be less than 2 percent. Interestingly, the study noted that the presence of added OCDD in the feed material increased the percentage of pre-dioxin conversion.

Wittsiepe et al. (1998) demonstrated that CDD/CDF can be formed through reaction of chlorophenols with myeloperoxidase (a component of neutrophile granulocytes, a subgroup of human leucocytes). The CDD/CDFs formed showed different homologue patterns and formation rates depending upon the degree of chlorination of the chlorophenol substrate. The formation rates ranged from 1 to 16 u mol of CDD/CDF per mole of chlorophenol substrate.

9.2. BIOTRANSFORMATION OF HIGHER CDD/CDFS

Results of several recent studies examining the fate of a range of CDD/CDF congeners in pure cultures, sediments, and sludges indicate that under certain conditions some CDD/CDF congeners will undergo biodegradation to form less chlorinated (and possibly more toxic) CDD/CDFs. However, the extent to which more toxic CDD/CDFs are formed in the environment via this mechanism cannot be estimated at this time. The

following paragraphs discuss studies that examined the products of biodegradation in sediments, compost, and sewage sludge.

Several recent reports indicate that CDDs and CDFs may undergo microbial dechlorination in anaerobic sediments. Adriaens and Grbic-Galic (1992; 1993) and Adriaens et al. (1995) reported the results of a series of microcosm studies using Hudson River sediment (contaminated with Aroclor 1242) and aquifer material (contaminated with CDDs) from Pensacola, Florida. Both types of substrates were spiked with several CDDs (1,2,3,4,6,7,8-HpCDD; 1,2,3,4,7,8-HxCDD; and 1,2,4,6,8,9-/1,2,4,6,7,9-HxCDD) and CDFs (1,2,3,4,6,7,8-HpCDF and 1,2,4,6,8-PeCDF) and monitored over a 16-month period, at an incubation temperature of 30°C. The Hudson River sediment was spiked with 144 μg/kg of each congener, and the Pensacola aquifer material was spiked with 63 μg/kg of each congener.

All of the congeners, with the exception of 1,2,3,4,6,7,8-HpCDF, showed a slow decrease in concentration over time, attributed to biologically mediated reductive dechlorination, with net disappearance rates ranging from 0.0031 $week^{-1}$ to 0.0175 $week^{-1}$ (i.e., half-lives of approximately 1 to 4 years). However, Adriaens et al. (1995) conclude that the actual half-lives may be orders of magnitude higher. The experiment with 1,2,3,4,6,7,8-HpCDD yielded formation of two HxCDDs (1,2,3,4,7,8- and 1,2,3,6,7,8-). Thus, removal of the peri-substituted (1,4,6,9) chlorines was favored, with enrichment of 2,3,7,8-substituted congeners. No lesser chlorinated congeners were identified from incubation with the other tested congeners. 1,2,4,6,8-PeCDF was also examined in dichlorophenol-enriched cultures. After 6 months incubation, several TCDFs were identified, which also indicated that peri-dechlorination was the preferred route of reduction.

Barkovskii and Adriaens (1995, 1996) reported that 2,3,7,8-TCDD (extracted from Passaic River sediments) was susceptible to reductive dechlorination when incubated at 30°C under methanogenic conditions in a mixture of aliphatic and organic acids inoculated with microorganisms obtained from Passaic River sediments. The initial concentration of 2,3,7,8-TCDD (20 $\pm$ 4 μg/L) decreased by 30 percent to 14 $\pm$ 2 μg/L over a period of 7 months with the consecutive appearance and disappearance of tri-, di-, and mono-CDDs. Experiments were also conducted by spiking the sediment with HxCDDs, HpCDDs, and OCDD. Up to 10 percent of the spiked OCDD was converted to hepta-, hexa-, penta-,

tetra-, tri-, di-, and monochlorinated isomers, but the reaction stoichiometry was not determined. Two distinct pathways of dechlorination were observed: the *peri*-dechlorination pathway of 2,3,7,8-substituted hepta- to penta-CDDs, resulting in the production of 2,3,7,8-TCDD, and the *peri*-lateral dechlorination pathway of non-2,3,7,8-substituted congeners.

Several studies reported that CDD/CDFs can be formed during composting operations through biological action on chlorophenols present in the compost feed material. The results of studies that specify likely involvement of chlorophenols are described in Section 9.1. Another possible formation mechanism was suggested by Vikelsoe et al. (1994), who reported that higher chlorinated CDD/CDF congeners are formed when humic acid is reacted with a peroxidase enzyme, hydrogen peroxide, and sodium chloride. It is expected that some organic material in compost and sewage sludge has a humic-like structure. Several additional studies are described below in which the potential involvement of chlorophenols could not be assessed because chlorophenol concentrations in the composts were not reported.

Schäfer et al. (1993) monitored the seasonal changes in the CDD/CDF content, as well as the extent of CDD/CDF formation, in the composts from a vegetable and garden waste composting operation in Germany. Finished compost samples were collected and analyzed every 2 months for 1 year. An annual cycle was observed in TEQ concentrations, with peak concentrations in the summer (approximately 8.5 ng I-TEQ_{DF}/kg) that were 2.5 times higher than the lowest concentrations observed in the winter (approximately 3.5 ng I-TEQ_{DF}/kg). No seasonal source was apparent that could explain the observed differences in seasonal levels. The CDD/CDF contents of the starting waste materials for two compost cycles (March and September) were measured to monitor the extent of CDD/CDF formation during composting. For the March cycle sample, most 2,3,7,8-substituted CDD/CDF congeners decreased in concentration during composting. Four CDF congeners showed a slight increase in concentration (less than 10 percent). For the September cycle sample, OCDD and HpCDD concentrations increased 300 percent during composting. Less than 10 percent increases were observed for HxCDDs and OCDF; all other 2,3,7,8-substituted CDD/CDF congeners showed decreases in concentrations during composting.

Krauss et al. (1994) measured the extent of CDD/CDF formation during the composting of household waste using a laboratory compost reactor. After 11 weeks, the TEQ content of the compost increased from 3.0 to 4.5 ng. The largest increases in mass content were observed for HpCDD (primarily 1,2,3,4,6,7,8-HpCDD) and OCDD. TCDD, PeCDD, and HxCDD showed no change in mass content. All CDF congener groups showed decreases in mass content; however, the concentrations in both the starting and finished compost were close to the analytical detection limits.

Oberg et al. (1994) reported the results of monitoring of two household waste composts and two garden composts. For the two household waste composts, total CDD/CDF content decreased in both composts over the 12-week test period. Total CDD content and PCB content decreased, but total CDF content increased in contrast to the findings of Krauss et al. (1994). However, a small increase in OCDD content in both composts was observed. The two garden composts were monitored by Oberg et al. (1994) for a 60-week period. Total CDD/CDF concentration increased, with the largest increases observed for OCDD and HpCDDs. The lower chlorinated CDFs decreased in concentration.

As a followup to a preliminary study (Hengstmann et al., 1990) that indicated CDD/CDF concentrations may increase and congener profiles may change during anaerobic digestion of sewage sludge, Weber et al. (1995) subjected sewage sludges from two German communities to anaerobic digestion and aerobic digestion in laboratory reactors for 60 days and 20 days, respectively. The initial average I-TEQ_{DF} concentrations in the raw sludges were 20 and 200 ng I-TEQ_{DF}/kg. No significant increase or decrease in total CDD/CDF content or congener group content was observed with either sludge. In contrast, a significant decrease in CDD/CDF content was observed in the aerobic digestion experiments on both sludges. The greatest percentage decreases in congener group concentrations (i.e., greater than 40 percent) were observed for TCDF, PeCDF, HxCDF, TCDD, and PeCDD in the sludge initially containing 20 ng I-TEQ_{DF}/kg and for TCDF, TCDD, HpCDD, and OCDD in the initially high-content sludge. The greatest percentage decreases in congener concentrations (i.e., greater than 40 percent) were observed for non-2,3,7,8-substituted congeners.

10. PHOTOCHEMICAL SOURCES OF CDD/CDF

10.1. PHOTOTRANSFORMATION OF CHLOROPHENOLS

Several researchers demonstrated that CDD/CDFs can be formed via photolysis of pentachlorophenol (PCP) under laboratory conditions. These studies are described below. However, the extent to which CDD/CDFs are formed in the environment via this mechanism cannot be estimated at this time.

Lamparski et al. (1980) conducted laboratory studies to determine the effect of simulated summer sunlight on the formation of OCDD, HpCDDs, and HxCDDs in wood that was pressure treated in the laboratory with PCP. In the first set of experiments, wood veneers (southern pine) treated with purified PCP or with Dowicide EC-7, using methylene chloride as the PCP carrier, were exposed to light for 70 days. The PCP concentration in the treated wood was 5 percent by weight, which approximates the concentration in the outer layer of PCP-treated wood utility poles. Photolytic condensation of PCP to form OCDD was observed, with the OCDD concentration increasing by a maximum factor of 3,000 for the purified PCP and by a factor of 20 for EC-7 at about day 20 before leveling off. HpCDD and HxCDD were also formed, apparently by photolytic degradation of OCDD rather than by condensation of PCP and tetrachlorophenols. The HxCDD concentration increased by a factor of 760 for the purified PCP and by a factor of 50 for EC-7 over the 70-day exposure period. The predominant HpCDD congener formed was 1,2,3,4,6,7,8-HpCDD as a result of an apparent preferential loss of chlorine at the peri position (i.e., positions 1, 4, 6, and 9).

In a second set of experiments conducted by Lamparski et al. (1980), a hydrocarbon oil (P-9 oil) was used as the carrier to treat the wood. The increases observed in the OCDD, HpCDD, and HxCDD were reported to be much lower relative to the increases observed in the first set of experiments, which used methylene chloride as the carrier. Results were reported only for OCDD. The OCDD concentration increased by a maximum factor of 1.5 for both EC-7 and technical PCP, and by a factor of 88 for purified PCP. The authors concluded that the oil either reduced condensation of PCP to OCDD or accelerated degradation to other species by providing a hydrocarbon trap for free-radical species.

Vollmuth et al. (1994) studied the effect of irradiating laboratory water and landfill seepage water that contained PCP under conditions simulating those used to purify water with ultraviolet (UV) radiation (i.e., 5-hour exposure to 254 nm radiation from low-pressure mercury lamps). Before irradiation, the three solutions tested contained approximately 1 mg/L of PCP or PCP-Na but the CDD/CDF content varied dramatically (1.5, 2,066, and 2,071 pg I-TEQ_{DF}/L). Irradiation resulted in nearly total destruction of PCP (greater than 99 percent loss) in all three experiments. An overall net increase in I-TEQ_{DF} content was observed in the initially low I-TEQ_{DF} content water, but a net decrease was observed for the two initially high I-TEQ_{DF} content waters.

- Irradiation of laboratory water containing purified PCP showed an increase in I-TEQ_{DF} concentration from 1.5 pg/L to 214.5 pg/L. The increase in I-TEQ_{DF} was due entirely to the formation of 1,2,3,4,6,7,8-HpCDD, OCDD, and 1,2,3,4,6,7,8-HpCDF. Formation of non-2,3,7,8-substituted HpCDDs and HpCDFs was also observed. The ratios of the concentrations of these non-2,3,7,8-congeners to the concentrations of the 2,3,7,8-congeners were 0.6 for HpCDDs and 5.0 for HpCDFs. The HpCDD and HpCDF congeners formed indicated that the operative mechanism is photoinduced dechlorination of OCDD at a peri position and dechlorination of OCDF at only the 1- and 9-peri positions.

- Irradiation of water containing technical PCP-Na (Dowicide-G) resulted in a net loss in I-TEQ_{DF} content, from 2,065.5 pg/L to 112.7 pg/L. The only 2,3,7,8-substituted congener showing an increased concentration was 1,2,3,6,7,8-HxCDD. The other congeners originally present in the technical PCP-Na showed reductions of 80.6 to 100 percent.

- The I-TEQ_{DF} content of seepage water from a landfill (2,071 pg I-TEQ_{DF}/L) was reduced by a factor of two to 1,088 pg I-TEQ_{DF}/L. However, several 2,3,7,8-substituted congeners did increase in concentration (1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,8-HpCDF, and OCDF).

Waddell et al. (1995) also studied the effect of irradiating distilled laboratory water containing PCP under conditions simulating those used to purify water with UV radiation. The results obtained were similar to those of Vollmuth et al. (1994). Analytical-grade PCP at a concentration of 10 mg/L was exposed for 12 minutes to 200–300 nm radiation from a medium-pressure mercury lamp. All CDD/CDF congener groups increased in concentration over the 12-minute exposure period, with the greatest increases observed for OCDD (75-fold increase) and HpCDDs (34-fold increase). The I-TEQ_{DF} content of the solution increased from 4.2 pg I-TEQ_{DF}/L to 137 pg I-TEQ_{DF}/L over the 12-minute period.

The dominant congeners formed, in terms of both concentration and contribution to I-TEQ_{DF}, were 1,2,3,4,6,7,8-HpCDD, OCDD, and 1,2,3,7,8,9-HxCDD.

10.2. PHOTOLYSIS OF HIGHER CDD/CDFS

Photolysis appears to be one of the few environmentally significant degradation mechanisms for CDD/CDFs in water, air, and soil. Although in most studies good mass balances were not obtained and the photolytic pathways for CDD/CDFs were not fully identified, a major photolysis pathway appears to be photodechlorination, resulting in formation of lower chlorinated CDD/CDFs. A preferential loss of chlorines from the peri positions (i.e., chlorines at the 1, 4, 6, and 9 positions) rather than from the lateral positions (i.e., chlorines at the 2, 3, 7, and 8 positions) was reported for some congener groups when irradiated as dry films, sorbed to soil, and as gas-phase CDD/CDFs (Choudhry and Webster, 1989; Kieatiwong et al., 1990; Sivils et al., 1994, 1995; Tysklind et al., 1992). Several researchers reported that carbon-oxygen cleavage and other mechanisms may be similarly or more important pathways for CDD/CDFs containing four or fewer chlorines.

Because of the difficulties inherent in controlling experimental variables for nonvolatile and highly lipophilic compounds like CDD/CDFs, few photolysis studies have been performed on natural waters, on soils, or particulates, and on atmospheric gases to examine the rates and products of photolysis under environmentally relevant conditions. Thus, it is not possible at this time to quantitatively estimate the mass of various CDD/CDF congeners formed in the environment annually via photolytic mechanisms. Sections 10.2.1–10.2.4 summarize the key findings of recent environmentally significant studies for the water, soil, and air media.

10.2.1 Photolysis in Water

Numerous studies demonstrate that CDD/CDFs will undergo photodechlorination following first order kinetics in organic solution, with preferential loss of chlorine from the lateral positions. Photolysis is slow in pure water, but it increases dramatically when solvents serving as hydrogen donors such as hexane, benzene, methanol, acetonitrile, hexadecane, ethyl oleate, dioxane, and isooctane are present. However, only a few studies have examined the photolysis of CDD/CDFs using natural waters and sunlight.

Choudhry and Webster (1989) experimentally determined the sunlight photolysis half-life of 1,3,6,8-TCDD in pond water to be 3.5 days (i.e., more than 10 times greater than the half-life predicted by laboratory experiments using a water/acetonitrile solution). The authors attributed this significant difference in photolysis rates to the light screening/quenching effects of dissolved organic matter.

Friesen et al. (1990) examined the photolytic behavior of 1,2,3,4,7-PeCDD and 1,2,3,4,6,7,8-HpCDD in water:acetonitrile (2:3, v/v) and in pond water under sunlight at 50 degrees north latitude. The observed half-lives of these two compounds in the water:acetonitrile solution were 12 and 37 days, respectively, but much shorter in pond water, 0.94 and 2.5 days, respectively. Similarly, Friesen et al. (1993) studied the photodegradation of 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF by sunlight using water:acetonitrile (2:3, v/v) and lake water. The observed half-lives of the 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF in the water:acetonitrile solution were 6.5 and 46 days, respectively, and 1.2 and 0.19 days, respectively, in lake water. The significant differences between the natural water and water:acetonitrile solution results were attributed to indirect or sensitized photolysis due to the presence of naturally occurring components in the lake and pond water.

Dung and O'Keefe (1992), in an investigation of aqueous photolysis of 2,3,7,8-TCDF and 1,2,7,8-TCDF, reported findings similar to those of Friesen et al. (1993). The photolysis rates of the two TCDF congeners observed in the river and lake water (half-lives of about 4 to 6 hours) were double the rates observed in pure water (half-lives of about 8 to 11 hours). Dung and O'Keefe (1992) attributed the difference in rates to the presence of natural organics in the river and lake water that may be acting as sensitizers.

10.2.2 Photolysis on Soil

Photolysis of CDD/CDFs on soil has not been well characterized. According to the data generated to date, however, photolysis is an operative degradation process only in the near-surface soil where UV light penetrates (i.e., the top few millimeters or less of soil), and dechlorination of peri-substituted chlorines appears to occur preferentially.

Miller et al. (1989) studied the CDD degradation products resulting from irradiation of ^{13}C-labeled OCDD on two soil types using sunlamps. Approximately 38 to 42 percent of the OCDD was degraded by day 5 of the experiment; no significant further loss of

OCDD was observed over the following 10 days. Although the authors determined that photodechlorination was not the dominant photolysis pathway, it was observed in both soils; approximately 10 to 30 percent of the lower chlorinated congeners were produced from the immediate higher chlorinated congeners. The HpCDD and HxCDD congeners observed as degradation products were present in proportions similar to the number of congeners in each congener group. However, Miller et al. (1989) observed greater yields of 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD than would be expected on the basis of the number of potential TCDD and PeCDD congeners. One-fifth to one-third of the total yield of PeCDDs was 1,2,3,7,8-PeCDD, and one-half of the total yield of TCDDs was 2,3,7,8-TCDD.

Kieatiwong et al. (1990) performed similar experiments to those of Miller et al. (1989) using natural sunlight rather than sunlamps for irradiation of ^{13}C-labeled OCDD on soils. Photodechlorination was estimated to account for approximately 10 percent of the loss of OCDD. One-third to one-half of the total yield of PeCDDs was 1,2,3,7,8-PeCDD, and one-half of the total yield of TCDDs was 2,3,7,8-TCDD. The findings of Miller et al. (1989) and Kieatiwong et al. (1990) indicate that the 2,3,7,8-substituted TCDD and PeCDD congeners were either preferentially formed or were photochemically less reactive than the other congeners that were formed.

Tysklind et al. (1992) studied the sunlight photolysis of OCDD on soil and reported results similar to those of Miller et al. (1989) and Kieatiwong et al. (1990). Photodechlorination was observed with production of HpCDDs, HxCDDs, PeCDDs, and TCDDs over the 16-day irradiation period. Photodechlorination at the peri-substituted positions was the preferred photodechlorination mechanism; the proportions of 2,3,7,8-substituted congeners present in the soils after 16 days for each congener group were as follows: HxCDD - 65 percent; PeCDD—40 percent; and TCDD—75 percent. Tysklind et al. (1992) also studied the sunlight photolysis of OCDF on soil. Photodechlorination was observed; however, unlike the case with OCDD, photodechlorination of the lateral-substituted positions was found to be the dominant photodechlorination mechanism, resulting in a relative decreasing proportion of 2,3,7,8-substituted congeners during the irradiation period. 2,3,7,8-TCDF was not observed in any of the irradiated samples.

10.2.3 Photolysis on Vegetation

Photolysis of CDD/CDFs sorbed on the surface of vegetation has not been well characterized, and the findings to date are somewhat contradictory. McCrady and Maggard (1993) reported that 2,3,7,8-TCDD sorbed on the surface of reed canary grass (*Phalaris arundinacea L.*) undergoes photolytic degradation with a half-life of 44 hours in natural sunlight. In contrast, Welsch-Pausch et al. (1995) found little difference in the CDD/CDF congener patterns between grass (*Lolium multiflorum*) grown on an outdoor plot and grass grown in a greenhouse (i.e., UV light transmission blocked). In an attempt to clarify this contradiction, Welsch-Pausch and McLachlan (1995) studied the photodegradation of CDD/CDFs on pasture grass (*Arrhenatherion elatioris*) during two growing cycles (summer and autumn) using two greenhouses. One greenhouse was constructed of glass that blocks UV transmission, and the other was constructed of plexiglass (4 mm) with a UV-light transmission of greater than 50 percent in the 280-320 mm range. In both the summer and autumn exposure periods, the concentrations of CDD/CDFs (on a congener group basis) were similar in the grass exposed to UV light and the grass that was not exposed. Welsch-Pausch and McLachlan (1995) concluded that if photodegradation was occurring, it was a relatively insignificant factor in the accumulation of CDD/CDF in pasture grass.

10.2.4 Photolysis in Air

Photolysis of CDD/CDFs in the atmosphere has not been well characterized. On the basis of data generated to date, however, photolysis appears to be a significant mechanism for degradation (principally, dechlorination of the peri-substituted chlorines) of those CDD/CDFs present in the atmosphere in the gas phase. For airborne CDD/CDFs sorbed to particulates, photolysis appears to proceed very slowly, if at all. Because of the low volatility of CDD/CDFs, few studies have been attempted to measure actual rates of photodegradation of gas-phase CDD/CDF, and only recently have studies examined the relative importance of photolysis to particulate-bound CDD/CDFs.

Sivils et al. (1994; 1995) studied the gas-phase photolysis of several CDDs (2,3,7-TrCDD; 2,3,7,8-TCDD; 1,2,3,4-TCDD; 1,2,3,7,8-PeCDD, and 1,2,4,7,8-PeCDD) by irradiating the effluent from a gas chromatograph with broadband radiation in the UV/visible region for periods up to 20 minutes. The irradiated sample was then introduced

into a second gas chromatograph to measure the extent of dechlorination. The results showed that degradation followed first order kinetics and that an inverse relationship exists between the degree of chlorination and the rate of disappearance. Although the lack of photoproducts prevented an independent confirmation of the preferential loss mechanism, the results indicated that laterally substituted congeners (i.e., chlorines at the 2, 3, 7, and 8 positions) degrade at a slower rate than the peri-substituted congeners (i.e., chlorines at the 1, 4, 6, and 9 positions). Although Sivils et al. (1994) did not present the rate constants, the degradation rate for 2,3,7,8-TCDD (30 percent loss in 20 minutes) was reported to be slower than the rates for all other tested CDDs. Also, 1,2,4,7,8-PeCDD (with two perichlorines) degraded significantly faster than 1,2,3,7,8-PeCDD (with only one perichlorine).

Mill et al. (1987) studied the photolysis of 2,3,7,8-TCDD sorbed onto small diameter fly ash particulates suspended in air. The results indicated that fly ash confers photostability on 2,3,7,8-TCDD. Little (8 percent) to no loss was observed on the two fly ash samples after 40 hours of illumination. Tysklind and Rappe (1991) and Koester and Hites (1992) reported similar results of photolysis studies with fly ash. Tysklind and Rappe (1991) subjected fly ash from two German incinerators to various simulated environmental conditions. The fraction of photolytically degradable CDD/CDF after 288 hours of exposure was in the range of 20 to 40 percent of the extractable CDD/CDF. However, a 10 to 20 percent reduction was also observed in the darkened control samples. With the exception of HpCDD and HpCDF, the concentration of all other congener groups either increased or stayed the same during the exposure period from hour 144 to hour 288. Koester and Hites (1992) studied the photodegradation of CDD/CDFs naturally adsorbed to fly ash collected from five electrostatic precipitators. They observed no significant degradation in 11 photodegradation experiments performed on the ash for periods ranging from 2 to 6 days. Koester and Hites (1992) concluded that (1) the absence of photodegradation is not due to the absence of a hydrogen-donor organic substance; (2) other molecules on the ash, as determined by a photolysis experiment with an ash extract, inhibit photodegradation, either by absorbing light and dissipating energy or by quenching the excited states of the CDD/CDFs; and (3) the surface of the ash itself may hinder photolysis by shielding the CDD/CDFs from light.

11. SOURCES OF DIOXIN-LIKE PCBs

The purpose of this chapter is twofold: (1) to identify sources that release dioxin-like polychlorinated biphenyls (PCB) congeners into the environment and (2) to derive national estimates for releases from these sources in the United States. PCBs have been found in all media and all parts of the world. PCBs were produced in relatively large quantities for use in commercial products such as dielectrics, hydraulic fluids, plastics, and paints. They are no longer commercially produced in the United States, but continue to be released to the environment through the use and disposal of these products. PCBs may also be inadvertently produced as by-products during the manufacture of certain organic chemicals and also as products of the incomplete combustion of some waste materials.

11.1. GENERAL FINDINGS OF THE EMISSIONS INVENTORY

Table 11-1 provides a list of known or suspected dioxin-like PCB-emitting source categories in the United States. The source categories included in this table represent a compilation of source categories for which dioxin-like PCB congener, PCB Aroclor, or PCB congener group emission measurements have been reported in government, industry, and trade association reports; in conference proceedings and journal articles; and in comments submitted to the Agency on previous versions of this document. The intent of Table 11-1 is to clearly present those source categories and media (i.e., air, water, land, and products) for which available data are either adequate or inadequate for reliably quantifying emissions of dioxin-like PCBs.

Nationwide emission estimates for the United States inventory are presented in Table 11-2 (emissions to air, water, land, and product) for those source categories for which emission estimates can be reliably quantified (i.e., the category has been assigned a confidence rating of A, B, or C) (see Section 1.4.2 of this report for details on confidence ratings). Table 11-2 also lists, in the far right column, preliminary estimates of the potential magnitude of emissions from "unquantified" sources (i.e., sources assigned a confidence rating of D) in reference year 1995. Because of large uncertainties for these category D estimates, they are not included in the "quantitative inventory."

Releases of "old" dioxin-like PCBs (i.e., dioxin-like PCBs manufactured prior to the ban) to the environment can occur from ongoing use and disposal practices. Prior to

regulations enacted beginning in the late 1970s that limited the manufacture/use/disposal of PCBs, significant quantities of PCBs were released to the environment in association with (1) the manufacture of PCBs; (2) the manufacture of products containing PCBs; and (3) the use and disposal of products containing PCBs, as well as materials that may have been contaminated with trace levels of PCBs from prior PCB use or disposal. Following the ban on PCB production, releases from these first two categories ceased to exist. The third type of releases, those associated with product use and disposal, will continue in at least four ways:

- Products containing greater than 2 pounds of PCBs (e.g., dielectric fluids in transformers and large capacitors) are controlled by disposal regulations that have minimized environmental releases.
- Disposal of products containing small quantities of PCBs (e.g., small capacitors, fluorescent lighting fixtures) or trace quantities of PCBs (e.g., wastepapers) are subject to disposal as municipal solid waste but may result in some release to the general environment.
- Leaks and spills occur in still-in-service PCBs.
- PCBs are disposed of illegally.

No significant release of newly formed dioxin-like PCBs is occurring in the United States. Unlike CDD/CDFs, PCBs were intentionally manufactured in the United States in large quantities from 1929 until production was banned in 1977. Although it has been demonstrated that small quantities of dioxin-like PCBs can be produced during waste combustion, no strong evidence exists that the dioxin-like PCBs are produced in significant quantities as byproducts during combustion or chemical processes. The widespread occurrence of dioxin-like PCBs in the U.S. environment most likely reflects past releases associated with PCB production, use, and disposal. Further support for this finding is based on observations of reductions since the 1980s in PCB concentrations in Great Lakes sediment and other areas.

11.2 RELEASES OF COMMERCIAL PCBs

PCBs were commercially manufactured by the direct batch chlorination of molten biphenyl with anhydrous chlorine in the presence of a catalyst, followed by separation and

purification of the desired chlorinated biphenyl fractions. The degree of chlorination was controlled by the chlorine contact time in the reactor. Commercial PCBs production is believed to have been confined to 10 countries. Total PCBs produced worldwide since 1929 (i.e., the first year of known production) has been estimated to total 1.5-million metric tons. Initially, PCBs were primarily used as dielectric fluids in transformers. After World War II, PCBs found steadily increasing use as dielectric fluids in capacitors, as heat-conducting fluids in heat exchangers, and as heat-resistant hydraulic fluids in mining equipment and vacuum pumps. PCBs also were used in a variety of "open" applications (i.e, uses from which PCBs cannot be recollected) including: plasticizers, carbonless copy paper, lubricants, inks, laminating agents, impregnating agents, paints, adhesives, waxes, additives in cement and plaster, casting agents, dedusting agents, sealing liquids, fire retardants, immersion oils, and pesticides (DeVoogt and Brinkman, 1989).

PCBs were manufactured in the United States from 1929 until 1977. U.S. production peaked in 1970 with a volume of 39,000 metric tons. In 1971, Monsanto Corporation, the major U.S. producer, voluntarily restricted the sales of PCBs to all applications with the exception of "closed electrical systems," and annual production fell to 18,000 metric tons in 1974. Monsanto ceased PCB manufacture in mid-1977 and shipped the last inventory in October 1977. Regulations issued by EPA beginning in 1977, principally under the Toxic Substances Control Act (TSCA) (40 CFR 761), have strictly limited the production, import, use, and disposal of PCBs. The estimated cumulative production and consumption volumes of PCBs in the United States from 1930 to 1975 were 635,000 metric tons produced, 1,400 metric tons imported (primarily from Japan, Italy, and France), 568,000 metric tons sold in the United States; and 68,000 metric tons exported (Versar, 1976). The reliability of these values is +5 percent and -20 percent (Versar, 1976).

Monsanto Corporation marketed technical grade mixtures of PCBs primarily under the trade name *Aroclor*. The Aroclors are identified by a four-digit numbering code in which the last two digits indicate the chlorine content by weight percent. The exception to this coding scheme is Aroclor 1016, which contains only mono- through hexachlorinated congeners with an average chlorine content of 41 percent. From 1957 until 1972, Monsanto also manufactured several blends of PCBs and polychlorinated terphenyls (PCTs) under the trade names Aroclor 2565 and Aroclor 4465; manufacture

and sales volumes are not available for these blends. Listed below are the percentages of total Aroclor production during the years 1957 to 1977 by Aroclor mixture as reported by Brown (1994).

Aroclor	1957-1977 U.S. Production (%)
1016	12.88
1221	0.96
1232	0.24
1242	51.76
1248	6.76
1254	15.73
1260	10.61
1262	0.83
1268	0.33

The trade names of the major commercial PCB technical grade mixtures manufactured in other countries included *Clophen* (Germany), *Fenclor* and *Apirolio* (Italy), *Kanechlor* (Japan), *Phenoclor* and *Pyralene* (France), *Sovtel* (USSR), *Delor* and *Delorene* (Czechoslovakia), and *Orophene* (German Democratic Republic) (DeVoogt and Brinkman, 1989). The mixtures marketed under these trade names had similar chlorine content (by weight percent and average number of chlorines per molecule) to those of various Aroclors. Listed below are comparable mixtures in terms of chlorine content marketed under several trade names.

Aroclor	Clophen	Pyralene	Phenoclor	Fenclor	Kanechlor
1232		2000			200
1242	A-30	3000	DP-3	42	300
1248	A-40		DP-4		400
1254	A-50		DP-5	54	500
1260	A-60		DP-6	64	600

Major advances in analytical separation and resolution techniques beginning in the 1970s enabled various researchers to identify and quantify PCB congeners present in Aroclors, Clophens, and Kanechlors (Jensen et al., 1974; Albro and Parker, 1979; Huckins et al., 1980; Albro et al., 1981; Duinker and Hillebrand, 1983; Kannan et al., 1987; Tanabe et al., 1987; Duinker et al., 1988; Schulz et al., 1989; Himberg and Sippola, 1990; Larsen et al., 1992; deBoer et al., 1993; Schwartz et al., 1993; Frame et al.,

1996a; Frame et al., 1996b; and Frame, 1997). Schulz et al. (1989) were the first to identify and quantify all PCB congeners present in a series of Aroclors and Clophens. Frame (1995) reported preliminary results of a nearly completed round robin study, one goal of which was to determine the distribution of all PCB congeners above 0.05 weight percent in various Aroclors (1221, 1016, 1242, 1260, and 1262) using 18 state-of-the-art gas chromatography/mass spectrometry (GC-MS) or electron capture detector (GC-ECD) systems.

Table 11-3 presents mean summary statistics on the concentrations of the dioxin-like PCBs in each mixture group (i.e., Aroclor 1248, Clophen A-40, and Kanechlor 400 are in one mixture group) reported by these researchers. Table 11-3 also presents calculation of the corresponding mean TEQ concentration of each congener in each mixture group as well as the total mean TEQ concentration in the mixture group. For each mixture group, the congeners detected were generally similar. There was, however, wide variability in the concentrations reported by some researchers for some congeners. Brown et al. (1995) compiled similar statistics using a somewhat different set of studies and derived significantly lower mean concentrations of some congeners in several Aroclors. Frame (1995) and Larsen (1995) attribute such differences either to potential limitations in the GC columns used by various researchers to separate similar eluting congeners or to actual differences in the congener concentrations in the Aroclor, Clophen, and Kanechlor lots analyzed by various research groups. In addition to the specific congener concentrations, the congener distributions also vary among the different mixtures. Therefore, the calculated TEQs also vary. The congener distributions for various lots of Aroclor 1254, and the corresponding TEQs, are presented in another study by Frame (1999). In this study, Frame (1999) reports that the relative TEQs for late production lots are much higher than the earlier production lots; however, the late production lots are estimated to account for only about one percent of the total production volume of Aroclor 1254. Therefore, the data for the later production lots were not included in the average TEQ calculation for Aroclor 1254 in Table 11-3. Because of the wide variability in the reported results, the uncertainty associated with the mean concentrations reported in Table 11-3 is very large.

In the environment, PCBs also occur as mixtures of congeners, but their composition will differ from the commercial mixtures. This is because after release to the

environment, the composition of PCB mixtures changes over time, through partitioning, chemical transformation, and preferential bioaccumulation (U.S. EPA, 1996g). Dioxin-like PCB congeners differ by up to one to two orders of magnitude in their water solubilities, vapor pressures, K_{ow} values, and Henry's Law constants. Thus, although all the dioxin-like PCB congeners are poorly soluble in water and have very low vapor pressures, they will volatilize and leach at different rates. Similarly, because the congeners differ somewhat in their rates of biodegradation, bioaccumulation, and photodegradation, the congener patterns found in environmental media and biota will vary from those found in commercial mixtures.

Although environmental mixtures are often characterized in terms of Aroclors, this characterization can be both imprecise and inappropriate. Qualitative and quantitative errors can arise from judgements in comparing GC/MS peaks for a sample with the characteristic peak patterns for different Aroclors, particularly for environmentally altered patterns (U.S. EPA, 1996g). For the same reason, it can be both imprecise and inappropriate to infer concentrations of dioxin-like PCB congeners in an environmental sample based on characterization of the sample's Aroclor content and knowledge of the dioxin-like congener content in the commercial Aroclor. Safe (1994) wrote, "Regulatory agencies and environmental scientists have recognized that the composition of PCBs in most enviromental extracts does not resemble the compositions of the commercial product." Similarly, ATSDR (1993) stated, "It is important to recognize that the PCBs to which people may be exposed are likely to be different from the original PCB source because of changes in congener and impurity composition resulting from differential partitioning and transformation in the environment and differential metabolism and retention."

11.2.1. Approved PCB Disposal/Destruction Methods

In 1978, EPA began regulating the disposal of PCBs and PCB-contaminated waste under the TSCA, PL 94-469. The disposal regulations, published in the Code of Federal Regulations, 40 CFR, Part 761, state that the preferred disposal method is incineration at 1,200°C or higher. If the waste contains material that can not be destroyed by incineration, EPA clearance must be obtained to dispose of the waste in a chemical waste landfill, or in another approved manner.

The PCB disposal regulations describe disposal of three distinct types of PCB waste: PCBs, PCB articles (i.e., items containing PCBs), and PCB containers. Within these categories of PCB waste, further distinctions are made based on the PCB concentration in the waste. The acceptable disposal methods are based on the PCB concentrations in the specific waste to be destroyed. The acceptable disposal methods are: Annex I incinerators, high-efficiency boilers, Annex II chemical waste landfills, and other approved methods. The following subsections and Table 11-4 provide brief descriptions of these disposal methods. More complete descriptions of the specific methodologies are provided in the Code of Federal Regulations, 40 CFR, Part 761.

Approved Incinerators/High Efficiency Boilers - PCB Annex I incinerators must meet the specific technical standards and criteria listed in Annex I of EPA's PCB regulations. The minimum operating requirements for disposal of liquid wastes are 2 seconds at 1,200°C (2,190°F) with 3 percent excess oxygen (measured in the stack gas), or 1.5 seconds at 1,600°C (2,910°F) and 2 percent excess oxygen (measured in the stack gas). Monitoring requirements, approval conditions, and trial burn requirements are prescribed in Annex I. Commercial or industrial incinerators intending to destroy liquid PCB wastes must demonstrate compliance with the Annex I requirements through a comprehensive trial burn program. Annex I incinerators operating at optimum performance level should destroy 99.997 percent of liquid PCB waste with a resulting maximum emission factor of 0.03 grams per kilogram (g/kg).

Criteria for Annex I incinerators were established for the destruction of liquid PCB wastes; however, these incinerators also may be used for disposal of nonliquid PCB items (such as capacitors), provided that a destruction and removal efficiency of 99.9999 percent and a maximum emission factor of 0.001 g/kg are met.

High-efficiency boilers may be used to destroy PCBs and PCB-contaminated waste with PCB concentrations not exceeding 500 ppm. Conventional industrial and utility boilers may be designated as high-efficiency boilers, if they are operated under the prescribed combustion conditions defined in the PCB disposal regulations. The PCB regulations do not specify a minimum PCB destruction efficiency for high-efficiency boilers; however, EPA-approved boilers operated according to the regulations have reported destruction efficiencies in excess of 99.99 percent, with a corresponding maximum emission factor of 0.1 g/kg (U.S. EPA, 1987c).

Approved Chemical Waste Landfills - Approved chemical waste landfills can be used for the disposal of some, but not all, PCB wastes. PCB-contaminated materials acceptable for land disposal in an approved landfill include PCB mixtures (e.g., certain PCB-contaminated soil/solid debris, PCB-contaminated dredged materials, and PCB-contaminated municipal sewage sludge), PCB articles that cannot feasibly be incinerated (e.g., drained and flushed transformers), and drained PCB containers. EPA must issue written approval to landfill PCB articles other than transformers. PCB-contaminated materials not acceptable for land disposal in an approved landfill include nonliquid PCB mixtures in the form of contaminated soil, rags, or other solid debris, and sealed capacitors. Typically, PCBs disposed in these landfills are placed in sealed containers, thereby, minimizing any PCB emissions.

Other Approved Disposal Methods - Other thermal and nonthermal destruction techniques may be approved by EPA Regional Administrators, if these processes can effect destruction of PCBs equivalent to that of incinerators or boilers. Subsequent to April 29, 1983, all other PCB disposal technologies (thermal and nonthermal) that are to be used in more than one EPA Region must be approved by EPA Headquarters. Examples of thermal technologies approved for commercial-scale use or for research and development projects include a pyrolysis process to treat contaminated soils, a fluid wall reactor, a cement kiln, a diesel engine, a steam-stripping operation, an aluminum melting furnace, and a molten salt process. Examples of approved nonthermal processes include chemical dechlorination processes, physical/chemical extraction techniques, and biological reduction methods. The physical/chemical techniques extract the PCBs from transformers or capacitors and concentrate them for disposal; they do not destroy the PCBs.

Emission Estimates - Table 11-5 lists the amounts of PCBs reported in EPA's Toxics Release Inventory (TRI) as transferred off-site for treatment, energy recovery, or disposal during the years 1988 through 1996. These quantities do not necessarily represent entry of PCBs into the environment. If it is assumed that all transferred PCBs are incinerated in high-efficiency boilers with a destruction and removal efficiency of 99.99 percent, then annual emissions of PCBs to air during 1988 and 1993 could have been as high as 264 kg and 31 kg, respectively. Because no stack testing data are available for dioxin-like PCBs, it is not possible to estimate what fraction of these potential PCB releases would have been the dioxin-like congeners.

11.2.2. Accidental Releases of In-Service PCBs

EPA banned PCB production and use in open systems in 1977. Subsequent to the 1977 ban, releases of commercially produced PCB to the environment (aside from minimal releases occurring during approved disposal and/or destruction) have been limited to accidental release of in-service PCBs (U.S. EPA, 1987c). Accidental releases are the result of leaks or spills during failure/breakage of an existing piece of PCB-containing equipment, or incomplete combustion occurring during accidental fires involving PCB-containing equipment. These two types of accidental releases are discussed in this section.

Leaks and Spills - PCBs that remain in active service at this time are those contained in "closed system" (i.e., those pieces of electrical equipment that completely enclose the PCBs and do not provide direct atmospheric access of the PCBs during normal use). This equipment includes PCB transformers, capacitors, voltage regulators, circuit breakers, and reclosures. With the exception of PCB transformers and probably small PCB capacitors, the majority of the PCB-containing electrical equipment in-service during 1981 was owned by the electrical utility industry. Approximately 70 percent of the estimated 140,000 PCB transformers in-service in 1981 were owned by nonutilities. No information was available on the relative distribution of small PCB capacitors (Versar, 1988).

The number of each of these items owned by the utility industry, the quantity of PCBs each contains, and an estimate of the annual quantity of PCBs leaked and/or spilled were investigated by the Edison Electric Institute and the Utility Solid Wastes Activity Group (EEI/USWAG) for EPA in 1981. The findings of this investigation were reported in a proposed modification to the PCB regulations (Federal Register, 1982a). The findings indicated that over 99 percent of the total quantity of PCBs contained in utility-owned electrical equipment in 1981 (73,700 metric tons) were in 40,000 PCB transformers (those containing > 500 ppm of PCBs) and large PCB capacitors (those containing > 3 lb of PCBs). An upper-bound estimate of the mass of PCBs that leached or spilled from this equipment in 1981 was 177 metric tons. Approximately 95 percent of the estimated releases were the result of leaks from large PCB capacitors (Federal Register, 1982a). Leaks/spills typically occur in transformers when the gasket joining the top to the body corrodes, tears, or physically fails. PCBs can then leak past this failed section and potentially spill onto the surrounding ground. PCB capacitors typically fail by rupturing,

exposing the contained PCBs to the environment. Failure is caused by environmental and weathering effects (e.g., lightning) or material failures (e.g., metal fatigue).

As of mid-1988, the total population of in-service PCB transformers and large PCB capacitors was estimated to have decreased from 140,000 to 110,000 and from 3.3 million to 1.9 million, respectively (Versar, 1988). PCB transformers have normal operating lifetimes of 30 years and 40 years, respectively. The accelerated retirement rate over this 7-year period was attributed to EPA's PCB Electrical Use Rule (Federal Register, 1982b), which required the removal of 950 food/feed industry transformers by 1985 and removal of 1.1 million unrestricted-access large PCB capacitors by October 1988. In addition, EPA's PCB Transformer Fires Rule (Federal Register, 1985b) required the removal by 1990 of 7,600 480-volt network transformers. More recent inventories of PCB-containing electrical equipment are not available. However, a recent Information Collection Request submitted by EPA to the Office of Management and Budget for information on uses, locations, and conditions of PCB electrical equipment estimated that there may be 150,000 owners of PCB-containing transformers used in industry, utilities, government buildings, and private buildings (Federal Register, 1997a). It is expected, and is demonstrated by the reported PCB transfers in TRI (see Table 11-5), that many owners of PCB electrical equipment have removed PCB-containing equipment to eliminate potential liability.

The proportion of spilled PCB that enters the atmosphere, runs off to surface water, or remains in or on the surface depends on a variety of factors including the porosity of the surface onto which the PCBs are spilled (concrete, soil), the PCB isomers that are spilled, ambient conditions (i.e., temperature, wind speed, precipitation), and the cleanup schedule. The number and diversity of factors affecting PCB emissions from spills and leaks make estimation of an emission factor difficult. A rough approximation of the annual amount that may be released to the environment from spills and leaks can be made using the release data reported by manufacturing facilities to EPA's TRI. Table 11-6 lists the amounts of PCBs reported in TRI to be released to the environment during 1988 through 1996. These data include emissions to the air, discharges to bodies of water, releases at the facility to land, as well as contained disposal into underground injection wells.

On the basis of TRI data, annual reported emissions of PCBs to air during 1988 and 1995 could have been as high as 2.7 kg and 0 kg, respectively. For purposes of deriving a preliminary rough estimate of potential releases of dioxin-like PCBs, it can be assumed that the ratio of TEQ to total PCB in the air emissions was 67:1-million (i.e., the average of the estimated mean TEQ contents for Aroclors 1242 and 1254 presented in Table 11-3). Based on this assumption, annual emissions of PCB TEQs in 1988 and 1995 could have been 0.2 and 0 grams, respectively. Similar assumptions for releases to water listed in Table 11-6 yield estimated TEQ emissions during 1988 and 1995 of 0.3 and 0 grams, respectively. For land, estimated TEQ emissions during 1988 and 1995 could have been 23 and 0 grams, respectively.

Accidental Fires - The available information is not adequate to support an estimate of potential annual releases of dioxin-like PCBs from accidental electrical equipment fires. For fires involving PCB transformers or capacitors, the amount of PCBs released is dependent upon the extensiveness of the fire and the speed at which it is extinguished. A number of these fires are documented. A New York fire, involving 200 gallons of transformer fluid containing some 65 percent by weight PCBs, resulted in a release of up to 1,300 pounds of PCBs. A capacitor fire that burned uncontrolled for 2 hours in Sweden resulted in the destruction of 12 large utility capacitors containing an estimated 25 pounds of PCBs each, for a total potential release of 300 pounds. However, data are incomplete on the exact amount of PCBs released as a result of these two fires.

EPA has imposed reporting requirements to ensure that the National Response Center is informed immediately of fires involving PCB transformers (40 CFR 761). The recordkeeping requirements are used to document the use, location, and condition of PCB equipment. Responses are mandatory, but may be claimed by the submitter to be confidential information. The annual number of PCB transformer fires is estimated at approximately 20 per year; the number of PCB capacitor fires is unknown (U.S. EPA, 1987c). As these PCB items reach the end of their useful lives and are retired, their susceptibility to fires will be eliminated, and the overall number of PCB transformer and capacitor fires will be reduced.

11.2.3. Municipal Wastewater Treatment

EPA conducted the National Sewage Sludge Survey in 1988 and 1989 to obtain national data on sewage sludge quality and management. As part of this survey, EPA analyzed sludges from 175 publicly owned treatment works (POTWs) that employed at least secondary wastewater treatment for more than 400 analytes including 7 of the Aroclors. Sludges from 19 percent of the POTWs had detectable levels of at least one of the following Aroclors: 1248, 1254, or 1260; none of the other Aroclors were detected in any sample (detection limit was typically about 200 μg/kg dry weight) (U.S. EPA, 1996a). Analyses were not performed for dioxin-like PCB congeners. The Aroclor-specific results of the survey are presented in Table 11-7. Gutenmann et al. (1994) reported similar results in a survey of sludges from 16 large U.S. cities for Aroclor 1260 content. At a detection limit of 250-μg/kg (dry weight), Gutenmann et al. (1994) detected Aroclor 1260 at only one facility (4,600 μg/kg). These results indicate that PCBs are not likely to be formed at POTWs, but rather are present because of disposal of PCB products or recirculation of previously disposed PCB.

Although PCBs, measured as Aroclors, were not commonly detected in sewage sludge at μg/kg levels by U.S. EPA (1996a) and Gutenmann et al. (1994), the presence of dioxin-like PCB congeners at lower concentrations may be more common. Green et al. (1995) and Cramer et al. (1995) reported the results of analyses of 99 samples of sewage sludge for PCB congener numbers 77, 81, 126, and 169. The sludge samples were collected from 74 wastewater treatment plants across the United States during the summer of 1994. These data are summarized in Table 11-8. Results from all samples collected from the same facility were averaged by Green et al. (1995) and Cramer et al. (1995) to ensure that results were not biased towards the concentrations found at facilities from which more than one sample were collected. If all nondetected values are assumed to be zero, then the POTW mean TEQ_p-WHO_{94} and TEQ_p-WHO_{98} concentrations were 25.1 and 24.2 ng TEQ/kg (dry weight basis), respectively. If the nondetected values are set equal to the detection limits, then the POTW mean TEQ_p-WHO_{94} and TEQ_p-WHO_{98} concentrations were 25.2 and 24.3 ng TEQ/kg, respectively.

EPA recently analyzed samples of sewage sludge collected from a POTW in Ohio for all of the TEQ_P-WHO_{94} and TEQ_P-WHO_{98} dioxin-like PCB congeners, with the exception of PCB 81 (Battelle, 1999). The results of the analyses presented in the draft test report

are listed in Table 11-9. The average TEQ content of the POTW sludge was 158 ng TEQ_P-WHO_{94}/kg (141 ng TEQ_P-WHO_{98}/kg). Three PCB congeners, 77, 126, and 169, accounted for more than 97 percent of the total TEQ in each sample.

Approximately 5.4 million dry metric tons of sewage sludge are estimated by EPA to be generated annually in the United States based on the results of the 1988/1989 EPA National Sewage Sludge Survey (Federal Register, 1993b). Table 11-10 lists the volume of sludge disposed of annually by use and disposal practices. Table 11-10 also lists the estimated amount of dioxin-like PCB TEQs that may be present in sewage sludge and potentially be released to the environment. These values were estimated using the POTW mean TEQ_p-WHO_{98} concentration calculated from the results reported by Green et al. (1995) and Cramer et al. (1995). Multiplying this TEQ concentration by the sludge volumes generated yields an annual potential total release of 101 g TEQ_P-WHO_{98} for nonincinerated sludges. Of this 101 g TEQ_P-WHO_{98}, 1.7 grams enter commerce as a product for distribution and marketing. The remainder is applied to land (51.1 grams) or is landfilled (48.2 grams).

These release estimates are assigned a confidence rating of B indicating high confidence in the production estimate and "medium" confidence in the emission factor estimates. The medium rating was based on the judgment that, although the 74 facilities tested by Green et al. (1995) and Cramer et al. (1995) may be reasonably representative of the variability in POTW technologies and sewage characteristics nationwide, the sample size was still relatively small, and not all dioxin-like PCB congeners were monitored.

11.3. CHEMICAL MANUFACTURING AND PROCESSING SOURCES

In the early 1980s, EPA investigated the extent of inadvertent generation of PCBs during the manufacture of synthetic organic chemicals (Hammerstrom et al., 1985). For example, phthalocyanine dyes and diarylide pigments were reported to contain PCBs in the mg/kg range. EPA subsequently issued regulations under TSCA (40 CFR 761.3) that banned the distribution in commerce of any products containing an annual average PCB concentration of 25 mg/kg (50 mg/kg maximum concentration at any time). In addition, EPA required manufacturers with processes inadvertently generating PCBs and importers of products containing inadvertently generated PCBs to report to EPA any process or

import for which the PCB concentration is greater than 2 mg/kg for any resolvable PCB gas chromatographic peak.

11.4. COMBUSTION SOURCES

11.4.1 Municipal Solid Waste Incineration

Municipal solid waste incinerators have long been identified as potential PCB air emission sources. Stack gas concentrations of PCBs for three incinerators were reported in U.S. EPA (1987c), and the average test results yields an emission factor of 18 μg PCBs/kg refuse. Stack gas emissions of PCBs from the three incinerators were quantified without determining the incinerator's PCB destruction efficiency. The PCB content of various consumer paper products was analyzed as part of the study. This study indicates that paper products such as magazine covers and paper towels contained up to 139 micrograms of PCB per kilogram of paper (μg/kg). These levels, which were reported in 1981, were attributed to the repeated recycle of waste paper containing PCBs. For example, carbonless copy paper manufactured prior to 1971 contained PCB levels as high as 7 percent. This copy paper then became a component of waste paper, which was recycled. The PCBs inevitably were introduced into other paper products, resulting in continued measurable levels in municipal refuse some 4 years after the PCB manufacturing ban was imposed. Refuse-derived fuel (RDF) manufactured from these paper products had PCB levels of 8,500 μg/kg, indicating that this fuel could be a source of atmospheric PCBs. Therefore, it was assumed in U.S. EPA (1987c) that municipal refuse does contain detectable levels of PCBs, and that some of these PCBs may enter the atmosphere when the refuse is incinerated.

Shane et al. (1990) analyzed fly ashes from five municipal solid waste (MSW) incinerators for PCB congener group content. Total PCB levels ranged from 99 to 322 μg/kg in these ashes with the tri-, tetra-, and penta-congener groups occurring in the highest concentrations. Shane et al. (1990) also analyzed seven bottom ashes and eight bottom ash/fly ash mixtures for total PCB measured as Aroclor 1254. The detection limit for this Aroclor analysis was 5 μg/kg. Aroclor 1254 was detected in two of the seven bottom ash samples (26 and 8 μg/kg) and in five of the eight fly ash/bottom ash mixtures (range of 6 to 33 μg/kg).

The development of more sensitive analytical methodologies has enabled researchers in recent years to detect dioxin-like PCB congeners in the stack gases and fly ash from full-scale and pilot-scale MSW incinerators (Sakai et al., 1993a; Sakai et al., 1993b; Boers et al., 1993; Schoonenboom et al., 1993; Sakai et al., 1994). Similarly, the advances in analytical techniques have enabled researchers to determine that dioxin-like PCBs can be formed during the oxidative solid combustion phase of incineration presumably due to dimerization of chlorobenzenes. Laboratory-scale studies have also recently demonstrated that dioxin-like PCBs can be formed from heat treatment of fly ash in air (Schoonenboom et al., 1993; Sakai et al., 1994). However, the available data are not adequate to support development of a quantitative estimate of a dioxin-like PCB emission factor for this source category.

11.4.2. Industrial Wood Combustion

Emissions of PCB congener groups, not individual congeners, were measured during stack testing of two industrial wood burning facilities by the State of California Air Resources Board (CARB, 1990e; 1990f). Table 11-11 presents the average of the congener group (i.e., mono- through decachlorobiphenyl) emission factors for these two facilities. No tetra- or more chlorinated congeners (i.e., the congener groups containing the dioxin-like PCBs) were detected at either facility at detection limits corresponding to emission factors in the low range of ng/kg of wood combusted.

In CARB (1990e), PCBs were measured in the emissions from two spreader stoker wood-fired boilers operated in parallel by an electric utility for generating electricity. The exhaust gas stream from each boiler is passed through a dedicated ESP after which the gas streams are combined and emitted to the atmosphere through a common stack. Stack tests were conducted both when the facility burned fuels allowed by existing permits and when the facility burned a mixture of permitted fuel supplemented by urban wood waste at a ratio of 70:30.

In CARB (1990f), PCBs were measured in the emissions from twin fluidized bed combustors designed to burn wood chips to generate electricity. The APCD system consisted of ammonia injection for controlling nitrogen oxides, and a multiclone and electrostatic precipitator for controlling particulate matter. During testing, the facility burned wood wastes and agricultural wastes allowed by existing permits.

11.4.3. Medical Waste Incineration

As discussed in Section 3.3, EPA recently issued nationally applicable emission standards and guidelines for medical waste incinerators (MWI) that address CDD/CDF emissions. Although PCBs are not addressed in these regulations, the data base of stack test results at MWIs compiled for this rulemaking does contain limited data on PCB congener group emission factors. Data are available for two MWIs lacking add-on APCD equipment and for two MWIs with add-on APCD equipment in place. The average congener group emission factors derived from these test data are presented in Table 11-12. Because data are available for only 4 of the estimated 2,400 facilities that make up this industry and because these data do not provide congener-specific emission factors, no national estimates of total PCB or dioxin-like PCB emissions are being made at this time.

11.4.4. Tire Combustion

Emissions of PCB congener groups, not individual congeners, were measured during stack testing of a tire incinerator by the State of California Air Resources Board (CARB, 1991a). The facility consists of two excess air furnaces equipped with steam boilers to recovery the energy from the heat of combustion. Discarded whole tires were fed to the incineration units at rates ranging from 2,800 to 5,700 kg/hr during the 3 testing days. The furnaces are equipped to burn natural gas as auxiliary fuel. The steam produced from the boilers drives electrical turbine generators that produce 14.4 megawatts of electricity. The facility is equipped with a dry acid gas scrubber and fabric filter for the control of emissions prior to exiting the stack. Table 11-13 presents the congener group (i.e., mono- through decachlorobiphenyl) emission factors for this facility. The emission factor for the total of the tetra- through hepta-chlorinated congener groups is about 1.2 μg/kg of tire processed.

EPA estimated that approximately 0.50 million metric tons of tires were incinerated in 1990 in the United States (U.S. EPA, 1992a). This production estimate is given a medium confidence rating, because it is based on both published data and professional judgment. The use of scrap tires as a fuel increased significantly during the late 1980s; however, no quantitative estimates were provided in U.S. EPA (1992a) for this period. In 1990, 10.7 percent of the 242 million scrap tires generated were burned for fuel. This percentage is expected to continue to increase (U.S. EPA, 1992a). Of the tires burned for

energy recovery purposes, pulp and paper facilities used approximately 46 percent; cement kilns, 23 percent; and one tire-to-energy facility, 19 percent (U.S. EPA, 1997b).

If it is assumed that 500 million kg of discarded tires are incinerated annually in the United States, then, using the sum of the average emission factors for the total tetra- through heptachlorinated congener groups (1.2 μg/kg tire processed) derived from stack data from the one tested facility, yields a total emission of 610 g/yr. However, it is not known what fraction of this emission is dioxin-like PCBs.

11.4.5. Cigarette Smoking

Using high-resolution mass spectrometry, Matsueda et al. (1994) analyzed tobacco from 20 brands of commercially available cigarettes collected in 1992 from Japan, the United States, Taiwan, China, the United Kingdom, Germany, and Denmark for the PCB congeners 77, 126, and 169. Table 11-14 presents the results of the study.

However, no studies have been reported which examined the tobacco smoke for the presence of these congeners. Thus, it is not known whether the PCBs present in the tobacco are destroyed or volatilized during combustion, or whether PCBs are formed during combustion. The combustion processes operating during cigarette smoking are complex and could be used to support either of these potential mechanisms. As reported by Guerin et al. (1992), during a puff, gas phase temperatures reach 850°C at the core of the firecone, and solid phase temperatures reach 800°C at the core and 900°C or greater at the char line. Thus, temperatures are sufficient to cause at least some destruction of CDD/CDFs initially present in the tobacco. Both solid and gas phase temperatures rapidly decline to 200 to 400°C within 2 mm of the char line. Formation of dioxin-like PCBs has been reported in combustion studies with other media in this temperature range (Sakai et al., 1994). However, it is known that a process likened by Guerin et al. (1992) to steam distillation takes place in the region behind the char line because of high localized concentrations of water and temperatures of 200 to 400°C. At least 1,200 tobacco constituents (e.g., nicotine, n-paraffin, some terpenes) are transferred intact from the tobacco into the smoke stream by distillation in this area, and it is plausible that PCBs present in the unburned tobacco would be subject to similar distillation.

In 1995, approximately 487 billion cigarettes were consumed in the United States and by U.S. Armed Forces personnel stationed overseas. Per capita U.S. cigarette

consumption in 1995, based on total U.S. population aged 16 and over, declined to 2,415 from a record high of 4,345 in 1963. In 1987, approximately 575 billion cigarettes were consumed domestically (The Tobacco Institute, 1995; USDA, 1997).

A preliminary rough estimate of potential emissions of dioxin-like PCBs can be made using the following assumptions: (1) the average TEQ_p-WHO_{98} content of seven brands of U.S. cigarettes reported by Matsueda et al. (1994), 0.64 pg/pack (or 0.032 pg/cigarette) is representative of cigarettes smoked in the United States; (2) dioxin-like PCBs are neither formed nor destroyed, and the congener profile reported by Matsueda et al. (1994) is not altered during combustion of cigarettes; and (3) all dioxin-like PCBs contributing to the TEQ are released from the tobacco during smoking. Based on these assumptions, the calculated annual emissions would be 0.018 g TEQ_p-WHO_{98} and 0.016 g TEQ_p-WHO_{98} for reference years 1987 and 1995, respectively.

11.4.6. Sewage Sludge Incineration

U.S. EPA (1996f) derived an emission factor of 5.4 μg of total PCBs per kg of dry sludge incinerated. This emission factor was based on measurements conducted at five multiple hearth incinerators controlled with wet scrubbers. In 1992, approximately 199 sewage sludge incineration facilities combusted 0.865 million metric tons of dry sewage sludge (Federal Register, 1993b). Given this mass of sewage sludge incinerated, the estimated annual release of total PCBs to air annually is 4,670 g. However, it is not known what fraction of this annual emission is dioxin-like PCBs.

EPA recently conducted stack testing at a sewage sludge incinerator in Ohio (Battelle, 1999) for all of the TEQ_P-WHO_{94} and TEQ_P-WHO_{98} dioxin-like PCB congeners with the exception of PCB 81. The results of the analyses (ng/dscm) presented in the draft test report are listed in Table 11-15. The average TEQ content of the stack gas was 0.119 ng TEQ_P-WHO_{94}/dscm (0.106 ng TEQ_P-WHO_{98}/dscm). Three PCB congeners, 77, 126, and 169, accounted for more than 97 percent of the total TEQ in each sample.

11.4.7. Backyard Barrel Burning

In many rural areas of the United States, disposal of residential solid waste may take place via open backyard burning in barrels or similar homemade devices. Although no national statistics on the prevalence of this practice have been reported, the results of a

telephone survey conducted in the early 1990s of residents in five central Illinois counties indicate that about 40 percent of the residents in a typical rural Illinois county burn household waste. The survey also found that, on average, those households that burn waste dispose of approximately 63 percent of their household waste through burning in barrels (Two Rivers Region Council of Public Officials and Patrick Engineering, 1994).

The low combustion temperatures and oxygen-starved conditions associated with this method may result in incomplete combustion and increased pollutant emissions (Lemieux, 1997). EPA's Control Technology Center, in cooperation with the New York State Departments of Health (NYSDOH) and Environmental Conservation (NYSDEC), recently conducted a study to examine, characterize, and quantify emissions from the simulated open burning of household waste materials in barrels (Lemieux, 1997). A representative waste to be burned was prepared based on the typical percentages of various waste materials disposed by New York State residents (i.e., nonavid recyclers); hazardous wastes (i.e., chemicals, paints, oils, etc.) were not included in the test waste. A variety of compounds, including dioxin-like PCBs, were measured in the emissions from the simulated open burning. The measured TEQ emission factors for waste, which had not been separated for recycling purposes, were 1.02E-2 μg TEQ_p-WHO_{94}/kg of waste burned and 5.26E-03 μg TEQ_p-WHO_{98}/kg (see Table 11-16).

The limited emission factor and activity level data available were judged inadequate for developing national emission estimates that could be included in the national inventory. The number of households nationwide burning waste in barrels and the total amount and variability of burned waste is unknown. The representativeness of the trash and burning conditions used in the experiments to conditions nationwide are unknown. However, combining the emission factor of 5.26E-03 μg TEQ_p-WHO_{98}/kg of waste burned with the following information/assumptions, allows a preliminary order of magnitude estimate to be made of potential national dioxin-like PCB TEQ emissions from backyard household trash burning.

- Forty percent of the rural population in the United States are assumed to burn their household waste in a barrel (Two Rivers Region Council of Public Officials and Patrick Engineering, 1994).

- On average, each U.S. citizen generates 3.72 pounds of solid waste (excluding yard waste) per day (or 616 kg/person-year) (U.S. EPA, 1996b).

- On average, for those individuals burning household waste, approximately 63 percent of waste generated are burned (i.e., 63 percent of 616 kg/person-year = 388 kg/person-year) (Two Rivers Region Council of Public Officials and Patrick Engineering, 1994).

- In 1992, 51.8 million people lived in nonmetropolitan areas (U.S. DOC, 1997).

Emissions = $(51.8 \times 10^6$ people)(40%)(388 kg/person-yr)(5.26E-03 µg TEQ_P-WHO_{98}/kg)(10^{-6} g/µg)
= 42.3 g TEQ_P-WHO_{98}/yr (82.1 g TEQ_P-WHO_{94}/yr)

11.4.8. Petroleum Refining Catalyst Regeneration

As discussed in Section 5.3, regeneration of spent catalyst used in catalytic reforming to produce high-octane reformates is a potential source of CDD/CDF air emissions. In 1998, emissions from the caustic scrubber used to treat gases from the external catalyst regeneration unit of a refinery in California were tested for CDD/CDFs, as well as PCB congener groups (CARB, 1999). This facility uses a continuous regeneration process. The reactor is not taken off line during regeneration; rather, small amounts of catalyst are continuously withdrawn from the reactor and are regenerated. The emissions from the regeneration unit are neutralized by a caustic scrubber before being vented to the atmosphere. The catalyst recirculation rate during the three tests ranged from 733 to 1,000 lb/hr.

All PCB congener groups were detected in each of the three samples collected. The average congener group emission factors in units of ng per barrel of reformer feed are presented in Table 11-17. The total PCB emission factor was 118 ng/barrel. This emission factor assumes that emissions are proportional to reforming capacity; emission factors may be more related to the amount of coke burned, APCD equipment present, and/or other process parameters.

Because emissions data are available for only one U.S. petroleum refinery (which represents less than 1 percent of the catalytic reforming capacity at U.S. refineries) and because these data do not provide congener-specific emission factors, no national estimates of total PCB or dioxin-like PCB emissions are being made at this time.

11.5. NATURAL SOURCES

11.5.1. Biotransformation of Other PCBs

Studies show that under anaerobic conditions, biologically mediated reductive dechlorination to less chlorinated congeners, followed by slow anaerobic and/or aerobic biodegradation, is a major pathway for destruction of PCBs in the environment. Research reported to date and summarized below indicates that biodegradation should result in a net decrease rather than a net increase in the environmental load of dioxin-like PCBs.

Laboratory studies (e.g., Bedard et al., 1986; Pardue et al., 1988; Larsson and Lemkemeier, 1989; Hickey, 1995; and Schreiner et al., 1995) have revealed that more than two dozen strains of aerobic bacteria and fungi, which are capable of degrading most PCB congeners with five or fewer chlorines, are widely distributed in the environment. Many of these organisms are of the genus *Pseudomonas* or the genus *Alcaligenes*. The major metabolic pathway involves addition of O_2 at the 2,3-position by a dioxygenase enzyme with subsequent dehydrogenation to the catechol followed by ring cleavage. Several bacterial strains have been shown to possess a dioxygenase enzyme that attacks the 3,4-position.

However, only a few strains have demonstrated the ability to degrade hexa- and more chlorinated PCBs. The rate of aerobic biodegradation decreases with increasing chlorination. The half-lives for biodegradation of tetra-PCBs in fresh surface water and soil are 7 to 60+ days and 12 to 30 days, respectively. For penta-PCBs and higher chlorinated PCBs, the half-lives in fresh surface water and soil are likely to exceed 1 year. PCBs with all or most chlorines on one ring and PCBs with fewer than two chlorines in the ortho position tend to degrade more rapidly. For example, Gan and Berthouex (1994) monitored over a 5-year period the disappearance of PCB congeners applied to soil with sewage sludge. Three of the tetra- and pentachlorinated dioxin-like PCBs (IUPAC Nos. 77, 105, and 118) followed a first-order disappearance model with half-lives ranging from 43 to 69 months. A hexa-substituted congener (IUPAC No. 167) and a hepta-substituted congener (IUPAC No. 180) showed no significant loss over the 5-year period.

Until recent years, little investigation focused on anaerobic microbial dechlorination or degradation of PCBs even though most PCBs eventually accumulate in anaerobic sediments (Abramowicz, 1990; Risatti, 1992). Environmental dechlorination of PCBs via losses of meta and para chlorines has been reported in field studies for freshwater,

estuarine, and marine anaerobic sediments including those from the Acushnet Estuary, the Hudson River, the Sheboygan River, New Bedford Harbor, Escambia Bay, Waukegan Harbor, the Housatonic River, and Woods Pond (Brown et al., 1987; Rhee et al., 1989; Van Dort and Bedard, 1991; Abramowicz, 1990; Bedard et al., 1995; and Bedard and May, 1996). The altered PCB congener distribution patterns found in these sediments (i.e., different patterns with increasing depth or distance from known sources of PCBs) have been interpreted as evidence that bacteria may dechlorinate PCBs in anaerobic sediment.

Results of laboratory studies reported recently confirm anaerobic degradation of PCBs. Chen et al. (1988) found that "PCB-degrading" bacteria from the Hudson River could significantly degrade the mono-, di-, and tri-PCB components of a 20 ppm Aroclor 1221 solution within 105 days. These congener groups make up 95 percent of Aroclor 1221. No degradation of higher chlorinated congeners (present at 30 ppb or less) was observed, and a separate 40-day experiment with tetra-PCB also showed no degradation.

Rhee et al. (1989) reported degradation of mono- to penta-substituted PCBs in contaminated Hudson River sediments held under anaerobic conditions in the laboratory (N_2 atmosphere) for 6 months at 25°C. Amendment of the test samples with biphenyl resulted in greater loss of PCB. No significant decreases in the concentrations of the more highly chlorinated (i.e., more than five chlorines) were observed. No evidence of degradation was observed in samples incubated in CO_2/H_2 atmospheres. Abramowicz (1990) hypothesized that this result could be an indication that, in the absence of CO_2, a selection is imposed favoring organisms capable of degrading PCBs to obtain CO_2 and/or low molecular weight metabolites as electron receptors.

Risatti (1992) examined the degradation of PCBs at varying concentrations (10,000 ppm, 1,500 ppm, and 500 ppm) in the laboratory with "PCB-degrading" bacteria from Waukegan Harbor. After 9 months of incubation at 22°C, the 500 ppm and 1,500 ppm samples showed no change in PCB congener distributions or concentrations, thus indicating a lack of degradation. Significant degradation was observed in the 10,000 ppm sediment with at least 20 congeners ranging from TrCBs to PeCBs showing decreases.

Quensen et al. (1988) also demonstrated that microorganisms from PCB-contaminated sediments (Hudson River) dechlorinated most tri- through hexa-PCBs in Aroclor 1242 under anaerobic laboratory conditions. The Aroclor 1242 used to spike the

sediment contained predominantly tri- and tetra-PCBs (85 mole percent). Three concentrations of the Aroclor, corresponding to 14-, 140-, and 700-ppm on a sediment dry-weight basis, were used. Dechlorination was most extensive at the 700-ppm test concentration; 53 percent of the total chlorine were removed in 16 weeks, and the proportion of TeCBs through HxCBs decreased from 42 to 4 percent. Much less degradation was observed in the 140-ppm sediment, and no observable degradation was found in the 14-ppm sediment. These results and those of Risatti (1992) suggest that the organism(s) responsible for this dechlorination may require relatively high levels of PCB as a terminal electron acceptor to maintain a growing population.

Quensen et al. (1990) reported that dechlorination of 500-ppm spike concentrations of Aroclor 1242, 1248, 1254, and 1260 by microorganisms from PCB-contaminated sediments in the Hudson River and Silver Lake occurred primarily at the meta- and para- positions; ortho-substituted mono- and di-PCBs increased in concentration. Significant decreases over the up to 50-week incubation period were reported for the following dioxin-like PCBs: 156, 167, 170, 180 and 189. Of the four dioxin-like TeCBs and PeCBs detected in the Aroclor spikes (i.e., IUPAC Nos. 77, 105, 114, and 118), all decreased significantly in concentration, with the possible exception of PeCB 114 in the Aroclor 1260-spiked sediment.

Nies and Vogel (1990) reported similar results with Hudson River sediments incubated anaerobically and enriched with acetone, methanol, or glucose. Approximately 300 ppm of Aroclor 1242 (31-mole percent TeCBs, 7-mole percent PeCBs, and 1-mole percent HxCBs) were added to the sediments prior to incubation for 22 weeks under an N_2 atmosphere. Significant dechlorination was observed, with dechlorination occurring primarily at the meta- and para-positions on the more highly chlorinated congeners (i.e., TeCBs, PeCBs, and HxCBs), resulting in the accumulation of less-chlorinated, primarily ortho-substituted mono- through tri-substituted congeners. No significant dechlorination was observed in the control samples (i.e., samples containing no added organic chemical substrate and samples that were autoclaved).

Bedard and May (1996) also reported similar findings in the sediments of Woods Pond, believed contaminated with Aroclor 1260. Significant decreases in the sediment concentrations of PCBs 118, 156, 170, and 180 (relative to their concentrations in

Aroclor 1260) were observed. No increases or decreases were reported for the other dioxin-like PCBs.

Bedard et al. (1995) demonstrated that it is possible to stimulate substantial microbial dechlorination of the highly chlorinated PCB mixture Aroclor 1260 *in situ* with a single addition of 2,6-dibromobiphenyl. Bedard et al. (1995) added 365 g of 2,6-dibromobiphenyl to 6-foot-diameter submerged caissons containing 400-kg sediment (dry weight) and monitored the change in PCB congener concentrations for a period of 1 year. At the end of the observation period, the hexa- through monochlorinated PCBs decreased 74 percent in the top of the sediment and 69 percent in the bottom. The average number of chlorines per molecule dropped 21 percent from 5.83 to 4.61, with the largest reduction observed in meta-chlorines (54 percent reduction) followed by para-chlorines (6 percent). The dechlorination stimulated by 2,6-dibromobiphenyl selectively removed meta-chlorines positioned next to other chlorines.

The findings of these latter studies are significant, because removal of meta- and para-chlorines from the dioxin-like PCBs should reduce their toxicity and bioaccumulative potential and also form less chlorinated congeners that are more amenable to aerobic biodegradation.

Van Dort and Bedard (1991) reported the first experimental demonstration of biologically mediated ortho-dechlorination of a PCB and stoichiometric conversion of that PCB congener (2,3,5,6-TeCB) to less chlorinated forms. In that study, 2,3,5,6-TeCB was incubated under anaerobic conditions with unacclimated methanogenic pond sediment for 37 weeks, with reported dechlorination to 2,5-DCB (21 percent); 2,6-DCB (63 percent); and 2,3,6-TrCB (16 percent).

11.5.2. Photochemical Transformation of Other PCBs

Photolysis and photo-oxidation may be major pathways for destruction of PCBs in the environment. Research reported to date and summarized below indicates that ortho-substituted chlorines are more susceptible to photolysis than are meta- and para-substituted congeners. Thus, photolytic formation of more toxic dioxin-like PCBs may occur. Oxidation by hydroxyl radicals, however, apparently occurs preferentially at the meta- and para-positions thus resulting in a net decrease rather than a net increase in the environmental load of dioxin-like PCBs.

Based on the data available in 1983, Leifer et al. (1983) concluded that all PCBs, especially the more highly chlorinated congeners and those that contain two or more chlorines in the ortho-position, photodechlorinate. In general, as the chlorine content increases, the photolysis rate increases. More recently, Lepine et al. (1992) exposed dilute solutions (4 ppm) of Aroclor 1254 in cyclohexane to sunlight for 55 days in December and January. Congener-specific analysis indicated that the amounts of many higher chlorinated congeners, particularly mono-ortho-substituted congeners decreased, while those of some lower chlorinated congeners increased. The results for the dioxin-like PCBs indicated a 43.5 percent decrease in the amount of PeCB 114; a 73.5 percent decrease in the amount of HxCB 156; and a 24.4 percent decrease in the amount of HxCB 157. However, TeCB 77 and PeCB 126 (the most toxic of the dioxin-like PCB congeners), which were not detected in unirradiated Aroclor 1254, represented 2.5 percent and 0.43 percent, respectively, of the irradiated mixture.

With regard to photo-oxidation, Atkinson (1987) and Leifer et al. (1983), using assumed steady-state atmospheric OH concentrations and measured oxidation rate constants for biphenyl and monochlorobiphenyl, estimated atmospheric decay rates and half-lives for gaseous-phase PCBs. Atmospheric transformation was estimated to proceed most rapidly for those PCB congeners containing either a small number of chlorines or those containing all or most of the chlorines on one ring. Kwok et al. (1995) extended the work of Atkinson (1987) by measuring the OH radical reaction rate constants for 2,2'-, 3,3'-, and 3,5-dichlorobiphenyl. These reaction rate constants, when taken together with the Atkinson's measurements for biphenyl and monochlorobiphenyl and the estimation method described in Atkinson (1991), were used to generate more reliable estimates of the gas-phase OH radical reaction rate constants for the dioxin-like PCBs. The persistence of the PCB congeners increases with increasing degree of chlorination. Table 11-18 presents these estimated rate constants and the corresponding tropospheric lifetimes and half-lives.

Sedlak and Andren (1991) demonstrated in laboratory studies that OH radicals, generated with Fenton's reagent, rapidly oxidized PCBs (i.e., 2-mono-PCB and the DiCBs through PeCBs present in Aroclor 1242) in aqueous solutions. The results indicated that the reaction occurs via addition of a hydroxyl group to one nonhalogenated site; reaction rates are inversely related to the degree of chlorination of the biphenyl. The results also

indicated that meta- and para-sites are more reactive than ortho-sites due to stearic hindrance effects. Based upon their kinetic measurements and reported steady-state aqueous system OH concentrations or estimates of OH radical production rates, Sedlak and Andren (1991) estimated environmental half-lives for dissolved PCBs (mono-through octa-PCB) in fresh surface water and in cloud water to be 4 to 11 days and 0.1 to 10 days, respectively.

11.6. PAST USE OF COMMERCIAL PCBS

An estimated 1.5 million metric tons of PCBs were produced worldwide (DeVoogt and Brinkman, 1989). Slightly more than one-third of these PCBs (568,000 metric tons) were used in the United States (Versar, 1976). Although the focus of this section is on reservoir sources of PCBs within the United States, it is necessary to note that the use and disposal of PCBs in many countries, coupled with the persistent nature of PCBs, have resulted in their movement and presence throughout the global environment. The ultimate sink of most PCBs released to the environment will be aquatic sediments. Currently, however, large quantities of PCBs are estimated to be circulating between the air and water environments or are present in landfills and dumps, some of which may offer the potential for re-release of PCBs into the air. Tanabe (1988) presented a global mass balance for PCBs that indicated that as of 1985, 20 percent of the total PCBs produced were present in seawater, whereas only 11 percent were in sediments. (See Table 11-19.) Nearly two-thirds of total global PCB production was estimated by Tanabe (1988) to still be in use in electrical equipment or to be present in landfills and dumps.

As discussed in Section 11.2, an estimated 568,000 metric tons of PCBs were sold in the United States during the period 1930-1975 (Versar, 1976). Table 11-20 presents annual estimates of domestic sales by year for each Aroclor during the period 1957-1974. Estimates of PCB usage in the United States by usage category during the period 1930-1975 are presented in Table 11-21. Prior to voluntary restrictions by Monsanto Corporation in 1972 on sales for uses other than "closed electrical systems," approximately 13 percent of the PCBs were used in "semi-closed applications," and 26 percent were used in "open-end applications." Most of this usage of PCBs for "semi-closed" and "open-end" applications occurred between 1960 and 1972 (Versar, 1976).

Table 11-22 presents estimates of the amounts of individual Aroclors that were released to the environment (i.e., to water, air, or soil) during the period 1930-1974. Because detailed usage data were not available for the period 1930-1957, Versar (1976) assumed that the usage pattern for this period followed the average pattern for the period 1957-1959. The basic assumptions used by Versar (1976) in deriving these estimates were that 5 percent of the PCBs used in "closed electrical systems" were released; 60 percent of the PCBs used in "semi-closed applications" were released; 25 percent of the PCBs used for plasticizers were released; and 90 percent of PCBs used for miscellaneous industrial uses had escaped. The reliability of these release estimates was assumed to be ±30 percent (Versar, 1976).

In addition to these estimates of direct releases to the environment, Versar (1976) estimated that 132,000 metric tons of PCBs were landfilled. This total was comprised of 50,000 metric tons from capacitor and transformer production wastes, 36,000 metric tons from disposal of obsolete electrical equipment, and 46,000 metric tons from disposal of material from "open-end applications." An additional 14,000 metric tons of PCBs, although still "in service" in various "semi-closed" and "open-end" applications in 1976 were estimated to ultimately be destined for disposal in landfills.

An estimated 3,702 kg of TEQ_P-WHO_{98} were released directly to the U.S. environment during the period 1930-1977 (See Table 11-23). These estimates are based on the Aroclor release estimates presented in Table 11-22 and the mean TEQ_p-WHO_{98} concentrations in Aroclors that were presented in Table 11-3.

Table 11-1. List of Known and Suspected Source Categories for Dioxin-like PCBs

Emission Source Category	Source Categories for Which Emissions Can Be Reliably Quantified								Source Categories for Which Emissions Cannot Be Reliably Quantified							
	Air		Water		Land		Product		Air		Water		Land		Product	
	1995	1987	1995	1987	1995	1987	1995	1987	1995	1987	1995	1987	1995	1987	1995	1987
Releases of Commercial PCBs																
Approved disposal							NA	NA	✔	✔	✔	✔	✔	✔	NA	NA
Accidental releases							NA	NA	✔	✔	✔	✔	✔	✔	NA	NA
Municipal Wastewater Treatment																
Nonincinerated sludge					✔	✔	✔	✔	✔	✔	✔	✔				
Chemical Manufacturing/Processing Sources																
Dyes and pigments									✔	✔	✔	✔	✔	✔	✔	✔
Combustion Sources																
Municipal waste incineration							NA	NA	✔	✔	✔	✔	✔	✔	NA	NA
Industrial wood combustion							NA	NA	✔	✔	✔	✔	✔	✔	NA	NA
Medical waste incineration							NA	NA	✔	✔	✔	✔	✔	✔	NA	NA
Tire combustion							NA	NA	✔	✔	✔	✔	✔	✔	NA	NA
Cigarette combustion			NA	NA	NA	NA	NA	NA	✔	✔	NA	NA	NA	NA	NA	NA
Sewage sludge incineration							NA	NA	✔	✔	✔	✔	✔		NA	NA
Backyard barrel burning			NA	NA			NA	NA	✔	✔	NA	NA	✔	✔	NA	NA

NA = This source category is not expected to generate releases to this environmental medium.

Table 11-2. Quantitative Inventory of Dioxin-Like PCB TEQ_p-WHO_{98} Releases in the United States

Emission Source Category	Quantitative Inventory Confidence Rating[a] Reference Year1995			Quantitative Inventory Confidence Rating[a] Reference Year 1987			Preliminary Estimate for 1995[b]
	A	B	C	A	B	C	
Releases (g TEQ_p-WHO_{98}/yr) to Air							
Releases of Commercial PCBs Approved disposal							
Accidental releases							0
Municipal Sludge Disposal Nonincinerated sludge							
Chemical Manufacturing/Processing Sources Dyes and pigments							
Combustion Sources Municipal waste incineration							
Industrial wood combustion							
Medical waste incineration							
Tire combustion							
Cigarettes							0.016
Sewage sludge incineration							
Backyard barrel burning							42.3
Petroleum refining catalyst regeneration							
Total Quantified Releases to Air[c]	0	0	0	0	0	0	42.3
Releases (g TEQ_p-WHO_{98}/yr) to Water							
Releases of Commercial PCBs Approved disposal							
Accidental releases							0
Municipal Sludge Disposal Nonincinerated sludge							
Chemical Manufacturing/Processing Sources Dyes and pigments							
Combustion Sources Municipal waste incineration							
Industrial wood combustion							
Medical waste incineration							
Tire combustion							
Sewage sludge incineration							
Total Quantified Releases to Water[c]	0	0	0	0	0	0	0
Releases (g TEQ_p-WHO_{98}/yr) to Land							
Releases of Commercial PCBs Approved disposal							
Accidental releases							0
Municipal Sludge Disposal Nonincinerated sludge	51.1			51.1			
Chemical Manufacturing/Processing Sources Dyes and pigments							

Table 11-2. Quantitative Inventorty of Dioxin-Like PCB TEQ_p-WHO_{98} Released in the United States (continued)

Emission Source Category	Quantitative Inventory Confidence Rating[a] Reference Year1995			Quantitative Inventory Confidence Rating[a] Reference Year 1987			Preliminary Estimate for 1995[b]
	A	B	C	A	B	C	
Combustion Sources Municipal waste incineration							
Industrial wood combustion							
Medical waste incineration							
Tire combustion							
Sewage sludge incineration							
Backyard trash burning							
Total Quantified Releases to Land[c]	0	51.1	0	0	51.1	0	0
Releases (g TEQ_p-WHO_{98}/yr) to Products							
Municipal Sludge Disposal Nonincinerated sludge		1.7			1.7		
Chemical Manufacturing/Processing Sources Dyes and pigments							
Total Quantified Releases to Products[c]	0	1.7	0	0	1.7	0	0

[a] A = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **High Confidence** in the **Emission Factor** and **High Confidence** in **Activity Level**.
B = Characterization of the Source Category judged to be **Adequate for Quantitative Esimation** with **Medium Confidence** in the **Emission Factor** and at least **Medium Confidence** in **Activity Level**.
C = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Low Confidence** in either the **Emission Factor** and/or the **Activity Level**.

[b] These are preliminary indications of the potential magnitude of emissions from "unquantified" sources in Reference Year 1995. These estimates were assigned a "confidence category" rating of D and are not included in the Inventory.

[c] TOTAL reflects only the total of the estimates made in this report.

Table 11-3. Weight Percent Concentrations of Dioxin-like PCBs in Aroclors, Clophens, and Kanechlors

Dioxin-Like PCB Congener	IUPAC Number	Number of Samples Analyzed	Number of Detections	Mean Conc. (ND = 0) (g/kg)	TEQ_p-WHO_{98} Conc. (ND = 0) (mg/kg)	Mean Conc.[a] (ND = 1/2DL) (g/kg)	TEQ_p-WHO_{98} Conc.[a] (ND = 1/2DL) (mg/kg)
AROCLOR 1016							
3,3',4,4'-TCB	77	5	0	0	0	0	0
3,4,4',5-TCB	81	3	0	0	0	0	0
2,3,3',4,4'-PeCB	105	4	1	0.0375	0.00375	0.109	0.011
2,3,4,4',5-PeCB	114	4	0	0	0	0	0
2,3',4,4',5-PeCB	118	4	1	0.0125	0.00125	0.091	0.009
2',3,4,4',5-PeCB	123	4	0	0	0	0	0
3,3',4,4',5-PeCB	126	4	0	0	0	0	0
2,3,3',4,4',5-HxCB	156	4	0	0	0	0	0
2,3,3',4,4',5'-HxCB	157	4	0	0	0	0	0
2,3',4,4',5,5'-HxCB	167	4	0	0	0	0	0
3,3',4,4',5,5'-HxCB	169	5	0	0	0	0	0
2,2',3,3',4,4',5-HpCB	170	4	0	0	0	0	0
2,2',3,4,4',5,5'-HpCB	180	4	0	0	0	0	0
2,3,3',4,4',5,5'-HpCB	189	4	0	0	0	0	0
				Total TEQ_p-WHO_{98} =	0.005	Total TEQ_p-WHO_{98} =	0.0200
				Total TEQ_p-WHO_{94} =	0.005	Total TEQ_p-WHO_{94} =	0.0200
AROCLOR 1221							
3,3',4,4'-TCB	77	4	4	1.075	0.1075	1.078	0.108
3,4,4',5-TCB	81	4	1	0.0875	0.00875	0.116	0.012
2,3,3',4,4'-PeCB	105	4	3	0.3875	0.03875	0.4	0.04
2,3,4,4',5-PeCB	114	4	0	0	0	0	0
2,3',4,4',5-PeCB	118	4	4	1.725	0.1725	1.725	0.173
2',3,4,4',5-PeCB	123	4	0	0	0	0	0
3,3',4,4',5-PeCB	126	4	0	0	0	0	0
2,3,3',4,4',5-HxCB	156	4	0	0	0	0	0
2,3,3',4,4',5'-HxCB	157	4	0	0	0	0	0
2,3',4,4',5,5'-HxCB	167	4	0	0	0	0	0
3,3',4,4',5,5'-HxCB	169	4	0	0	0	0	0
2,2',3,3',4,4',5-HpCB	170	3	0	0	0	0	0
2,2',3,4,4',5,5'-HpCB	180	3	0	0	0	0	0
2,3,3',4,4',5,5'-HpCB	189	4	0	0	0	0	0
				Total TEQ_p-WHO_{98} =	0.328	Total TEQ_p-WHO_{98} =	0.333
				Total TEQ_p-WHO_{94} =	0.749	Total TEQ_p-WHO_{94} =	0.752
AROCLOR 1242, Clophen A-30, and Kanechlor 300							
3,3',4,4'-TCB	77	15	15	3.30	0.33	3.301	0.33
3,4,4',5-TCB	81	7	6	1.09	0.11	1.089	0.109
2,3,3',4,4'-PeCB	105	11	11	4.02	0.40	4.024	0.402
2,3,4,4',5-PeCB	114	8	5	1.13	0.57	1.201	0.601
2,3',4,4',5-PeCB	118	9	9	8.04	0.80	8.044	0.804
2',3,4,4',5-PeCB	123	9	7	1.12	0.11	1.157	0.116
3,3',4,4',5-PeCB	126	14	8	0.049	4.94	0.094	9.404
2,3,3',4,4',5-HxCB	156	9	8	0.39	0.20	0.424	0.212
2,3,3',4,4',5'-HxCB	157	8	2	0.021	0.011	0.096	0.048
2,3',4,4',5,5'-HxCB	167	8	2	0.021	0.00021	0.096	0.001
3,3',4,4',5,5'-HxCB	169	14	2	0.000013	0.00013	0.048	0.476
2,2',3,3',4,4',5-HpCB	170	6	2	0.19	0	0.244	0
2,2',3,4,4',5,5'-HpCB	180	5	2	0.16	0	0.218	0
2,3,3',4,4',5,5'-HpCB	189	7	0	0	0	0	0
				Total TEQ_p-WHO_{98} =	7.47	Total TEQ_p-WHO_{98} =	12.50
				Total TEQ_p-WHO_{94} =	8.70	Total TEQ_p-WHO_{94} =	13.74
AROCLOR 1248, Clophen A-40, and Kanechlor 400							
3,3',4,4'-TCB	77	13	13	4.36	0.44	4.36	0.44
3,4,4',5-TCB	81	6	4	1.76	0.18	1.77	0.18
2,3,3',4,4'-PeCB	105	9	8	10.12	1.01	10.12	1.01
2,3,4,4',5-PeCB	114	7	6	3.39	1.69	3.40	1.70
2,3',4,4',5-PeCB	118	8	8	20.98	2.10	20.98	2.10
2',3,4,4',5-PeCB	123	7	7	1.48	0.15	1.48	0.15
3,3',4,4',5-PeCB	126	11	6	0.11	10.55	0.14	13.51
2,3,3',4,4',5-HxCB	156	8	8	1.13	0.56	1.13	0.56
2,3,3',4,4',5'-HxCB	157	7	3	0.19	0.09	0.20	0.10
2,3',4,4',5,5'-HxCB	167	7	3	0.16	0.0016	0.16	0.0016
3,3',4,4',5,5'-HxCB	169	12	3	0.01	0.1006	0.041	0.41
2,2',3,3',4,4',5-HpCB	170	5	4	0.96	0	0.97	0
2,2',3,4,4',5,5'-HpCB	180	4	4	1.24	0	1.24	0
2,3,3',4,4',5,5'-HpCB	189	6	1	0.0018	0.0001833	0.06	0.006
				Total TEQ_p-WHO_{98} =	16.87	Total TEQ_p-WHO_{98} =	20.16
				Total TEQ_p-WHO_{94} =	18.55	Total TEQ_p-WHO_{94} =	21.83

Table 11-3. Weight Percent Concentrations of Dioxin-like PCBs in Aroclors, Clophens, and Kanechlors (continued)

Dioxin-Like PCB Congener	IUPAC Number	Number of Samples Analyzed	Number of Detections	Mean Conc. (ND = 0) (g/kg)	TEQ_p-WHO_{98} Conc. (ND = 0) (mg/kg)	Mean Conc.[a] (ND = 1/2DL) (g/kg)	TEQ_p-WHO_{98} Conc.[a] (ND = 1/2DL) (mg/kg)
AROCLOR 1254, Clophen A-50, and Kanechlor 500							
3,3',4,4'-TCB	77	15	12	0.80	0.0795	0.83	0.08
3,4,4',5-TCB	81	6	1	7.85	0.79	7.86	0.79
2,3,3',4,4'-PeCB	105	12	11	35.83	3.58	35.83	3.58
2,3,4,4',5-PeCB	114	9	6	12.17	6.08	12.23	6.11
2,3',4,4',5-PeCB	118	11	11	81.65	8.17	81.65	8.17
2',3,4,4',5-PeCB	123	8	8	4.59	0.46	4.59	0.46
3,3',4,4',5-PeCB	126	14	12	0.99	99.46	1.02	101.70
2,3,3',4,4',5-HxCB	156	10	10	11.08	5.54	11.08	5.54
2,3,3',4,4',5'-HxCB	157	9	8	1.91	0.95	1.93	0.97
2,3',4,4',5,5'-HxCB	167	10	9	2.74	0.0274	2.74	0.03
3,3',4,4',5,5'-HxCB	169	14	6	0.08	0.80	0.12	1.23
2,2',3,3',4,4',5-HpCB	170	8	8	5.06	0	5.06	0
2,2',3,4,4',5,5'-HpCB	180	7	7	5.79	0	5.79	0
2,3,3',4,4',5,5'-HpCB	189	7	2	0.045	0.0045429	0.13	0.013
				Total TEQ_p-WHO_{98} =	125.94	Total TEQ_p-WHO_{98} =	128.67
				Total TEQ_p-WHO_{94} =	126.04	Total TEQ_p-WHO_{94} =	128.78
AROCLOR 1260, Clophen A-60, and Kanechlor 600							
3,3',4,4'-TCB	77	15	6	0.13	0.01256	0.17	0.017
3,4,4',5-TCB	81	6	1	0.08	0.0075	0.10	0.010
2,3,3',4,4'-PeCB	105	11	10	1.59	0.16	1.59	0.16
2,3,4,4',5-PeCB	114	9	4	0.71	0.35	0.77	0.39
2,3',4,4',5-PeCB	118	11	10	9.51	0.95	9.51	0.95
2',3,4,4',5-PeCB	123	8	1	0.0005	0.00005	0.08	0.008
3,3',4,4',5-PeCB	126	14	7	1.81	180.89	1.84	183.82
2,3,3',4,4',5-HxCB	156	11	11	6.89	3.45	6.89	3.45
2,3,3',4,4',5'-HxCB	157	8	8	1.59	0.79	1.59	0.79
2,3',4,4',5,5'-HxCB	167	10	9	2.87	0.03	2.87	0.03
3,3',4,4',5,5'-HxCB	169	14	5	0.16	1.64	0.19	1.92
2,2',3,3',4,4',5-HpCB	170	8	8	32.94	0	32.94	0
2,2',3,4,4',5,5'-HpCB	180	7	7	82.61	0	82.61	0
2,3,3',4,4',5,5'-HpCB	189	8	8	1.74	0.1739792	1.74	0.17
				Total TEQ_p-WHO_{98} =	188.45	Total TEQ_p-WHO_{98} =	191.71
				Total TEQ_p-WHO_{94} =	192.62	Total TEQ_p-WHO_{94} =	195.89

[a] Calculated for a congener only when at least one sample contained detectable levels of that congener.

References:
Schulz et al. (1989)
Duinker and Hillebrand (1983)
deBoer et al. (1993)
Schwartz et al. (1993)
Larsen, et al. (1992)
Kannan et al. (1987)
Huckins et al. (1980)
Albro and Parker (1979)
Jensen et al. (1974)
Albro et al. (1981)
Duinker et al. (1988)
Tanabe et al. (1987)
Himberg and Sippola (1990)
Frame et al. (1996a)
Frame et al. (1996b)
Frame (1997)

g/kg = grams per kilogram.
mg/kg = milligrams per kilogram.

Table 11-4. Disposal Requirements for PCBs and PCB Items

	Waste Characterization		Disposal Requirements
PCBs	Mineral oil dielectric fluids from PCB transformers	Those analyzing > 500 ppm PCB	Annex I incinerator[a]
	Mineral oil dielectric fluids from PCB-contaminated transformers	Those analyzing 50-500 ppm PCB	Annex I incinerator High efficiency boiler (40 CFR 761.10(a)(2)(iii)) Other approved incinerator[b] Annex II chemical waste landfill[c]
	PCB liquid wastes other than mineral oil dielectric fluid	Those analyzing > 500 ppm PCB	Annex I incinerator
		Those analyzing 50-500 ppm PCB	Annex I incinerator High efficiency boiler (40 CFR 761.10(a)(2)(iii)) Other approved incinerator[b] Annex II chemical waste landfill[c]
	Nonliquid PCB wastes (e.g., contaminated materials from spills)		Annex I incinerator Annex II chemical waste landfill
	Dredged materials and municipal sewage treatment sludges containing PCBs		Annex I incinerator Annex II chemical waste landfill Other approved disposal method (40 CFR 761.10(a)(5)(iii)
PCB Articles	Transformers	PCB transformers	Annex I incinerator Drained and rinsed transformers may be disposed of in Annex II chemical waste landfill
		PCB contaminated transformers	Disposal of drained transformers is not regulated
	PCB capacitors		Annex I incinerator
	PCB hydraulic machines	Those containing > 1,000 ppm PCB	Drained and rinsed machines may be disposed of as municipal solid waste or salvaged
		Those containing < 1,000 ppm PCB	Drained machines may be disposed of as municipal solid waste or salvaged
	Other PCB articles	Those containing PCB fluids	Drained machines may be disposed of per Annex I or Annex II
		Those not containing PCB fluids	Annex I incinerator or Annex II chemical waste landfill
PCB Containers	Those used to contain only PCBs at a concentration < 500 ppm		As municipal solid waste provided any liquid PCBs are drained prior to disposal
	Other PCB containers		Annex I incinerator Annex II, provided any liquid PCBs are drained prior to disposal Decontaminate per Annex IV

[a] Annex I incinerator defined in 40 CFR 761.40.
[b] Requirements for other approved incinerators are defined in 40 CFR 761.10(e).
[c] Annex II chemical waste landfills are described in 40 CFR 761.41. Annex II disposal is permitted if the PCB waste contains less than 500 ppm PCB and is not ignitable as per 40 CFR Part 761.41(b)(8)(iii).
[d] Disposal of containerized capacitors in Annex II landfills was permitted until March 1, 1981; thereafter, only Annex I incineration has been permitted.
ppm = parts per million

Table 11-5. Off-site Transfers of PCBs Reported in TRI (1988-1996)

Year	No. of TRI Forms Filed	Reported Transfers (kg)		
		Transfers to POTWs	Transfers for Treatment/ Disposal	TOTAL TRANSFERS
1996	NA	0	160,802	160,802
1995	NA	0	308,347	308,347
1994	NA	0	466,948	466,948
1993	16	120	463,385	463,505
1992	20	0	766,638	766,638
1991	26	0	402,535	402,535
1990	NA	0	1,181,961	1,181,961
1989	NA	0.5	2,002,237	2,002,237
1988	122	113	2,642,133	2,642,246

NA = Not available
kg = kilograms
POTWs = Publicly owned treatment works

Sources: U.S. EPA (1993h), U.S. EPA (1995g), U.S. EPA (1998b)

Table 11-6. Releases of PCBs Reported in TRI (1988-1996)

Year	No. of TRI Forms Filed	Reported Releases (kg)					
		Fugitive or Nonpoint Air Emissions	Stack or Point Air Emissions	Surface Water Discharges	Underground Injection	On-Site Releases to Land	TOTAL ON-SITE RELEASES
1996	NA	2.3	114	0	0	4,179	4,295
1995	NA	0	0	0	0	0	0
1994	NA	0	0	0	0	0	0
1993	16	0	0	0	0	120	120
1992	20	0	0	0	0	0.5	0.5
1991	26	0	0	0	0	0	0
1990	NA	2.3	0	0	0	32,372	32,374
1989	NA	0	0	120	0	453	573
1988	122	2.7	0	4.5	0	341	348

Sources: U.S. EPA (1993h); U.S. EPA (1995g); U.S. EPA (1998b)

NA = Not available.

Table 11-7. Aroclor Concentrations Measured in EPA's National Sewage Sludge Survey

Aroclor	Percent Detected	Maximum Concentration (ng/kg)	Median Concentration (ng/kg)	
			Nondetects Set to Det. Limit	Nondetects Set to Zero
1016	0	--	--	0
1221	0	--	--	0
1232	0	--	--	0
1242	0	--	--	0
1248	9	5.20	0.209	0
1254	8	9.35	0.209	0
1260	10	4.01	0.209	0
Any Aroclor (total)	19	14.7	1.49	0

Source: U.S. EPA (1996a); for POTWs with multiple samples, the pollutant concentrations were averaged before the summary statistics presented in the table were calculated. All concentrations are in units of nanograms per kilogram (ng/kg) dry weight.

Table 11-8. Dioxin-Like PCB Concentrations Measured in Sludges Collected from 74 U.S. POTWs During 1994[a]

Congener	IUPAC Number	Percent Detected	Maximum Concentration (ng/kg)	Median Concentration (ng/kg)		Mean Concentration (ng/kg)	
				Nondetects Set to 1/2 Det. Limit	Nondetects Set to Zero	Nondetects Set to 1/2 Det. Limit	Nondetects Set to Zero
3,3',4,4'-TCB	77	100	22,900	783	783	2,243	2,243
3,4,4',5-TCB	81	86	1,250	27.3	27.0	65.2	63.5
2,3,3',4,4'-PeCB	105						
2,3,4,4',5-PeCB	114						
2,3',4,4',5-PeCB	118						
2',3,4,4',5-PeCB	123						
3,3',4,4',5-PeCB	126	99	3,020	91.6	91.6	237	237
2,3,3',4,4',5-HxCB	156						
2,3,3',4,4',5'-HxCB	157						
2,3',4,4',5,5'-HxCB	167						
3,3',4,4',5,5'-HxCB	169	22	1,470	8.5	0	32.5	26.2
2,2',3,3',4,4',5-HpCB	170						
2,2',3,4,4',5,5'-HpCB	180						
2,3,3',4,4',5,5'-HpCB	189						
Total TEQ_p-WHO_{94}				9.5	9.5	25.2	25.1
Total TEQ_p-WHO_{98}				9.3	9.2	24.3	24.2

ng/kg = nanograms per kilogram

a For POTWs with multiple samples, the sample concentrations were averaged by Cramer et al. (1994) to POTW averages before calculation of the total TEQ mean and median values presented in the table. The TEQ_p-WHO_{94} and TEQ_p-WHO_{98} values were calculated on a facility-level basis.

NOTE: Blank cells indicate that no measurements of these congeners were made.

Source: Green et al. (1995); Cramer et al. (1995)

Table 11-9. Dioxin-Like PCB Concentrations in Sludges Collected from a U.S. POTW During 1999

Congener	IUPAC Number	Run 1 (ng/kg, dry)	Run 2 (ng/kg, dry)	Run 3 (ng/kg, dry)	Average Conc. (ng/kg)
3,3',4,4'-TCB	77	40,899	41,096	45,386	42,460
3,4,4',5-TCB	81				
2,3,3',4,4'-PeCB	105	7,015	7,389	7,289	7,231
2,3,4,4',5-PeCB	114	691	674	738	701
2,3',4,4',5-PeCB	118	12,250	13,497	12,856	12,868
2',3,4,4',5-PeCB	123	231	276	241	249
3,3',4,4',5-PeCB	126	1,118	1,214	1,479	1,270
2,3,3',4,4',5-HxCB	156	1,772	1,883	1,876	1,844
2,3,3',4,4',5'-HxCB	157	472	565	536	524
2,3',4,4',5,5'-HxCB	167	878	968	959	935
3,3',4,4',5,5'-HxCB	169	453	601	656	570
2,2',3,3',4,4',5-HpCB	170	2,526	2,572	2,776	2,625
2,2',3,4,4',5,5'-HpCB	180	6,002	6,780	6,711	6,498
2,3,3',4,4',5,5'-HpCB	189	181	198	218	199
Total TEQ_P-WHO_{94}		141	152	181	158
Percent due to PCBs 77, 81, 126, and 169		97.3%	97.3%	97.8%	97.5%
Total TEQ_P-WHO_{98}		124	135	163	141
Percent due to PCBs 77, 81, 126, and 169		97.2%	97.3%	97.8%	97.4%

* For POTWs with multiple samples, the sample TEQ concentrations were averaged to POTW averages before calculation of the TEQ mean and median values presented in the table.

NOTE: Blank cells indicate that no measurements of these congeners were made.

Source: Battelle (1999)

Table 11-10. Quantity of Sewage Sludge Disposed of Annually by Primary, Secondary, or Advanced Treatment POTWs and Potential Dioxin-Like PCB TEQ Releases

Use/Disposal Practice	Volume Disposed (thousands of dry metric tons/year)	Percent of Total Volume	Potential TEQ_p-WHO_{98} Release[c] (g of TEQ/yr)	Potential TEQ_p-WHO_{94} Release[c] (g of TEQ/yr)
Land Application	1,714	32.0[e]	41.5	43.0
Distribution and Marketing	71	1.3	1.7	1.8
Surface Disposal Site/Other	396	7.4	9.6	9.9
Sewage Sludge Landfill	157	2.9	4.2	3.9
Co-Disposal Landfills[a]	1,819	33.9	44.0	45.6
Sludge Incinerators and Co-Incinerators[b]	865	16.1	(f)	
Ocean Disposal	(336)[d]	(6.3)[d]	(0)[d]	
TOTAL	5,357	100.0	101.0	104.2

[a] Landfills used for disposal of sewage sludge and solid waste residuals.

[b] Co-incinerators treat sewage sludge in combination with other combustible waste materials.

[c] Potential TEQ release for nonincinerated sludges was estimated by multiplying the sludge volume generated (i.e., column 2) by the mean dioxin-like PCB TEQ concentration in 74 POTW sludges reported by Green et al. (1995) and Cramer et al. (1995) (i.e., 24.2 ng TEQ_p-WHO_{98}/kg and 25.1 ng TEQ_p-WHO_{94}/kg).

[d] The Ocean Dumping Ban Act of 1988 generally prohibited the dumping of sewage sludge into the ocean after December 31, 1991. Ocean dumping of sewage sludge ended in June 1992 (Federal Register, 1993b). The current method of disposal of the 336,000 metric tons of sewage sludge that were disposed in the oceans in 1988 has not been determined.

[e] Includes 21.9 percent applied to agricultural land, 2.8 percent applied as compost, 0.6 percent applied to forestry land, 3.1 percent applied to "public contact" land, 1.2 percent applied to reclamation sites, and 2.4 percent applied in undefined settings.

[f] See Section 11.4.6 for for a discussion of dioxin-like PCB releases to air from sewage sludge incinerators.

Sources: Federal Register (1990); Federal Register (1993b); Green et al. (1995); Cramer et al. (1995).

Table 11-11. PCB Congener Group Emission Factors for Industrial Wood Combustors

Congener Group	Number of Sites	Number of Detections	Maximum Concentration Detected (ng/kg wood)	Mean Concentration (ng/kg)	
				Nondetects Set to Det. Limit	Nondetects Set to Zero
Monochlorobiphenyls	2	1	32.1	39.4	16.0
Dichlorobiphenyls	2	1	23.0	50.9	11.5
Trichlorobiphenyls	2	1	19.7	42.3	9.8
Tetrachlorobiphenyls	2	0	--	22.7	--
Pentachlorobiphenyls	2	0	--	17.6	--
Hexachlorobiphenyls	2	0	--	17.0	--
Heptachlorobiphenyls	2	0	--	17.9	--
Octachlorobiphenyls	2	0	--	15.8	--
Nonachlorobiphenyls	2	0	--	25.0	--
Decachlorobiphenyls	2	0	--	36.3	--

ng/kg = nanograms per kilogram.

Source: CARB (1990e, 1990f)

Table 11-12. PCB Congener Group Emission Factors for Medical Waste Incinerators (MWIs)

Congener Group	Mean Emission Factor (ng/kg) (2 MWIs without APCD)		Mean Emission Factor (ng/kg) (2 MWIs with APCD)	
	Nondetects Set to Det. Limit	Nondetects Set to Zero	Nondetects Set to Det. Limit	Nondetects Set to Zero
Monochlorobiphenyls	0.059	0.059	0.311	0
Dichlorobiphenyls	0.083	0.083	0.340	0
Trichlorobiphenyls	0.155	0.155	0.348	0
Tetrachlorobiphenyls	4.377	4.377	1.171	0
Pentachlorobiphenyls	2.938	2.938	17.096	9.996
Hexachlorobiphenyls	0.238	0.238	1.286	1.078
Heptachlorobiphenyls	0.155	0.155	0.902	0
Octachlorobiphenyls	0.238	0.238	0.205	0
Nonachlorobiphenyls	0.155	0.155	--	--
Decachlorobiphenyls	0.155	0.155	0.117	0

APCD = Air Pollution Control Device
ng/kg = nanograms per kilogram.
-- = Not reported.

Source: See Section 3.3 for details on tested facilities.

Table 11-13. PCB Congener Group Emission Factors for a Tire Combustor

Congener Group	Number of Samples	Number of Detections	Maximum Emission Factor (ng/kg)	Mean Emission Factor (ng/kg)	
				Nondetects Set to Det. Limit	Nondetects Set to Zero
Monochlorobiphenyls	3	0	--	0.04	--
Dichlorobiphenyls	3	1	34.8	11.7	11.6
Trichlorobiphenyls	3	1	29.5	11.8	9.8
Tetrachlorobiphenyls	3	0	--	10.0	--
Pentachlorobiphenyls	3	2	2,724	1,092	1,092
Hexachlorobiphenyls	3	1	106.5	55.9	35.5
Heptachlorobiphenyls	3	1	298.6	107.7	99.5
Octachlorobiphenyls	3	0	--	20.9	--
Nonachlorobiphenyls	3	0	--	17.7	--
Decachlorobiphenyls	3	0	--	41.9	--

ng/kg = nanograms per kilogram.

Source: CARB (1991a)

Table 11-14. Dioxin-Like PCB Concentrations in Cigarette Tobacco

Congener	IUPAC Number	Concentrations in brands from various countries (pg/pack)						
		U.S. Brands (Avg of 7 brands)	Japan (Avg of 6 brands)	United Kingdom (Avg of 3 brands)	Taiwan (1 brand)	China (1 brand)	Denmark (1 brand)	Germany (1 brand)
3,3',4,4'-TCB	77	105.7	70.2	53.0	133.9	12.6	21.7	39.3
3,4,4',5-TCB	81							
2,3,3',4,4'-PeCB	105							
2,3,4,4',5-PeCB	114							
2,3',4,4',5-PeCB	118							
2',3,4,4',5-PeCB	123							
3,3',4,4',5-PeCB	126	6.2	7.8	6.1	14.5	2.4	2.2	7.3
2,3,3',4,4',5-HxCB	156							
2,3,3',4,4',5'-HxCB	157							
2,3',4,4',5,5'-HxCB	167							
3,3',4,4',5,5'-HxCB	169	0.9	0.9	0.9	2.4	0.4	0.5	1.6
2,2',3,3',4,4',5-HpCB	170							
2,2',3,4,4',5,5'-HpCB	180							
2,3,3',4,4',5,5'-HpCB	189							
Total TEQ_p-WHO_{94}		0.68	0.82	0.64	1.54	0.25	0.24	0.76
Total TEQ_p-WHO_{98}		0.64	0.80	0.62	1.49	0.24	0.23	0.75

Source: Matsueda et al. (1994)

NOTE: Blank cells indicate that no measurements of these congeners were made.

Table 11-15. Dioxin-Like PCB Concentrations in Stack Gas Collected from a U.S. Sewage Sludge Incinerator

Congener	IUPAC Number	Run 1 (ng/dscm) (@ 7% O2)	Run 2 (ng/dscm) (@ 7% O2)	Run 3 (ng/dscm) (@ 7% O2)	Average Conc. (ng/dscm) (@ 7% O2)
3,3',4,4'-TCB *	77	49.20	38.18	13.26	33.54
3,4,4',5-TCB	81				
2,3,3',4,4'-PeCB	105	5.23	4.32	1.75	3.77
2,3,4,4',5-PeCB	114	0.76	0.60	0.25	0.54
2,3',4,4',5-PeCB	118	11.20	9.27	4.10	8.19
2',3,4,4',5-PeCB	123	0.23	0.20	0.07	0.17
3,3',4,4',5-PeCB	126	1.37	1.03	0.39	0.93
2,3,3',4,4',5-HxCB	156	1.26	0.99	0.39	0.88
2,3,3',4,4',5'-HxCB	157	0.43	0.32	0.15	0.30
2,3',4,4',5,5'-HxCB	167	0.76	0.59	0.25	0.54
3,3',4,4',5,5'-HxCB	169	1.10	0.82	0.26	0.73
2,2',3,3',4,4',5-HpCB	170	2.12	1.70	0.81	1.54
2,2',3,4,4',5,5'-HpCB	180	5.27	4.18	1.59	3.68
2,3,3',4,4',5,5'-HpCB	189	0.19	0.13	0.08	0.13
Total TEQ_P-WHO_{94}		1.76E-01	1.33E-01	4.94E-02	1.19E-01
Percent due to PCBs 77, 126, and 169		98.2%	98.1%	97.8%	98.1%
Total TEQ_P-WHO_{98}		1.56E-01	1.17E-01	4.40E-02	1.06E-01
Percent due to PCBs 77, 126, and 169		98.1%	98.0%	97.7%	98.0%

* PCB-77 concentrations were greater than the highest point on the lab's PCB calibration curve.
NOTE: Blank cells indicate that no measurements of these congeners were made.

Source: Battelle (1999)

Table 11-16. Dioxin-Like PCB Emission Factors from Backyard Barrel Burning

Congener	IUPAC Number	Emission Factors (ug/kg)		
		Test 1	Test 2	Average
3,3',4,4'-TCB	77	9.3	15.2	12.3
3,4,4',5-TCB	81			
2,3,3',4,4'-PeCB	105	5.9	4.9	5.4
2,3,4,4',5-PeCB	114			
2,3',4,4',5-PeCB	118	8.3	14.3	11.3
2',3,4,4',5-PeCB	123	18.6	28.7	23.7
3,3',4,4',5-PeCB	126			
2,3,3',4,4',5-HxCB	156			
2,3,3',4,4',5'-HxCB	157			
2,3',4,4',5,5'-HxCB	167			
3,3',4,4',5,5'-HxCB	169			
2,2',3,3',4,4',5-HpCB	170			
2,2',3,4,4',5,5'-HpCB	180			
2,3,3',4,4',5,5'-HpCB	189			
Total TEQ_P-WHO_{94}		7.93E-03	1.24E-02	1.02E-02
Total TEQ_P-WHO_{98}		4.21E-03	6.31E-03	5.26E-03

Source: Lemieux (1997)
NOTE: Blank cells indicate that the congener was not detected in either of the two duplicate samples.

Table 11-17. PCB Congener Group Emission Factors for a Petroleum Catalytic Reforming Unit

Congener Group	Number of Samples	Number of Detections	Mean Concentration (ng/dscm) (at 12% O2)	Mean Emission Rate (lb/hr)	Mean Emission Factor (lb/1000bbl)	Mean Emission Factor (ng/barrel)
Monochlorobiphenyls	3	3	166	5.51E-08	7.11E-09	3.23E+00
Dichlorobiphenyls	3	3	355	1.17E-07	1.52E-08	6.89E+00
Trichlorobiphenyls	3	3	743	2.45E-07	3.17E-08	1.44E+01
Tetrachlorobiphenyls	3	3	849	2.81E-07	3.62E-08	1.64E+01
Pentachlorobiphenyls	3	3	914	3.02E-07	3.88E-08	1.76E+01
Hexachlorobiphenyls	3	3	780	2.57E-07	3.30E-08	1.50E+01
Heptachlorobiphenyls	3	3	1,430	4.73E-07	6.01E-08	2.73E+01
Octachlorobiphenyls	3	3	698	2.32E-07	2.95E-08	1.34E+01
Nonachlorobiphenyls	3	3	179	5.99E-08	7.59E-09	3.44E+00
Decachlorobiphenyls	3	3	41.3	1.39E-08	1.76E-09	7.98E-01
Total PCBs			6,155	2.04E-06	2.61E-07	1.18E+02

Source: CARB (1999)

Table 11-18. Estimated Tropospheric Half-Lives of Dioxin-Like PCBs with Respect to Gas-Phase Reaction with the OH Radical

Congener Group	Dioxin-Like Congener	Estimated OH Reaction Rate Constant (10^{-12} cm^3/molecule-sec)	Estimated Tropospheric Lifetime (days)[a]	Estimated Tropospheric Half-Life (days)[a]
TCB	3,3',4,4'-TCB	0.583	20	14
	3,4,4',5-TCB	0.710	17	12
PeCB	2,3,3',4,4'-PeCB	0.299	40	28
	2,3,4,4',5-PeCB	0.383	31	22
	2,3',4,4',5-PeCB	0.299	40	28
	2',3,4,4',5-PeCB	0.482	25	17
	3,3',4,4',5-PeCB	0.395	30	21
HxCB	2,3,3',4,4',5-HxCB	0.183	65	45
	2,3,3',4,4',5'-HxCB	0.214	56	39
	2,3',4,4',5,5'-HxCB	0.214	56	39
	3,3',4,4',5,5'-HxCB	0.266	45	31
HpCB	2,2',3,3',4,4',5-HpCB	0.099	121	84
	2,2',3,4,4',5,5'-HpCB	0.099	121	84
	2,3,3',4,4',5,5'-HpCB	0.125	95	66

cm^3 = cubic centimeters.

[a] Calculated using a 24-hour, seasonal, annual, and global tropospheric average OH radical concentration of 9.7×10^5 molecule/cm^3 (Prinn et al., 1995).

Source: Atkinson (1995) [Based on Atkinson (1991) and Kwok et al. (1995)].

Table 11-19. Estimated PCB Loads in the Global Environment as of 1985

Environment	PCB Load (metric tons)	Percentage of PCB Load	Percentage of World Production
Terrestrial and Coastal			
Air	500	0.13	
River and Lake Water	3,500	0.94	
Seawater	2,400	0.64	
Soil	2,400	0.64	
Sediment	130,000	35	
Biota	4,300	1.1	
Total (A)	143,000	39.00	
Open Ocean			
Air	790	0.21	
Seawater	230,000	61	
Sediment	110	0.03	
Biota	270	0.07	
Total (B)	231,000	61.00	
Total Load in Environment (A + B)	374,000	100	31
Degraded and Incinerated	43,000		4
Land-stocked[a]	783,000		65
World Production	1,200,000		100

[a] Still in use in electrical equipment and other products, and deposited in landfills and dumps.

Source: Tanabe (1988); note that a world production of 1.2-million metric tons is assumed by Tanabe (1988). DeVoogt and Brinkman (1989) estimated worldwide production to have been 1.5-million metric tons.

Table 11-20. Domestic Sales of Aroclors (1957-1974)

Year	Estimated Domestic Sales									Total PCB Releases (metric tons)
	Aroclor 1016 (metric tons)	Aroclor 1221 (metric tons)	Aroclor 1232 (metric tons)	Aroclor 1242 (metric tons)	Aroclor 1248 (metric tons)	Aroclor 1254 (metric tons)	Aroclor 1260 (metric tons)	Aroclor 1262 (metric tons)	Aroclor 1268 (metric tons)	
1957	0	10	89	8,265	807	2,023	3,441	14	0	14,651
1958	0	7	51	4,737	1,161	3,035	2,713	83	33	11,821
1959	0	115	109	6,168	1,535	3,064	3,002	163	46	14,202
1960	0	47	70	8,254	1,282	2,761	3,325	148	86	15,973
1961	0	43	109	8,993	1,825	2,855	2,966	164	72	17,027
1962	0	64	102	9,368	1,571	2,869	2,991	196	95	17,256
1963	0	164	6	8,396	2,274	2,681	3,459	188	129	17,296
1964	0	270	6	10,692	2,376	2,849	3,871	202	86	20,352
1965	0	167	3	14,303	2,524	3,509	2,645	253	89	23,494
1966	0	239	7	17,943	2,275	3,191	2,665	348	129	26,797
1967	0	200	11	19,529	2,134	3,037	2,911	381	130	28,334
1968	0	62	41	20,345	2,220	4,033	2,382	327	127	29,536
1969	0	230	124	20,634	2,563	4,455	2,013	323	136	30,479
1970	0	670	118	22,039	1,847	5,634	2,218	464	150	33,140
1971	1,512	1,005	78	9,970	97	2,114	782	0	0	15,559
1972	9,481	78	0	330	366	1,585	138	0	0	11,978
1973	10,673	16	0	2,812	0	3,618	0	0	0	17,119
1974	9,959	26	0	2,815	0	2,805	0	0	0	15,605
TOTALS	31,625	3,412	924	195,596	26,856	56,120	41,525	3,255	1,307	360,620
% of Total	8.8%	0.9%	0.3%	54.2%	7.4%	15.6%	11.5%	0.9%	0.4%	100.0%

Source: Versar (1976)

Table 11-21. Estimated U.S. Usage of PCBs by Use Category (1930-1975)

Use Class	Use Category	Amount Used (1,000 metric tons)	Percent of Total Usage	Reliability of Estimate
Closed Electrical Systems	Capacitors	286	50.3	±20%
	Transformers	152	26.8	±20%
Semi-Closed Applications	Heat transfer fluids	9	1.6	±10%
	Hydraulics and lubricants	36	6.3	±10%
Open-End Applications	Plasticizer uses	52	9.2	±15%
	Carbonless copy paper	20	3.5	±5%
	Misc. industrial	12	2.1	±15%
	Petroleum additives	1	<1	±50%
TOTAL		568	100	

Source: Versar (1976)

Table 11-22. Estimated Direct Releases of Aroclors to the U.S. Environment (1930-1974)[a]

Year	Estimated Environmental Releases					Total PCB Releases (metric tons)
	Aroclor 1016 (metric tons)	Aroclor 1242 (metric tons)	Aroclor 1248 (metric tons)	Aroclor 1254 (metric tons)	Aroclor 1260 (metric tons)	
1930-56	0	8,486	2,447	2,269	1,614	14,817
1957	0	903	319	307	423	1,952
1958	0	649	483	416	355	1,903
1959	0	1,042	724	518	507	2,792
1960	0	1,340	556	449	540	2,885
1961	0	1,852	792	587	611	3,841
1962	0	1,811	659	554	571	3,594
1963	0	1,655	935	529	682	3,801
1964	0	2,085	980	555	755	4,375
1965	0	2,689	1,025	660	497	4,872
1966	0	3,180	876	566	472	5,094
1967	0	3,376	814	525	504	5,219
1968	0	3,533	853	733	433	5,552
1969	0	4,165	993	985	452	6,596
1970	0	4,569	697	1,168	474	6,907
1971	76	1,466	51	325	121	1,963
1972	474	22	0	104	9	135
1973	534	141	0	181	0	322
1974	498	141	0	140	0	281
TOTALS	1,582	43,103	13,205	11,572	9,019	76,898
% of Total	2.1%	56.1%	17.2%	15.0%	11.7%	100.0%

a Does not include an additional 132,000 metric tons estimated to have been landfilled during this period.

Source: Versar (1976)

Table 11-23. Estimated Releases of Dioxin-Like PCB TEQs
to the U.S. Environment During 1930-1977

Aroclor	Percent of U.S. Sales[a] (1957-1974)	Estimated PCB Releases (1930-1974)[b] (metric tons)	Estimated Mean TEQ_p-WHO_{98} Concentration[c] (mg/kg)	Estimated Total TEQ_p-WHO_{98} Released (kilograms)
Aroclor 1016	12.88%	1,582	d	d
Aroclor 1221	0.96%	--	0.328	--
Aroclor 1232	0.24%	--	--	--
Aroclor 1242	51.76%	43,103	7.47	322
Aroclor 1248	6.76%	13,205	16.87	223
Aroclor 1254	15.73%	11,572	125.94	1,457
Aroclor 1260	10.61%	9,019	188.45	1,700
Aroclor 1262	0.83%	--	--	--
Aroclor 1268	0.33%	--	--	--
				Total = 3,702

μg/kg = micrograms per kilogram.

"--" indicates that release estimates were not been made because of relatively low usage amounts.

[a] Sales during the period 1957-1974 constitute 63% of all PCB sales during 1930-1977; sales data for individual Aroclors are not available for years prior to 1957. However, sales of Aroclors 1221, 1232, 1262, and 1268 were minor even prior to 1957.

[b] From Table 11-22.

[c] From Table 11-3 (assumes not detected values are zero).

[d] Data are available for only a few samples of Aroclor 1016 where only 2 dioxin-like PCB congeners were detected. The total TEQ_P-WHO_{98} released is less than 0.01 kilograms.

Source: Versar (1976)

12.0 RESERVOIR SOURCES OF CDD/CDF AND DIOXIN-LIKE PCBs

National CDD/CDF source inventories have been conducted in several nations, including the United Kingdom, The Netherlands, Germany, Austria, and Sweden to characterize emissions from various source categories and estimate annual CDD/CDF emissions to air (and sometimes other media). These inventories focused primarily on emissions from primary sources (i.e., emissions from the site or process where the CDD/CDF are formed). The authors of these inventories (Rappe, 1991; Harrad and Jones, 1992b; Bremmer et al., 1994; Thomas and Spiro, 1995 and 1996; Eduljee and Dyke, 1996; Jones and Alcock, 1996; Duarte-Davidson et al., 1997) indicated that the annual estimates of releases to air provided in these inventories may be underestimates of actual emissions for several reasons. First, from an empirical basis, estimates of the amounts of CDD/CDFs deposited annually from the atmosphere were greater than the estimates of annual CDD/CDF emissions to the atmosphere. Second, the investigators indicated that because of limited emission test data the inventories may underestimate releases from known sources or may not identify all primary sources. Third, the investigators acknowledged the existence of potential reservoir (or secondary) sources but were not able to reliably quantify emissions from these sources. Potential reservoir sources identified by these investigators included volatilization of CDD/CDFs from PCP-treated wood, volatilization from soil, and resuspension of soil particles. Relatively little research of either a monitoring or theoretical nature has been performed to identify reservoir sources and to quantify the magnitude of current or potential future releases from these sources.

This chapter presents background information on reservoir sources of CDD/CDF/PCBs. Section 12.1 presents a working definition for reservoir sources. Section 12.2 describes major environmental reservoirs (i.e., soil, water, sediment, and biota) and presents information on: (1) the potential magnitude (mass) of CDD/CDF/PCBs in each reservoir; (2) the chemical/physical mechanisms responsible for releases of these compounds; and (3) estimates of potential annual releases from each reservoir, if such estimates are feasible, given the available state of knowledge. Section 12.3 presents a summary of the information presented in this chapter.

12.1. POTENTIAL RESERVOIRS

Chapters 2 through 11 have discussed both known and suspected sources of newly formed dioxin-like compounds to the environment in the United States. Once released into the open environment, CDDs, CDFs, PCBs partition to air, soils, water, sediments and biota according to both the nature of the release, and the contaminant's chemical and physical properties (see Volume 2, Chapter 2). The definitions adopted for this analysis of reservoirs and reservoir sources are as follows:

> *Reservoirs* are materials or places that contain previously formed CDD/CDFs or dioxin-like PCBs and have the potential for redistribution and circulation of these compounds into the environment. Potential reservoirs include soils, sediments, biota, water and some anthropogenic materials. Reservoirs become sources when they have releases of dioxin-like compounds to the circulating environment over a defined time and space. Like other sources they would not include purely intermediate products or materials properly disposed in a secure landfill.

Reservoir sources are not included in the quantitative inventory of contemporary sources because they do not involve original releases, but rather the recirculation of past releases. They can, however, contribute to human exposure and, therefore, are important to consider. Figure 12-1 presents a conceptual diagram of flux and exchange of dioxin-like compounds to multiple environmental compartments including the principal environmental reservoirs: soil, water, air, sediment, and biota. This dynamic system consists of fluxes in and out of the atmosphere, as well as other exchanges between reservoirs and the atmosphere. Movement between media can be induced by volatilization, wet and dry atmospheric particle and vapor deposition, adsorption, erosion and runoff, resuspension of soils into air, and resuspension of sediments into water. The rate of movement from one environmental medium to another is termed 'flux,' and refers to the direction and magnitude of flow and exchange over a reference time period and space.

12.2. CHARACTERIZATION OF RESERVOIR SOURCES

This section is organized according to reservoir type (soil, water, sediment, and biota) with each subsection providing information in three parts: (1) the potential magnitude (mass) of dioxin-like compounds in the reservoir; (2) the chemical/physical mechanisms responsible for releases of these compounds; and (3) estimates of potential annual releases from the reservoir, if such estimates are feasible, given the available state of knowledge. Although, anthropogenic structures are potential reservoir sources, they are not discussed here because they were covered earlier in Chapter 8 (the most detailed discussion is on PCP, Section 8.3.8.).

12.2.1. Soil

Potential Mass of Dioxin-Like Compounds Present

The companion document to this report, Volume 2 (Fate, Environmental Levels, and Exposure), presents a compilation of CDD/CDF/PCB concentrations in surface soils reported in various published studies. Based on this compilation of studies, the mean TEQ values for background urban and rural soils are estimated to be 13.4 and 4.1 ng I-TEQ_{DF}/kg of soil, respectively (or 11.9 and 3.6 ng TEQ_{DF}-WHO_{98}/kg, respectively). It should be noted that no comprehensive survey of CDD/CDF concentrations in U.S. soils has yet been performed. The surface area of the United States (excluding Alaska) is approximately 7.85 million square kilometers (sq km). Land use statistics for 1992 indicate that 0.37 million sq km are classified as "developed" and can be considered to be principally urban areas. The remaining 7.48 million sq km are considered rural. Of this rural area, 1.55 million sq km are cropland (U.S. DOC, 1997). Further breakdown of the rural land area into pasture land, range land, and forest land is available, but the available monitoring data are considered to be inadequate for deriving background CDD/CDF concentrations for these land use types.

In estimating burdens for the United Kingdom, Harrad and Jones (1992) and Duarte-Davidson et al. (1997) assumed that the majority of CDD/CDFs in soil is present in the top 5 centimeters (except possibly in cropland, which may involve a deeper depth due to plowing) and that the soil density is 1,000 kg/m^3. Coupling these assumptions regarding depth of contamination and average soil density with the rural and urban U.S. surface areas and TEQ concentrations yields soil burden estimates of 1,530 kg I-TEQ_{DF} (1,350 kg

TEQ_{DF}-WHO_{98}) in rural soils and 250 kg I-TEQ_{DF} (220 kg TEQ_{DF}-WHO_{98}) in urban soils in the United States.

Higher concentrations of CDD/CDFs than those presented above for background urban and rural soils may be present in soils underlain by municipal and industrial waste and in soils at contaminated industrial sites. The lack of comprehensive data on CDD/CDF concentrations in these soils, as well as the lack of data on the mass of these soils nationwide, precludes estimating total national soil burdens for these soils at present. Higher concentrations of CDD/CDFs may also be present in the soils of areas that have been treated with pesticides contaminated with CDD/CDFs. For the same reasons presented above for industrially contaminated soil, it is not possible to estimate current soil burdens of CDD/CDF associated with past pesticide use. However, estimates can be made of the total mass of CDD/CDF TEQs that have been applied to soil from past use of the pesticides 2,4-D and 2,4,5-T.

2,4-Dichlorophenoxy acetic acid (2,4-D) and its salts and esters are widely used in agricultural and nonagricultural settings in the United States as post-emergence herbicides for control of broadleaf weeds and brush. In terms of volumes of pesticides used annually, 2,4-D ranks among the top 10 pesticides in the United States (U.S. EPA, 1994b, 1997e) and has been in large-scale, large-volume commercial use for many years (U.S. EPA, 1975). Commercial production of 2,4-D in the United States started in 1944 (Esposito et al., 1980). Table 12-1 presents a compilation of historical domestic production, sales, and usage volumes for 2,4-D and its salts and esters.

As described in Section 8.3.8, CDD/CDFs were detected in several formulations of 2,4-D and its derivatives during analyses performed to comply with EPA's 1987 Data Call-In (DCI) for CDD/CDFs. Although the analytical results of these tests indicated that CDD/CDFs were seldom above the regulatory limits of quantification (LOQ) established by EPA for the DCI, several registrants detected and quantified CDD/CDFs at lower LOQs. The results of these tests are summarized in Table 8-25. The average TEQ in these tests was 0.70 μg I-TEQ_{DF}/kg (1.10 μg TEQ_{DF}-WHO_{98}/kg). Schecter et al. (1997) recently reported similar concentrations in 2,4-D samples manufactured in Europe and Russia; lower levels were observed in U.S. products. The results of Schecter et al. (1997) are presented in Table 8-27.

If it is assumed that the EPA DCI results (i.e., average TEQ level of 0.70 μg I-TEQ_{DF}/kg or 1.10 μg TEQ_{DF}-WHO_{98}/kg) are typical of CDD/CDF levels in 2,4-D pesticides over the past 20 years and that the average annual use of these pesticides in the United States has been approximately 25,000 metric tons, then the estimated CDD/CDF TEQ released to the environment from 2,4-D use during the period 1975 to 1995 was 350 g I-TEQ_{DF} (550 g TEQ_{DF}-WHO_{98}).

2,4,5-Trichlorophenoxy acetic acid (2,4,5-T) was used in the United States for a variety of herbicidal uses until the late 1970s to early 1980s. The major use of 2,4,5-T (about 41 percent of annual usage) was for control of woody and herbaceous weed pests on rights-of-way. The other major herbicidal uses were forestry (28 percent of usage), rangeland (20 percent of usage), and pasture (5 percent of usage). As discussed in Section 3.4.2.8, uses of 2,4,5-T for home or recreation areas and for lakes, ponds, and ditches were suspended by EPA in 1970. Rights-of-way, forestry, and pasture uses were suspended by EPA in 1979, and all uses were canceled in 1983.

Table 12-2 presents a compilation of historical domestic production, sales, and usage volumes for 2,4,5-T and its salts and esters. As shown in Table 12-2, production and use of 2,4,5-T generally increased each year following its introduction in the 1940s until the late 1960s. Production, sales, and usage information for the 1970s are generally not available but are reported to have steadily declined during that period (Federal Register, 1979; Esposito et al., 1980).

Some information is available on the 2,3,7,8-TCDD content of 2,4,5-T, but little information is available on the concentrations of the other 2,3,7,8-substituted CDD/CDFs that may have been present.

- Plimmer (1980) reported that 2,3,7,8-TCDD concentrations as high as 70,000 μg/kg were detected in 2,4,5-T during the late 1950s.

- In a study of 42 samples of 2,4,5-T manufactured before 1970, Woolson et al. (1972) found 500 to 10,000 μg/kg of TCDDs in 7 samples, and another 13 samples contained 10,000 to 100,000 μg/kg of TCDDs. HxCDDs were found in four samples at levels between 500 and 10,000 μg/kg and in one sample at a concentration exceeding 10,000 μg/kg, but less than 100,000 μg/kg. The detection limit in the study was 500 μg/kg.

- The average 2,3,7,8-TCDD concentration in 200 samples of Agent Orange, a defoliant containing about a 50/50 mixture of the butyl esters of 2,4,5-T and

2,4-D that was used by the U.S. Air Force in Vietnam, was 1,910 μg/kg (Kearney et al., 1973). Of the 200 samples, 64 (or 32 percent) contained more than 500 μg/kg of 2,3,7,8-TCDD, with the highest concentration reported to be 47,000 μg/kg.

- Storherr et al. (1971) reported detecting 2,3,7,8-TCDD at concentrations ranging from 100 to 55,000 μg/kg in five samples of 2,4,5-T.

- Kearney et al. (1973) reported that production samples of 2,4,5-T obtained from the three principal 2,4,5-T manufacturers in 1971 contained 2,3,7,8-TCDD at levels of $<$100 μg/kg, 100μg/kg, and 2,300 μg/kg.

- A 1975 survey of 10 lots of a commercial formulation containing 2,4,5-T showed 2,3,7,8-TCDD concentrations ranging from 10 to 40 μg/kg (Dow Chemical Co., undated).

- Analyses by EPA of 16 technical grade 2,4,5-T samples from five different manufacturers revealed 2,3,7,8-TCDD contents ranging from $<$10 to 25 μg/kg (Federal Register, 1979).

- Schecter et al. (1997) recently reported the analytical results of one sample of 2,4,5-T purchased from Sigma Chemical Co. (product number T-5785, lot number 16H3625). The results, presented in Table 12-3, indicate a total I-TEQ_{DF} concentration of 2.88 μg/kg (3.26 μg TEQ_{DF}-WHO_{98}/kg).

Because of the wide variability (i.e., three orders of magnitude) in the available limited information on the 2,3,7,8-TCDD content of 2,4,5-T (particularly the 2,4,5-T used in the 1950s) and incomplete information on domestic usage, it is difficult to reliably estimate the amount of 2,3,7,8-TCDD that was released to the U.S. environment as a result of 2,4,5-T use. A very uncertain estimate can be made using the following assumptions: (1) the average annual consumptions during the 1950s, 1960s, and 1970s were 2,000 metric tons/yr, 4,000 metric tons/yr, and 1,500 metric tons/yr, respectively; and (2) the average 2,3,7,8-TCDD concentrations in 2,4,5-T used over these three decades were 10,000 μg/kg in the 1950s, 4,000 μg/kg in the 1960s, and 100 μg/kg in the 1970s. Based on these assumptions, the very uncertain estimate of 2,3,7,8-TCDD input from 2,4,5-T use over the period 1950-1979 is 36,000 g.

Another source contributing to the soil reservoir is CDD/CDF in sewage sludge applied to land (i.e., surface disposal or land farming) is estimated to have been 103 g I-TEQ_{DF} in 1995 (75 g TEQ_{DF}-WHO_{98}) [Note: See Section 8.4.1 for details]. If this same amount of TEQ had been applied each year during the period 1975 to 1995, the total amount applied would have been 2,000 g I-TEQ_{DF} (1,500 g TEQ_{DF}-WHO_{98}).

Mechanisms Responsible for Releases from Surface Soils

Atmospheric deposition is believed to be the current primary means of supply of dioxin-like compounds to surface soil. CDD/CDFs/PCBs are highly lipid soluble, low volatility compounds, and tend to partition to soil instead of into air or water. Once present in or on soils, physical/chemical and biological mechanisms (i.e., photolysis and biodegradation) can slowly alter the composition and amount of CDD/CDFs/PCBs present. Studies indicate that the dioxin-like compounds (particularly the more highly chlorinated CDD/CDFs) exhibit little downward mobility once deposited in or on soil (Puri et al. 1989; Freeman and Schroy, 1985; Orazio et al., 1992; and Paustenbach et al., 1992). However, remobilization of the compounds to the atmosphere is possible through volatilization and resuspension of soil particles.

For example, Young (1983) conducted field studies on the persistence and movement of 2,3,7,8-TCDD during 1973-1979 on a military test area that had been aerially sprayed with 73,000 kg of 2,4,5-T during 1962-1970. TCDD levels of 10 to 1,500 ng/kg could be found in the top 15 cm of soil 14 years after the last application of herbicide at the site. Although actual data were not available on the amount of 2,3,7,8-TCDD originally applied as a contaminant of the 2,4,5-T, best estimates indicated that less than 1 percent of the applied 2,3,7,8-TCDD remained in the soil after 14 years. Photodegradation at the time of and immediately after aerial application was believed by Young (1983) to be responsible for most of the disappearance. However, once incorporated into the soil, the data indicated a half-life of 10 to 12 years (Young, 1983). Similarly, Paustenbach et al. (1992), concluded that half-lives of 2,3,7,8-TCDD in soils at the surface might be 9 to 15 years and half-lives below the surface could be 25 to 100 years.

Ayris and Harrad (1997) studied the mechanisms affecting volatilization fluxes of several PCB congeners (PCB numbers 28, 52, 101, 138, and 180) from soil and found positive correlations between flux and soil temperature, soil moisture content, and soil PCB concentration. For PCBs, secondary releases from soils (primarily via volatilization) are believed to currently exceed primary emissions in the United Kingdom (Harner et al., 1995; Jones and Alcock, 1996). Lee et al. (1998) recently quantified PCBs in air samples taken every 6 hours over a 7-day period in the summer at a rural site in England and found a strong correlation between air temperature and PCB congener concentrations. The

concentrations followed a clear diurnal cycle, thus providing some evidence that rapid, temperature controlled soil to air exchange of PCBs influences air concentrations and enables regional/global scale cycling of these compounds.

CDD/CDFs and PCBs sorbed to soil and urban dust particles can also be moved from the terrestrial environment to the aquatic environment via stormwater runoff/erosion. Results of recent research indicate that, for at least some waterbodies, erosion/stormwater runoff is currently the dominant mechanism for CDD/CDF input. For example, Smith et al. (1995) analyzed CDD/CDF concentrations in sediment cores, air, precipitation, soil, and stormwater runoff in an effort to determine the contributing sources of these compounds to the lower Hudson River. The mass balance estimates developed from these data for 1990-1993 are: stormwater runoff entering tributaries (76 percent of total CDD/CDF input), anthropogenic wastes (19 percent), atmospheric deposition (4 percent), and shoreline erosion (less than 1 percent). Smith et al. (1995) also projected the percent contribution of these same sources for 1970 as: anthropogenic wastes (70 percent), stormwater runoff into tributaries (15 percent), atmospheric deposition (15 percent), and shoreline erosion (0.1 percent).

Lebeuf et al. (1996) analyzed sediment cores from different locations in the lower St. Lawrence River Estuary and the Gulf of St. Lawrence. The congener group profiles found in the samples indicate that the input of CDD/CDFs is primarily from the atmosphere. Comparison of the CDD/CDF concentrations in sediments collected from areas where sediment accumulation is due primarily to fluvial transport with sediments from areas where sediment accumulation is due primarily to direct atmospheric deposition onto the water indicates that the contribution of CDD/CDF from direct atmospheric deposition represents less than 35 percent of the sediment burden. Thus, the primary source of CDD/CDFs is emissions to the atmosphere upwind of the Estuary that are deposited within the watershed and subsequently transported downstream by fluvial waters.

Paustenbach et al. (1996) and Mathur et al. (1997) reported that stormwater runoff from 15 sites in the San Francisco area contained CDD/CDF TEQ at levels ranging from 0.01 to 65 pg I-TEQ_{DF}/L; most samples contained less than 15 pg I-TEQ_{DF}/L. The sites differed widely in land use; the highest levels measured were obtained from an urban, but nonindustrialized area. A distinct variability was noted in the results obtained at the same sampling location during different rain events. The profiles of CDD/CDFs in the urban

stormwater samples were similar particularly in samples collected at the onset of rain events. Stowe (1996) reported similar findings from analyses of sediments from three stormwater basins collecting runoff from a military base, city street, and parking lots.

Fisher et al. (1998) reported that urban runoff samples from eight sites (15 samples) in the Santa Monica Bay watershed contained CDD/CDF TEQ at levels ranging from 0.7 to 53 pg I-TEQ_{DF}/L (all but one sample were in the range of 0.7 to 10 pg I-TEQ_{DF}/L). The samples were collected in 1988/1989 from continuously flowing storm drains during both dry and storm periods. The mean concentration measured during storm events, 18 pg I-TEQ_{DF}/L, was higher than concentration observed during dry periods, 1 pg I-TEQ_{DF}/L.

Estimated Annual Releases from Soil to Water

Nonpoint sources of CDD/CDFs to waterways include stormwater runoff from urban areas and soil erosion in rural areas during storms. Approaches to estimate national loadings to water for both of these sources are described below. The estimate derived below for the potential annual national loading of CDD/CDFs in urban runoff to waterways is uncertain, but suggests that the loading may be comparable to the contribution from known industrial point sources (at least 20 g I-TEQ_{DF} in 1995). Similarly, the estimate derived below for the potential annual national loading of CDD/CDFs in rural eroded soils to waterways is uncertain, but has a stronger analytical base than the urban run off estimate. This loading estimate, however, is significantly higher than the contribution from known industrial point sources.

Urban Runoff - Few data on CDD/CDF concentrations in urban runoff have been reported. The most recent and largest data sets were reported in studies conducted in the San Francisco Bay and Santa Monica Bay regions (Mathur et al, 1997; Fisher et al., 1998). These studies found a wide range of CDD/CDF levels in samples of stormwater runoff from 23 sites, varying from 0.01 to 83 pg I-TEQ_{DF}/L. The wide variability and limited geographic coverage of these data preclude derivation of a national emission estimate at this time. However, by making a number of assumptions, a preliminary estimate of the potential CDD/CDF magnitude from this source can be made. In order to estimate the amount of rainfall in urbanized areas of the conterminous United States, a Geographic Information Systems (GIS) analysis was performed to: determine the total area of every U.S. Census

urbanized area; to determine the 30-year annual average rainfall for each of those areas; and to calculate the product of the total areas of urbanized areas with the annual average rainfall (Lockeed Martin, 1998). This approach yields an estimate of 1.9×10^{14} L/year. If it is assumed that urban runoff in the United States averages 1 pg I-TEQ_{DF}/L (or 1 pg TEQ_{DF}-WHO_{98}/L) (i.e., approximately the midpoint of the range reported by Mathew et al. (1997) and Fisher et al. (1998)), this source could contribute a total of 190 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} per year to U.S. waterways. No data were available to make similar estimates for PCBs.

Rural Soil Erosion - The total annual sheet and rill erosion in the United States during 1992 has been estimated as 1.6 billion metric tons from rangeland and 1.1 billion metric tons from cropland (USDA, 1995). The total amount of eroded soil entering waterways is greater than this value, because this value does not include soil erosion from construction areas, forests, and other non-crop and non-rangelands. The data summarized in the companion document to this report (Volume 2) suggest that typical concentrations of CDD/CDFs in soils in rural areas is about 4.1 ng I-TEQ_{DF}/kg (or 3.6 ng TEQ_{DF}-WHO_{98}/kg. It is not known how well this estimate represents eroded soil from cropland and rangeland. If these soils contain an average of 1 ng TEQ/kg (i.e., slightly lower than the background value for all types of rural soil), they would contribute 2,700 g TEQ/yr (I-TEQ_{DF} and TEQ_{DF}-WHO_{98}) to the Nation's waterways. As with urban runoff, no data were available to make similar estimates for PCBs.

Estimated Annual Releases from Soil to Air

No quantitative estimates of the mass of dioxin-like compounds that may be released to the atmosphere annually from U.S. soils have been published in the literature and none are developed in this report. As noted above, the vapor flux of these compounds from soil to air is dependent on the soil and air concentrations of dioxin-like compounds, and the temperature, moisture content, and organic carbon content of the soil. Most of these parameters are not adequately characterized for the United States as a whole to enable a reliable estimate to be made at present. Particle flux is dependent on many factors including wind speed, vegetative cover, activity level, particle size, soil type/conditions, moisture content and particle density. Through use of models and various assumptions, Kao and Venkataraman (1995) estimated the fraction of ambient air

CDD/CDF concentrations in the upper Midwest United States that may be the result of atmospheric reentrainment of soil particles. Similarly, through use of models and various assumptions, Jones and Alcock (1996) and Harner et al. (1995) reached tentative conclusions about the relative importance of volatilization of dioxin-like compounds from soils in the United Kingdom.

Modeling re-entrainment of soil to the atmosphere was conducted by Kao and Venkataraman (1995). The soil re-entrainment model incorporated information on particle sizes, deposition velocities, and concentrations of CDD/CDFs in soils. Smaller particulates, with median diameters ranging from about 0.01 μm to 0.3 μm, are primarily formed from combustion sources when hot vapors condense and through accumulation of secondary reaction products on smaller nuclei. Particles at the upper end of this size range will deposit to the ground in several days. Large or coarse particles, having median diameters of about 8 μm, are generated from wind-blown dust, sea spray, and mechanically-generated particles. CDD/CDFs absorbed onto re-entrained soil would be included in this larger particle size. These larger particles have a lifetime in the atmosphere from a few to many hours (Kao and Venkataraman, 1995).

The fraction of ambient air concentration of CDD/CDF that results from soil re-entrainment was established based on the contribution of crustal sources to the ambient aerosol. Data on typical crustal soil concentrations in air (15 to 50 $\mu g/m^3$ for rural areas and 5 to 25 $\mu g/m^3$ for urban areas) were combined with data on the average concentrations of CDD/CDFs in soils (73 ng/kg for rural, 2,075 ng/kg for urban, and 8,314 ng/kg for industrial soils) published by Birmingham (1990) for Ontario, Canada, and several Midwest States. This analysis estimated the concentrations of CDD/CDFs in the ambient aerosol that originate from soils to be 1×10^{-3} to 4×10^{-3} pg/m^3 in rural areas and 0.01 to 0.05 pg/m^3 in urban areas. These particulate dioxin concentrations were compared to average total particulate dioxin levels of 1.36 pg/m^3 by Eitzer and Hites (1989) to arrive at the conclusion that soil re-entrainment could only account for 1 to 4 percent of the particulate dioxins in the atmosphere in urban areas and 0.1 to 0.3 percent for rural regions (Kao and Venkataraman, 1995).

This information on the size distribution of ambient aerosols and relative CDD/CDF concentrations in different particle size fractions was integrated with particle size-deposition velocities to estimate the relative contribution to the total mass deposition flux

for small and large particle sizes. Even though re-entrained soil may constitute only a small fraction of the atmospheric levels of CDD/CDFs, the contribution of dioxins in re-entrained surface soil to the total deposition flux could be significant, because coarse particles dominate dry deposition. Soil re-entrainment could possibly account for as much as 70 to 90 percent of the total dry deposition of CDD/CDFs in urban areas and 20 to 40 percent in rural regions (Kao and Venkataraman, 1995).

Two approaches were used by Jones and Alcock (1996) to assess the potential significance of CDD/CDF volatilization from soils: (1) the fugacity quotient concept and (2) a simple equilibrium partitioning model. The fugacity quotient model compares fugacities of individual CDD/CDF compounds in different environmental media to determine the tendency for these compounds to accumulate in particular environmental compartments (McLachlan, 1996). Fugacities for individual compounds, by media, were estimated by Jones and Alcock (1996) based on physical/chemical properties of the compounds, as well as the concentrations in the media. In this instance, fugacity quotients were calculated for air and soil by dividing each compound's fugacity for air by that of soil. Quotients near 1 indicate equilibrium conditions between media; values greater than 1 represent a tendency for flux (volatilization) from soil to air, while values less than 1 indicate a net flux to the soil from the air. The equilibrium partitioning model used by Jones and Alcock (1996) predicts the maximum (possible 'worst case') flux of CDD/CDFs from soil to the atmosphere. Air phase to soil partition coefficients were calculated using the ratios of soil and air fugacity capacities. Equilibrium air concentrations were then calculated using typical U.K. soil concentrations for both urban and rural settings.

From the fugacity quotient model, Jones and Alcock (1996) concluded that the lower-chlorinated CDD/CDFs may be close to soil-air equilibrium in the United Kingdom while for other congeners, soil is a sink rather than a source to the atmosphere. Jones and Alcock (1996) reported that the equilibrium partitioning model predicted that 0.15 kg I-TEQ volatilizes annually from soil in the United Kingdom. However, the authors discounted this estimate and concluded that soil volatilization is unlikely to be a significant contributor to emissions. The likelihood that these estimates were high was attributed to the fact that: (1) assumptions were made that the concentrations of CDD/CDFs in air were zero and (2) the model does not consider the resistance of CDD/CDFs to volatilize from soil.

Harner et al. (1995) developed a model to predict the long-term fate of PCBs in soils, with emphasis on soil to air exchanges. Using data on levels of PCBs in air, soil, and vegetation in the U.K., Harner et al. (1995) developed a mass balance model to simulate the fate of PCBs in U.K. soils from 1935 to 1994. Specifically, monitoring data and physical/chemical property data were compiled to calculate fugacities for PCB congeners 28, 52, 138, and 153. The model was designed to provide an order-of-magnitude-level of accuracy, due in part to the inherent variability in the input data. The mass balance equations in the model included a bell-shaped function for rates of emissions of PCBs, with the maximum emission rate occurring in 1967. From these emissions rates, fluxes between air and soil over several decades were estimated. Table 12-4 summarizes the calculated fluxes. During the 1960s and 1970s, levels of total PCBs in U.K. soils reached average levels of approximately 300 μg/kg as a result of atmospheric deposition. Because of restrictions on PCB use during the last two decades, air concentrations have fallen, and the primary source to the atmosphere is now believed to be volatilization from soils. The mass balance model estimated a net flux of 700 kg/yr of total PCBs from soils to the atmosphere in 1994. However, this estimate is presented with the caveat that the model tends to underestimate the rate of reduction of PCB concentrations in recent years, which could be attributed to other mechanisms such as biodegradation, photolysis, and other degradation processes.

12.2.2. Water

Potential Mass of Dioxin-Like Compounds Present

The surface area of inland waters (including the Great Lakes) in the United States is about 359,000 sq km (U.S. DOC, 1995a). Assuming that the mean depth of inland water is 10 meters (Duarte-Davidson et al., 1997), the total inland water volume is approximately 3,600 billion m^3. No compilation of CDD/CDF measurements in inland surface waters is made for this report. However, if it is assumed that the "typical" value used by Duarte-Davidson et al. (1997) for rivers in the United Kingdom, 38 pg I-TEQ_{DF}/m^3, is representative of U.S. waters, then the burden is calculated to be 137 g I-TEQ_{DF}.

Mechanisms Responsible for Supply to and Releases from Water

As discussed previously in Section 12.2.1, dioxin-like compounds enter surface water from atmospheric deposition, stormwater runoff erosion, and discharges of anthropogenic wastes. Volatilization is the primary mechanism for release of dioxin-like compounds from the water column to the atmosphere. Several studies have addressed the water-air exchange of dioxin-like PCBs through volatilization in the Great Lakes (Achman et al., 1993; Hornbuckle et al., 1993; Swackhamer and Armstrong, 1986; Baker and Eisenreich, 1990). No similar body of literature has been developed to address volatilization of CDD/CDFs from water.

Most studies that have addressed PCB water/air exchange have used the two-film model developed by Whitman (1927) and made popular by Liss and Slater (1974). When assessing gas exchange between air and water, the interface between the two phases can be considered as a two-layer (film) system consisting of well-mixed gas and liquid films adjacent to the interface; the rate of transfer is controlled by molecular diffusion through the stagnant boundary layer (Achman et al., 1993). Liss and Slater (1974) applied the model to assess the flux of various gases, specifically in the air-sea systems, and indicated the possibility of its use at any air-water interface in the environment, if the necessary data are available. Hornbuckle et al. (1993) concluded that the two-film model is the best available tool for estimating regional and local flux of PCBs from natural waters. The following paragraph, from Achman et al. (1993), succinctly summarizes the model. The basic equation used to describe the rate of transfer across the interface is

$$F = K_{ol}(C_w - C^*) \qquad \text{(Eqn. 12-1)}$$

where F is the flux (mol/m^2-day), C_w (mol/m^3) is the dissolved PCB concentration in the bulk water, and C* (P/H, mol/m^3) is the air concentration expressed as a water concentration in equilibrium with the air. The variable P is the vapor-phase air concentration measured (mol/m^3) and converted to units of pressure using the ideal gas law. H is Henry's Law constant (atm•m^3/mol). The overall mass-transfer coefficient, K_{ol}, has units of velocity (m/day). The concentration gradient determines the direction of flux and drives the mass transfer; whereas, K_{ol} is a kinetic parameter that quantifies the rate of transfer. The value of K_{ol} is dependent on the physical and chemical properties of the

compound as well as environmental conditions. The reciprocal of K_{ol} is the total resistance to transfer expressed on a gas- (RT/Hk_a) and liquid- ($1/k_w$) phase basis:

$$1/K_{ol} = 1/k_w + RT/Hk_a \qquad \text{(Eqn. 12-2)}$$

where k_w is the water-side mass-transfer coefficient (m/day) and k_a is the air-side mass-transfer coefficient (m/day). H is Henry's Law constant, R is the universal gas constant (8.2057×10^{-5} atm•m^3/mol K), and T is the absolute temperature, K.

Achman et al. (1993) and Hornbuckle et al. (1993) calculated the volatilization rates of PCBs from Green Bay on Lake Michigan, based on air and water samples simultaneously collected over a 14-day period above and below the air-water interphase and analyzed for 85 PCB congeners. Air samples collected over nearby land were also analyzed for the 85 PCB congeners. The direction and magnitude of flux for each congener were then calculated using Henry's Law and meteorological and hydrological parameters in the "two-film" model. (See Eqn. 12-1.)

The net total PCB transfer rate (i.e., sum of all congener transfer rates) was found to be from water to air (i.e., volatilization). However, during cool water temperature periods (i.e., October), the direction of transfer reversed for many congeners. Calculated transfer rates to air ranged from 15 to 300 ng/m^2 per day at low wind speeds (1-3 m/sec) to 50 to 1,300 ng/m^2 per day at higher wind speeds (4-6 m/sec). On a congener basis, the lower chlorinated congeners dominated total fluxes. The summary of flux calculations is presented in Table 12-5. The most important factors influencing the magnitude of volatilization were the water concentration of PCBs, wind speed, and water temperature. In addition, Achman et al. (1993) and Hornbuckle et al. (1993) found that (1) atmospheric PCB concentrations are higher over contaminated water than over nearby land, (2) atmospheric PCBs over water tend to increase with increasing dissolved PCB concentrations, and (3) the congener distribution in the atmosphere correlates linearly with the congener distributions in the adjacent water.

Achman et al. (1993) also summarized the PCB volatilization rates reported by other researchers (Baker and Eisenreich, 1990; Swackhamer and Armstrong, 1986; Strachan and Eisenreich, 1988; and Swackhamer et al., 1988) for Great Lakes water bodies. The results of these other studies, presented below, also show net flux of PCBs from water to air.

Water Body	Total PCB Volatilization Rate (ng/m^2-day)	Reference
Lake Superior	141	Baker and Eisenreich (1990)
Lake Michigan	240	Strachan and Eisenreich (1988)
Lake Superior	63	Strachan and Eisenreich (1988)
Siskiwit Lake	23	Swackhamer et al. (1988)
Lake Michigan	15	Swackhamer and Armstrong (1986)

12.2.3. Sediment

Potential Mass of Dioxin-Like Compounds Present

EPA conducted congener-specific measurements of CDD/CDFS in the sediments from 11 U.S. lakes located in areas relatively unimpacted by nearby industrial activity. The mean TEQ concentration in the uppermost sediment layers from these 11 lakes is 5.3 ng I-TEQ_{DF}/kg (dry weight) (or 5.3 ng TEQ_{DF}-WHO_{98}/kg). For most of the lakes, the uppermost layer represents about 10 years worth of sedimentation. CDD/CDF concentrations in lakes impacted by industrial activity may have higher concentrations. For example, Duarte-Davidson et al. (1997) report a TEQ concentration of 54 ng I-TEQ_{DF}/kg for urban sediments in the United Kingdom.

The surface area of inland waters in the United States is approximately 359,000 sq km (U.S. DOC, 1995a). In their calculations of sediment burdens in the United Kingdom, Duarte-Davidson et al. (1997) assumed that (1) the sediment surface area equals the water surface area, (2) the majority of CDD/CDF are located in the top 5 cm of sediment, and (3) that sediment density is 0.13 g dry weight/cm^3. Applying these assumptions to the water surface area and background TEQ concentration for U.S. sediments yields a burden of at least 120 kg I-TEQ_{DF} (or 120 kg TEQ_{DF}-WHO_{98}).

Mechanisms Responsible for Supply to and Releases from Sediment

Because sediment is closely connected to the water column above it, evaluating the potential for sediment to act as a reservoir of dioxin-like compounds is complex and likely to be more difficult than studying dioxin-like compounds in a single medium such as water or soil. Volatilization and sedimentation are two mechanisms whereby persistent chemicals such as CDD/CDF/PCBs are lost from water bodies/columns. Numerous authors

have noted that sediments are a likely sink for persistent hydrophobic organic compounds, because these compounds are likely to be strongly bound to organic particles in the sediment (Swackhamer and Armstrong, 1986; Muir et al., 1985; Ling et al., 1993).

For example, Muir et al. (1985) radiolabeled 2,3,7,8-TCDD and studied its dissipation from sediments (collected from a farm pond and a lake) to the water column in laboratory studies under static aerobic conditions at 10°C. After 675 days, more than 80 percent of the labeled TCDD were still present in the pond sediment, and 87 percent were still present in the lake sediment. Aeration had little effect on the dissipation rates.

The concept of fugacity is a useful way to estimate the behavior of dioxin-like compounds in sediments. Fugacity (tendency of a chemical to escape from a phase) is expressed in units of pressure (pascals or Pa) and is the partial pressure exerted by the chemical in each medium. Fugacity models estimate equilibrium concentrations in specific media at given chemical concentrations in the environment. Clark et al. (1988) suggested evaluating contaminant concentrations in multiple environmental media by comparing fugacity of adjoining media (e.g., comparing sediment fugacity with water column fugacity to determine the chemical's tendency to move from one to the other). The authors evaluated fugacities of certain organochlorine compounds, including PCBs, in air, water, sediment, fish, fish-eating birds, and their eggs. The authors presented PCBs fugacities developed from data collected in a study of the Lake Ontario region. The fugacities of PCBs in various media can be ranked as birds > fish > water > bottom sediment, indicating that PCBs and other similar chemicals are likely to remain in bottom sediment and are less likely to re-enter the water column (Clark et al., 1988).

Estimated Annual Releases from Sediment to Water

Ling et al. (1993) evaluated the fate of various chemicals, including PCBs, in Hamilton Harbour, located in Ontario, Canada, using a modified version of the Quantitative Water Air Sediment Interaction (QWASI) fugacity model. Among the processes evaluated were diffusion between air and water, and sediment and water; sediment deposition, resuspension, and burial; and sediment transformation. Three primary compartments were studied: air, water, and bottom sediments. The sediment was treated as a simple, well-mixed surface layer of active sediment and the buried sediment underneath. Chemicals in the active sediment were assumed to be able to exchange with the overlying

water; chemicals in the buried sediment were assumed to be isolated from the sediment-water exchange. Sediment is assumed to be homogenous instead of heterogenous. The epi- and hypolimnetic compartments of the water column were defined based on a thermocline, and the atmosphere was defined as a semi-infinite medium of constant, defined composition.

Ling et al. (1993) estimated rates of PCB movement based on 1987 loadings using two models: a model with and a model without a thermocline. The results for the water-sediment transfer using the model with a thermocline were: ~32 kg/yr enter the hypolimnion from the epilimnion; ~27 kg/yr enter the surface sediment from the hypolimnion; and ~18 kg/yr (> 50%) go to burial. For sediment to water transfer, ~7 kg/yr and 12.5 kg/yr transfer to the hypolimnion and then to the epilimnion, respectively. Similar numbers were found in the single water column model (i.e., model without a thermocline). Both models predicted volatilization from the water to the atmosphere: 1.6 and 1.8 kg/yr for thermocline and the single water column models, respectively. However, the actual contribution of PCBs from sediment to air was not determined. A comparison of estimated concentrations with observed values are presented in Table 12-6. For PCBs, 68 percent were buried in the sediment, 20 percent exported to Lake Ontario, 5.4 percent degraded in the water and sediment, and 6 percent volatilize. The authors note that these percentages are uncertain. At the sediment water exchange, more than 90 percent of each chemical are contained in the sediment because of particle deposition and the high affinity of the chemical for sediment. There was no indication that contaminants buried in the bottom sediments are transferred through diffusion mechanisms back to the surface sediments. However, episodic release of these chemicals from surface sediments can occur through mechanisms such as resuspension during flooding or lake inversions and uptake/ingestion by benthic biota.

12.2.4. Biota

Potential Mass of Dioxin-Like Compounds Present

The mass of CDD/CDFs in biota in the United States was not estimated as part of this reassessment. However, to place perspective on the potential magnitude of this reservoir, 82 g I-TEQ_{DF} have been estimated to be present in biota in the United Kingdom (50 g in humans and 32 g in vegetation), which is about three orders of magnitude less

than that estimated to be present in U.K. surface soils (Duarte-Davidson et al., 1997; Eduljee and Dyke, 1996). Applying this ratio to the estimates of CDD/CDF TEQ soil burden in the United States that were presented in Section 12.2.1 (i.e., 1,780 kg I-TEQ_{DF}) yields a biota burden in the United States of about 2 kg I-TEQ_{DF}.

Mechanisms Responsible for Supply to and Releases from Biota

Apparently, very little of the dioxin-like compounds contained in contaminated soil, unlike certain other compounds and heavy metals, is ultimately taken up by the vegetation growing in the soil. For example, Kjeller et al. (1991) analyzed concentrations of CDD/CDFs in archived soil and grass samples collected at an English experimental station from mid-1840s to the present and found that only 0.006 to 0.02 percent of the soil burden of CDD/CDFs was taken up by the grass. In addition, scientists generally agree that, once taken up by plant tissue, CDD/CDFs are not translocated to other parts of the plant (e.g., fruits, shoots, etc.) (Bacci and Gaggi, 1985; Hülster and Marschner, 1993, 1994; Nakamura et al., 1994).

Researchers have found that the concentration of dioxin-like compounds in the plant should reach equilibrium with the vapor phase concentrations of dioxin-like compounds in the surrounding air (Bacci et al., 1990a, 1990b; Frank and Frank, 1989; Horstman and McLachlan, 1992; McCrady and Maggard, 1993; McLachlan et al., 1995; Paterson et al., 1991; Simonich and Hites, 1994; Tolls and McLachlan, 1994; Welsch-Pausch et al., 1995). Horstman and McLachlan (1992) stated that the leaf-air transfer of volatile compounds is a reversible process governed by concentration gradients. If CDD/CDF concentrations are higher in the surrounding air than they are in the air spaces within plant tissue, CDD/CDF should diffuse into the plant. Once equilibrium is reached and CDD/CDF concentrations in the plant equal that of surrounding air, no more CDD/CDF should be taken into the plant. When CDD/CDF concentrations in surrounding air begin to decrease, CDD/CDFs should diffuse (probably at a slow rate) out of the plant tissue. Apparently, CDD/CDFs are not bioconcentrated to a significant extent in the lipid portion of the leaf cuticle (Gaggi et al., 1985). The CDD/CDFs present in the leaf tissue are predominantly released from the plant through leaf fall onto soil. As a result, vegetation is not likely to be a long-term reservoir of dioxin-like compounds.

Research suggests that dioxin-like compounds within animal tissue, unlike in vegetation, seldom, if ever, reach equilibrium with vapor phase concentrations in the surrounding atmosphere (or water column concentrations in the case of aquatic life). Rather, animals exposed to dioxin-like compounds are known to bioaccumulate these compounds, primarily in body fat (U.S. EPA, 1993a; 1993j). Nonetheless, animals, unlike plants, can metabolize certain chlorinated hydrocarbons after they enter the body (Carlberg et al., 1983). Dioxin-like compounds can be released from an animal's body (at congener-specific rates) through metabolic processes or through weight loss, breast-feeding, or sweating. McLachlan (1996) reported the half-life for the clearance of 2,3,7,8-TCDD from humans to be 7 years. As a result, animal life has a greater potential than does vegetation for being a long-term reservoir source of CDD/CDFs. The majority of the dioxin-like compounds released by animals in the form of waste materials will be released to water or soil. Similarly, upon death, the dioxin-like compounds remaining in the body will be deposited onto soil or aquatic sediments or will be ingested by other animals.

Approaches to Measure and Estimate Releases from Biota - Researchers have investigated the uptake and release of CDD/CDFs by vegetation through measurement of actual concentrations of CDD/CDFs during uptake and release by vegetation grown in closed systems (greenhouses). Bacci et al. (1992) conducted uptake and release studies of 1,2,3,4-TCDD by plant foliage in a closed system (specially constructed greenhouse). Concentrations of TCDD vapor in the greenhouse air were maintained during the 370-hour uptake phase at a mean concentration of 0.0062 ng/L (air concentration varied slightly from 0.0050 to 0.0075 ng/L). To begin the release phase, the TCDD vapor source (amended sand), as well as the greenhouse walls were removed, and release of CDD/CDFs from the leaves was measured for 500 hours. Bacci et al. (1992) concluded that during uptake, TCDD concentration in the leaves varied as a function of time and was dependent on the concentration of vapor-phase TCDD in the surrounding air. These researchers estimated the release of TCDD from the vegetation to be relatively slow with a half-life of TCDD of 3,300 hours.

McCrady and Maggard (1993) conducted a mass balance study of uptake and release of dioxin in grass foliage. The results indicated a half-life of dioxin in grass of 128 hours (McCrady and Maggard, 1993). These researchers also noted that photodegradation

of dioxins on the foliage appeared to be a significant removal mechanism in addition to volatilization. They calculated the photodegradation half-life to be 44 hours (McCrady and Maggard, 1993).

Interpretation of uptake and release data over variable exposure times and contaminant concentrations has led to the development of models describing air-to-vegetation equilibrium and kinetics controlling the behavior of dioxin in vegetation. Some earlier fugacity modeling attempts described the leaf of a plant as behaving as a single compartment. One-compartment models were described by Bacci et al. (1990a; 1990b), Trapp et al. (1990), and Schramm et al. (1987) (as cited in Tolls and McLachlan, 1994). Researchers presenting most of the recently developed models claim that the available data better support the concept of a leaf behaving as two-compartments (Riederer, 1990; Paterson et al., 1991; Horstman and McLachlan, 1992; McCrady and Maggard, 1993; Tolls and McLachlan, 1994; McLachlan et al., 1995). Input parameters considered by most models include critical chemical characteristics of the contaminant, characteristics of the plant, exposure times, and contaminant concentrations measured within the plant.

Riederer (1990) suggested treating a leaf as multiple compartments, having different accessibility to the atmosphere and different diffusion resistances. Input parameters for the two-compartment model are octanol/water coefficients, cuticle/water partition coefficients, aqueous solubility, and saturation vapor pressure of the chemical of concern. Outputs of the model are prediction of equilibrium concentration in different leaf tissues, estimates of air-to-vegetation bioconcentration equilibria, and identification of leaf compartments in which compounds are likely to accumulate. Riederer (1990) also presents an approach for using the model to semiquantitatively assess the potential for revolatilization of dioxins from vegetation.

One advantage of the model presented by Riederer (1990) is that it considers critical plant characteristics in the release of dioxins. A plant is an active organism, responding to changes in its environment, and acting accordingly to ensure its survival. Certain plant characteristics, such as the action of stomata (specialized cells usually on the lower leaf surface that open and close to control passage of vapors into and out of the leaf interior) and total leaf volume, are important factors that effect the release rates of vapor phase contaminants from vegetation.

Paterson et al. (1991) also presented a two-compartment model for release of dioxin-like compounds from vegetation. This model describes a plant as being made up of compartments in terms of their volume fractions of air, water, and nonpolar (lipid-soluble, or octanol-equivalent) organic matter. Paterson et al. (1991) attempted to show that leaf-air equilibrium and kinetics can be correlated with chemical properties of the contaminant and properties of the leaf. Paterson et al. (1991) suggest that the clearance rate constant (k_2) can be correlated with the bioconcentration factor (BCF). This model does not consider critical plant characteristics, such as action of the stomata, and for this reason may be less reliable than models that do consider plant characteristics, such as the model presented by Riederer (1990).

Horstman and McLachlan (1992) developed a fugacity model to describe release of semivolatile organic compounds from the surface of a solid (spruce needles). Their approach was slightly different in that their goal was instrument/method development, but their data supported the behavior of a leaf as a two-compartment system.

McCrady and Maggard (1993) also collected data supporting the importance of viewing a leaf as a two-compartment system. They used a two-compartment model similar to the one described by Paterson et al. (1991), which also does not consider critical plant characteristics, and may be less reliable than models that do (e.g., Reiderer, 1990).

Tolls and McLachlan (1994) exposed grass cultures for up to 240 hours to several semivolatile organic compounds and then measured the release of contaminants from the grass. They developed a two-compartment partitioning model based on the data they collected. The model consisted of a small surface compartment (the leaf cuticle) and large interior reservoir (air spaces within the leaf). Their model assumes the flux of a chemical is the product of the fugacity difference (surface fugacity minus reservoir fugacity) and the conductance between the leaf compartments.

In an attempt to validate this model, McLachlan et al. (1995) compared concentrations of semivolatile organic compounds measured in grass grown under field conditions with concentrations predicted by their previous laboratory work with a fugacity meter. The concentrations measured in the grass cultures agreed with results predicted by the mathematical model described by Tolls and McLachlan (1994).

12.3. SUMMARY AND CONCLUSIONS

As depicted in Figure 12-1 a set of complex relationships exist among reservoirs and between reservoirs and contemporary formation sources. The significance of reservoirs for human exposure is more dependent on their ability to affect the concentration of dioxin-like compounds in other media than on their size or net release rate. This Section, first summarizes and draws conclusions from the limited information available regarding the character and magnitude of reservoir sources. Second, it uses this information to discuss the implications of reservoir sources to human exposure.

12.3.1. Reservoir Sources

Noted below are some summary statements about soil reservoir sources

- Soil is likely to be the reservoir source with the greatest potential for release of CDD/CDFs to other environmental media, particularly to water. This is due in part to its relatively large mass of stored CDD/CDF, but more importantly, it is due to the existence of demonstrated transport mechanisms for intermedia exchange, i.e. soil erosion to surface waters and particle resuspension to air.

- The preliminary estimates of CDD/CDF runoff from urban areas to waterways is comparable to known industrial point source releases and runoff from agricultural areas to surface waters is over 100 times greater. It is unclear how much of the soil erosion and runoff represents recently deposited CDD/CDFs from primary sources or longer term accumulation. Much of the eroded soil comes from tilled agricultural lands which would include a mix of CDD/CDFs from various deposition times. The age of CDD/CDFs in urban runoff is less clear.

- Based on the limited information currently available (i.e., primarily fugacity modeling), volatilization of CDD/CDFs from soils is not believed to significantly alter ambient air concentrations. However, volatilization of PCBs from soil may be a significant process.

- Based on the limited information currently available, resuspension of soil may account for a small fraction (~4 percent) of CDD/CDF concentrations in air. This resuspended soil may, however, constitute a more significant portion of dry deposition.

Noted below are some summary statements about water reservoir sources:

- It is unclear if volatilization of CDD/CDFs from water can significantly alter air concentrations. For PCBs, however, the water-air exchange appears to

be significant and for some water bodies results in a net transfer from water to air.

- Water is the major media contributing CDD/CDF/PCBs to sediment. Note that most of the CDD/CDF in sediments originally came from soils. For specific water bodies, however, the CDD/CDFs/PCBs in sediments may have been dominated by local industrial discharges to water.

Noted below are some summary statements about sediment reservoir sources:

- It is important to distinguish between surface and deep sediments. Surface sediments are commonly resuspended and introduced back into the water and deep sediments generally do not interact with the water column. Surface sediments can contribute significantly to the CDD/CDF/PCB concentration in water; whereas deep sediments do not.

- There is little, if any, movement of dioxin-like compounds once they are buried in the bottom sediments. Bottom sediments may be considered as sinks.

Noted below are some summary statements about biota reservoir sources:

- The mass of CDD/CDF in vegetation at any given time is likely to be small compared to the mass in soil. Vegetation does play an important role in transferring CDD/CDF from the air to the soil via the decay of plant biomass.

- Release by volatilization from vegetation has been studied and modeled using the fugacity approach, and half-lives have been estimated. Based on these results, volatilization is not believed to be a significant mechanism for release of CDD/CDFs or PCBs except possibly during forest/brush fires.

- The mass of CDD/CDF in animals at any given time is likely to be small compared to the mass in soil. Similarly releases are small and occur primarily by excretion and decomposition of dead biomass.

12.3.2. Implications for Human Exposure

Although, the ability to make quantitative estimates of releases from reservoir sources is limited at present, it is reasonable to conclude that the contribution of reservoir sources to human exposure may be significant. As explained in Volume 2, the diet accounts for over 95% of human exposure. Although the size of the biota reservoir is small compared to the soil and sediment reservoirs, it is clearly the key contributor to human exposure. The potential contribution of the other reservoirs to human exposure is discussed below.

PCB Reservoir Releases: Since current sources of newly formed PCBs are most likely negligible, human exposure to the dioxin-like PCBs is thought to be derived almost completely from current releases of old PCBs stored in reservoir sources. Key pathways involve releases from both soils and sediments to both aquatic and terrestrial food chains. As discussed in Volume 2, one third of general population TEQ_{DFP} exposure is due to PCBs. Thus, at least one third of the overall risk to the general population from dioxin-like compounds comes from reservoir sources.

CDD/CDF Releases from Soil and Sediments to Water and Exposure via the Aquatic Pathway: The earlier discussion has shown that soils can have significant inputs to waterways via soil erosion and runoff. Similarly the sediment reservoir contributes significantly to CDD/CDF concentration in water. These releases appear to be greater than those from the primary sources included in the inventory. Dioxins in waterways bioaccumulate in fish and fish consumption causes human exposure. Fish consumption makes up about one third of the total general population CDD/CDF TEQ exposure. This suggests that a significant portion of the CDD/CDF TEQ exposure could be due to releases from the soil and sediment reservoir.

CDD/CDF Releases from Soil to Air and Exposure via the Terrestrial Pathway: Potentially, soil reservoirs could have vapor and particulate releases which deposit on plants and enter the terrestrial food chain. The magnitude of this contribution, however, is unknown. EPA plans future studies in agricultural areas which will compare modeled air concentrations from primary sources to measured levels as a way to get further insight to this issue.

Table 12-1. Historical Production, Sales, and Usage Quantities for 2,4-D[a]

Year	2,4-D, acid			2,4-D, esters and salts (as reported)		
	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)
1994/95	--	--	21,800-26,300[i]			
1993	--	--	16,800-20,400[c]	--	--	
1992	--	--	16,800-20,400[c]	--	--	
1991	--	--	18,100-29,500[d]	--	--	
1990	--	--	18,100-29,500[d]	--	--	
1989	--	--	18,100-29,500[e]	--	--	
1988	--	--	23,600-30,400[f]	--	--	
1987	--	--	23,600-30,400[g]	--	--	
1986	--	--		8,618	12,150	
1985	--	--		--	0	
1984	--	--		--	0	
1983	--	--		7,702	8,234	
1982	--	--		8,762	8,400	
1981	5,859	3,275		8,987	8,002	
1980	6,164	3,137		11,313	11,147	
1979	5,763	6,187		11,874	13,453	
1978	--	--		8,958	9,256	
1977	--	--		12,552	10,196	
1976	--	--	17,418[b]	10,913	7,813	
1975	--	--		16,134	13,414	
1974	--	--		6,558	5,991	
1973	--	--		13,400	13,698	
1972	24,948[b]	--	21,772[b]	10,192	10,899	
1971	--	5,619	15,700[b]	--	18,654	
1970	19,766	7,159		--	19,920	
1969	21,354	8,521		25,854	20,891	
1968	35,953	10,352		42,690	30,164	
1967	34,990	15,432		37,988	29,300	
1966	30,927	12,710	28,985[h]	32,895	25,075	
1965	28,721	11,816	22,906[h]	28,740	21,454	
1964	24,364	11,343	19,958[h]	24,660	18,263	

Table 12-1. Historical Production, Sales, and Usage Quantities for 2,4-D[a] (Continued)

Year	2,4-D, acid			2,4-D, esters and salts (as reported)		
	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)
1963	21,007	9,446	15,059[h]	20,178	16,333	
1962	19,503	7,716	16,284[h]	16,831	13,075	
1961	19,682	7,591	14,107[h]	16,683	12,533	
1960	16,413	--	14,107[h]	15,436	13,661	
1959	13,282	7,240	15,468[h]	12,438	7,070	
1958	14,036	6,234	9,662[h]	11,295	5,649	
1957	15,536	6,871		12,392	7,125	
1956	13,079	6,465		9,635	7,294	
1955	15,656	5,924		13,390	8,121	
1954	--	4,838		10,268	6,886	
1953	11,761	--		10,733	8,855	
1952	13,933	--		11,358	9,637	
1951	--	--		--	--	
1950	6,421	4,301		5,274	3,219	
1949	6,852	2,991		5,829	3,211	
1948	9,929	4,152		2,458	1,598	
1947	2,553	2,320		1,468	1,108	
1946	2,479	2,330		515	81	
1945	416	286		--	--	

"--" = Not reported to avoid disclosure of proprietary data.

[a] All values from the U.S. International Trade Commission's (USITC) annual report series entitled Synthetic Organic Chemicals - United States Production and Sales unless footnoted otherwise (USITC, 1946-1994).
[b] U.S. EPA (1975).
[c] U.S. EPA (1994b).
[d] U.S. EPA (1992f).
[e] U.S. EPA (1991h).
[f] U.S. EPA (1990e).
[g] U.S. EPA (1988c).
[h] USDA (1970).
[i] U.S. EPA (1997e).

Table 12-2. Historical Production, Sales, and Usage Quantities 2,4,5-T[a]

Year	2,4,5-T, acid			2,4,5-T, esters and salts (as reported)		
	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)
1993	--	--		--	--	
1992	--	--		--	--	
1991	--	--		--	--	
1990	--	--		--	--	
1989	--	--		--	--	
1988	--	--		--	--	
1987	--	--		--	--	
1986	--	--		--	--	
1985	--	--		--	--	
1984	--	--		--	--	
1983	--	--		--	--	
1982	--	--		--	--	
1981	--	--		--	--	
1980	--	--	900[f]	--	--	
1979	3,200-4,100[b]	--		--	--	
1978	--	--	3,200[h]	--	--	
1977	--	--	4,100[b]	--	--	
1976	--	--		--	--	
1975	--	--	3,200[h]	--	--	
1974	--	--	900[c]	--	--	
1973	--	--		--	--	
1972	--	--		--	--	
1971	--	--	694[d]	--	1,675	
1970	--	--	3,200[h]	5,595	3,272	
1969	2,268	--		5,273	2,576	
1968	7,951	1,329	~7,000[e,g]	19,297	15,021	
1967	6,601	757	~7,000[e,g]	12,333	11,657	
1966	7,026	2,312	7,756[e]	8,191	4,553	
1965	5,262	--	3,266[e]	6,131	5,977	
1964	5,186	1,691	4,037[e]	5,880	3,128	
1963	4,123	1,928	3,266[e]	4,543	2,585	

Table 12-2. Historical Production, Sales, and Usage Quantities 2,4,5-T[a] (continued)

Year	2,4,5-T, acid			2,4,5-T, esters and salts (as reported)		
	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)	Production Volume (metric tons)	Sales Volume (metric tons)	Domestic Usage/ Disappearance (metric tons)
1962	3,796	1,021	3,674[e]	4,765	2,543	
1961	3,134	1,196	2,449[e]	3,536	2,372	
1960	2,874	--	2,676[e]	3,594	1,891	
1959	2,516	1,039	2,495[e]	3,644	1,843	
1958	1,668	692	1,724[e]	2,372	1,151	
1957	2,419	--		3,098	1,337	
1956	2,345	816		3,196	1,473	
1955	1,327	662	1,300[h]	1,720	1,077	
1954	1,223	639		1,761	615	
1953	2,395	--		2,443	1,817	
1952	1,583	--		1,423	569	
1951	--	--	1,100[h]	--	--	
1950	852	297		--	--	
1949	--	--		--	--	
1948	--	--		--	--	
1947	--	--		--	--	
1946	--	--		--	--	
1945	--	--		--	--	

"--" = Not reported to avoid disclosure of proprietary data.

[a] All values from the U.S. International Trade Commission's annual report series entitled Synthetic Organic Chemicals - United States Production and Sales (U.S. ITC, 1946-1994) unless footnoted otherwise.
[b] Federal Register (1979).
[c] U.S. EPA (1977).
[d] USDA (1971); reflects farm usage only.
[e] USDA (1970); values include military shipments abroad.
[f] Esposito et al. (1980).
[g] Kearney et al. (1973) reports slightly lower domestic consumption for the years 1967 and 1968 than for 1966.
[h] Thomas and Spiro (1995).

Table 12-3. CDD/CDF Concentrations in Recent Sample of 2,4,5-T

Congener/Congener Group	2,4,5-T Sample (μg/kg)
2,3,7,8-TCDD	1.69
1,2,3,7,8-PeCDD	0.412
1,2,3,4,7,8-HxCDD	0.465
1,2,3,6,7,8-HxCDD	2.28
1,2,3,7,8,9-HxCDD	1.35
1,2,3,4,6,7,8-HpCDD	18.1
OCDD	33.9
2,3,7,8-TCDF	0.087
1,2,3,7,8-PeCDF	0.102
2,3,4,7,8-PeCDF	0.183
1,2,3,4,7,8-HxCDF	1.72
1,2,3,6,7,8-HxCDF	0.356
1,2,3,7,8,9-HxCDF	ND (0.012)
2,3,4,6,7,8-HxCDF	0.126
1,2,3,4,6,7,8-HpCDF	2.90
1,2,3,4,7,8,9-HpCDF	0.103
OCDF	3.01
Total 2,3,7,8-CDD*	58.2
Total 2,3,7,8-CDF*	8.59
Total I-TEQ_{DF} *	2.88
Total TEQ_{DF}-WHO_{98} *	3.26
Total TCDD	NR
Total PeCDD	NR
Total HxCDD	NR
Total HpCDD	NR
Total OCDD	NR
Total TCDF	NR
Total PeCDF	NR
Total HxCDF	NR
Total HpCDF	NR
Total OCDF	NR
Total CDD/CDF	NR

ND = Nondetected; value in parenthesis is the detection limit.
NR = Not reported.
* = Calculation assuming not detected values are zero.

μg/kg = micrograms per kilogram

Source: Schecter et al. (1997)

Table 12-4. PCB 138 Fluxes Predicted by Harner et al. (1995)

Year	Concentration in Air (pg/m^3)	Fugacity in Air (Pascals x 10^{-9})	Fugacity in Soil (Pascals x 10^{-9})	Concentration in Soil (ng/g)	Net Flux/Direction
1950	48	0.24	1.1	--	air → soil (444 kg/yr)
1965	280	1.5	12	--	air → soil (1,000 kg/yr)
1975	--	--	16	--	
1980	49	--	--	--	soil → air (820 kg/yr)
1994	6	--	8.3	--	soil → air (700 kg/yr)

-- = Not reported.

pg/m^3 = picograms per cubic meter
ng/g = nanograms per gram
kg/yr = kilograms per year

Source: Harner et al. (1995).

Table 12-5. Summary of Flux Calculations for Total PCBs in Green Bay, 1989

Date	Site	Flux[a,b,c] (ng/m^2-day)
6-4	18	40
6-5	18	40
6-6	10	95
6-7	10	155
6-10	4	325
6-11	10	13
7-28	18	330
7-29	21	70
7-30	14	225
7-31	10	90
8-1	4	800
10-21	14	555
10-22	10	1,300
10-23	4	30

[a] Numbers indicate water to air transfer of total PCBs.
[b] Represents the sum of individual PCB congener fluxes.
[c] Described as "daily" fluxes because they correspond to air samples collected over 5-10 hours and water samples collected over ~1 hour.

mg/m^2-day = nanograms per square meter per day

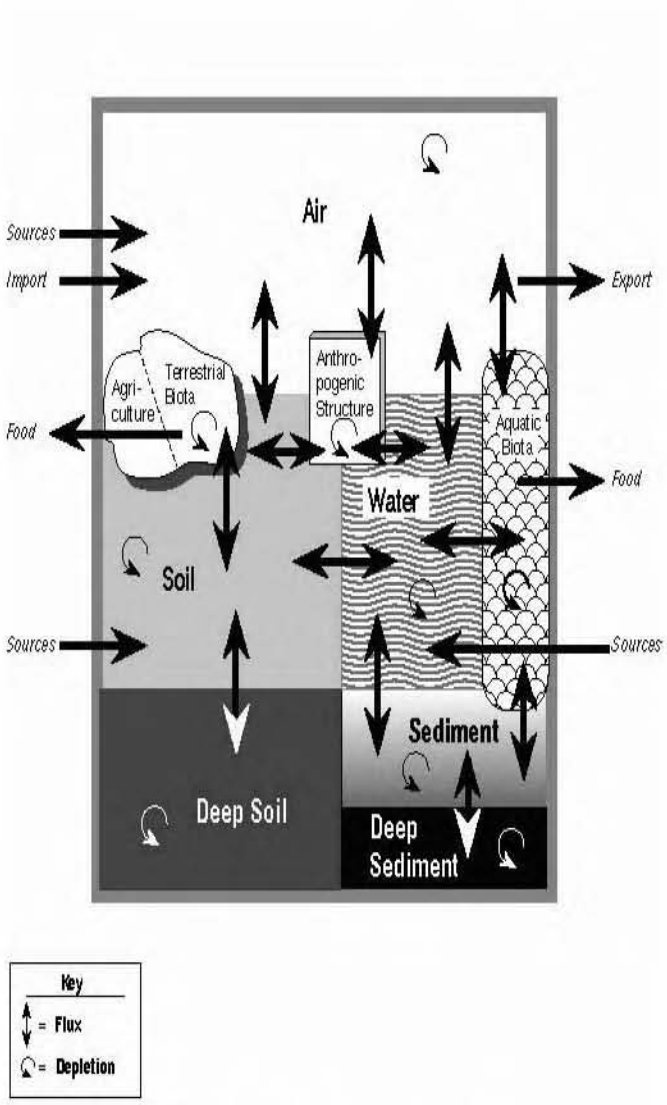
Source: Achman et al. (1993).

Table 12-6. Comparison of Estimated PCB Concentrations with Observed Values

Variable	Units	PCBs
Observed Concentration [C]		
Sediment	μg/g	0.23-1.04
Water	μg/m^3	$<$20
Estimated [C] from Model Without Thermocline		
Sediment	μg/g	0.518
Water	μg/m^3	8.33
Amount in Sediment	kg	74.9
Amount in Water	kg	2.33
Total Mass	kg	77.2
Estimated [C] from Model with Thermocline		
Sediment	μg/g	0.527
Hypolimnion	μg/m^3	8.48
Epilimnion	μg/m^3	7.93
Amount in Sediment	kg	76.3
Amount in Hypo	kg	1.28
Amount in EPI	kg	1.02
Total Mass	kg	78.6

μg/g = micrograms per gram
μg/m^3 = micrograms per cubic meter
kg = kilograms

Source: Ling et al. (1993).



Fluxes Among Dioxin Reservoirs

Figure 12-1. Fluxes Among Reservoirs

13. BALL CLAY

13.1 INTRODUCTION

The purpose of this chapter is to evaluate the potential for environmental releases of dioxin-like compounds during the mining of ball clay and its subsequent uses. The presence of dioxin-like compounds in ball clay was discovered in 1996 as a result of an investigation to determine the sources of relatively high levels of dioxin found in two chicken fat samples during a national survey of poultry. The survey was conducted jointly by the U.S. Department of Agriculture and U.S. Environmental Protection Agency to assess the national prevalence and concentrations of CDDs, CDFs, and coplanar PCBs in poultry (Ferrario et al., 1997). The results of the investigation indicated soybean meal added to chicken feed was the source of dioxin contamination (Ferrario, Byrne and Cleverly, 2000). Further investigation showed that the CDD contamination came from the ball clay added to the soymeal as an anticaking agent. The ball clay was added at approximately 0.3% to 0.5% of the soybean meal. Samples of raw ball clay were subsequently taken at the mine of origin in Mississippi. Analysis of the ball clay obtained from the active mine showed elevated levels of CDDs having a congener profile similar to the CDD profiles found in the soymeal, chicken feed and immature chickens.

13.2 CHARACTERISTICS OF MISSISSIPPI EMBAYMENT BALL CLAYS

The ball clays from the mine discussed above are part of a larger ball clay resource which spans portions of western Kentucky, Tennessee, and Mississippi. These clays were deposited along the shores of the Mississippi Embayment during the early to middle Eocene Epoch which occurred approximately 40-45 million years ago. The Mississippi Embayment ball clays are secondary clays comprised mainly of poorly defined crystalline kaolinite. Other minerals present include illite, smectite, and chlorite. Quartz sand is the major nonclay mineral. These deposits of ball clay occur in lenses surrounded by layers of sand, silt, and lignite. These clays can have a gray appearance caused by the presence of finely divided carbonaceous particles. It is not uncommon to find black carbonized imprints of fossil leaves and other plant debris in the clay (Patterson and Murray, 1984).

The plasticity of ball clay makes this an important natural resource for the ceramic industry. The breakdown of the ceramic uses of ball clay include: 33% floor and wall tile;

24% sanitary ware; 11% pottery; and 32% other industrial and commercial uses (Virta, 2000). A minor use of ball clay was as an anticaking agent in animal feeds, which has subsequently been discontinued by the U.S. Food and Drug Administration (Headrick et al., 1999). Total mining of ball clay in 1999 was 1.14 million metric tons (Virta, 2000).

13.3 LEVELS OF DIOXIN-LIKE COMPOUNDS IN BALL CLAY

The joint EPA/FDA and USDA investigation of ball clay as a source of dioxin contamination in animal feeds resulted in sampling the clay at an operational mine in western Mississippi. Eight samples of raw (unprocessed) ball clay were collected from an open mining pit at a depth of about 10 to 15 m. Samples were prepared and analyzed by EPA using high resolution gas chromatography coupled with high resolution mass spectrometry (HRGC/HRMS) using EPA Method 1613 (Ferrario et al., 2000). The concentrations of the CDD/CDFs present in the raw ball clay samples from the one mine are shown in Table 13-1. The Limits of Detection (LOD):Limits of Quantification (LOQ) for the CDD/CDFs in the clay samples were 0.5:1 pg/g (ppt) d.w for the tetras, 1.0:2.0 pg/g for the pentas, hexas, and heptas, and 5.0/10.0 pg/g for the octas. The mean concentrations of all of the CDDs exceeded 100 ppt (d.w.). OCDD is found at the highest concentration in all of the samples followed by either 1,2,3,4,6,7,8-HpCDD or 1,2,3,7,8,9-HxCDD. The maximum OCDD concentration in the eight samples was approximately 59,000 pg/g. The most toxic tetra- and penta-congeners were present at unusually high concentrations in all of the samples with average concentrations of 711 pg/g and 508 pg/g for 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD, respectively. Although the ball clays show elevated levels of 2,3,7,8-substituted CDDs, they show very low levels of 2,3,7,8-substituted CDFs. In addition, there was a consistent ratio within the HxCDD congener distribution across all samples (i.e., 1,2,3,7,8,9-HxCDD was present at higher concentrations than the other 2,3,7,8-substituted HxCDD congeners). The average percent distribution among the three individual 2,3,7,8-hexa congeners was 5:17:78. This congener pattern was observed in all the raw ball clay samples analyzed. The mean total TEQ_{DF}-WHO_{98} for the raw ball clay was determined to be 1,513 pg/g, d.w. 2,3,7,8-TCDD accounted for 47% of the TEQ_{DF}-WHO_{98}, followed by 1,2,3,7,8-PeCDD at 34%. As expected, even though present at the highest concentration, OCDD contributed less than 1% percent of the total TEQ_{DF}-WHO_{98} due to its relatively small WHO-TEF. In

comparison, the typical range of background TEQ_{DF}-WHO_{98} concentrations in North American urban and rural surface soils samples are 2 to 21 pg/g and 0.1 to 6 pg/g, respectively (see Volume 3: Properties, Environmental Levels, and Background Exposures, EPA/600/P-00/001Bc). In soil samples, all 2,3,7,8-CDD/CDF congeners are detected, and 2,3,7,8-TCDD represents less than one percent of total CDD/CDF present. The most prevalent congeners in soils are OCDD followed by OCDF. Table 13-2 compares the mean CDD/CDF congener group concentrations in ball clay to the mean congener group concentrations in rural and urban background soils. This comparison indicates there are no similarities in the congener group distributions between the ball clay and soils.

13.4 EVIDENCE FOR BALL CLAY AS A NATURAL SOURCE

Several lines of evidence suggest that dioxin-like compounds in ball clay are of natural origin:

- The clay samples were obtained from undisturbed deposits. It is unknown how human activity could have contaminated these deposits without disturbing them.

- EPA's Laboratory in Athens, Georgia, analyzed the Mississippi mine clays using a broad screen for anthropogenic contaminants and no compounds were found outside of the normal range. All known anthropogenic sources of dioxin have associated with them a wide variety of other contaminants. The absence of elevated levels of other compounds is strong evidence that the dioxins found in the clay are not the result of waste disposal.

- The congener profiles of ball clay do not match known anthropogenic sources (these profiles are presented in Chapters 2 - 8 of this Volume). Cleverly et al. (1997) reported on the congener profiles that are typical of known anthropogenic sources of dioxin-like compounds in the United States. These analyses were used as a basis for comparison to the profile of the raw ball clay.

    - The congener pattern characteristic of waste combustion sources differs significantly from the ball clay profile in several aspects. In combustion source emissions, all 2,3,7,8-substituted CDD and CDF congeners are measured and 2,3,7,8-TCDD is usually 0.1 to 1.0 percent of total CDD/CDF mass emitted. In ball clay, 2,3,7,8-TCDD is approximately 5% of total mass of dioxins present. As with the ball clay, the most prevalent 2,3,7,8-Cl substituted CDD congeners in most incinerator emissions are OCDD and 1,2,3,4,6,7,8-HpCDD. However, combustion emissions contain appreciable amounts of CDFs of which the 1,2,3,4,6,7,8-HpCDF, OCDF, 1,2,3,4,7,8-HxCDF, 2,3,7,8-TCDF and 2,3,4,6,7,8-HxCDF congeners dominate.

    - The combustion of wood generates a congener profile not unlike that of waste incinerator, (i.e., the ratio of CDD/CDF <1), and all laterally substituted

congeners can be detected in emissions. The combustion of tree bark produces a congener profile in which the CDD/CDF ratio is >1, showing only minimal and barely detectable levels of CDFs in the smoke, the exception being that 2,3,7,8-TCDF is present at approximately 2% of total mass. The dominant congener in tree bark combustion emissions is OCDD (>30% total CDD/CDF mass), followed by 1,2,3,4,6,7,8-HpCDD and 1,2,3,7,8,9-HxCDD.

- The congener profile of 2,4-D salts and esters seems to mimic a combustion source profile in the number of congeners represented, and in the minimal amount of 2,3,7,8-TCDD relative to all 2,3,7,8-Cl substituted congeners. Nevertheless, unlike the combustion source profile, the 1,2,3,7,8-PeCDD and the 1,2,3,4,6,7,8-HpCDF constitute major fractions of total CDD/CDF contamination present in 2,4-D.

- The congener profile of technical grade pentachlorophenol (PCP) is clearly dominated by OCDD and 1,2,3,4,6,7,8-HpCDD. However, only trace amounts of 2,3,7,8-TCDD are detected in PCP, and 1,2,3,4,6,7,8-HpCDF and OCDF constitute roughly 15% of typical formulations.

- Metal smelting and refining processes, such as secondary aluminum, copper and lead smelting, also have all the 2,3,7,8-Cl substituted CDD/CDF congeners in stack emissions. In secondary aluminum smelting, 2,3,7,8-TCDD is less than 0.1% of total CDD/CDFs whereas PeCDF is nearly 25% of total emissions of dioxin-like compounds, and the CDD/CDF ratio is <1. Secondary copper operations show a similar pattern of CDD/CDF emissions, but with five compounds dominating emissions: 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, OCDF, OCDD, and 1,2,3,4,6,7,8-HpCDD. In iron ore sintering, the dominant congener in emissions of 2,3,7,8-Cl substituted compounds is 2,3,7,8-TCDF.

- A number of studies have shown that natural processes can produce chlorinated aromatic compounds including dioxin-like compounds. Gribble (1994) reviewed the biological production of a wide variety of halogenated organic compounds in nature. For example, the Mississippi salt march grass "needlerush" (*Juncus roemerianus*) contains the aromatic compound 1,2,3,4-tetrachlorobenzene and the blue-green alga, *Anacystis marina* naturally contains chlorophenol (Gribble, 1994). The soil fungus, *Penicillium sp.*, produces 2,4-dichlorophenol, and the common grasshopper is known to secrete 2,5-dichlorophenol (Gribble, 1994). Urhahn and Ballschmiter (1998) also provide a good review of the chemistry of the biosynthesis of chlorinated organic compounds under natural conditions. It has been hypothesized that CDDs, CDFs, and other chlorinated aromatic compounds can be naturally formed from halogenated humic substances and halomethanes through chloroperoxidase-mediated reactions in undisturbed peat bogs (Silk et al., 1997). A similar chloroperoxidase-mediated biochemical formation of CDD/CDFs from chlorophenols was achieved under laboratory conditions by Oberg and Rappe (1992). It has been observed that chlorophenols can be biosynthesized (Gribble, 1994; Silk et al., 1997), and that chorophenols are readily adsorbed into peat-bentonite mixtures (Virarghavan and Slough, 1999). Hoekstra et al. (1999) offered

the hypothesis that 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, and 1,2,3,7,8,9-HxCDD can be naturally formed in soils of coniferous forests from chlorinated phenol. These same congeners are also the predominant congeners in the ball clay from the Mississippi Embayment. Although none of these natural processes can be directly attributed to the presence of dioxin in ball clay, the existence of such mechanisms lends plausibility to a hypothesis that they are of natural origin.

- CDD/CDFs have been found in other clays quite distant from Mississippi Embayment ball clay deposits. No evidence of anthropogenic sources have been discovered in these areas either. Recently the presence of the CDDs have been discovered in kaolinitic clay mined in Germany (Jobst and Aldag, 2000). Because no anthropogenic source could be determined to explain the presence and levels of CDDs in the ball clay, Jobst and Aldag (2000) speculated that the CDDs were the result of an unknown geologic process. In addition, the German clay also has a congener profile similar to that observed in the Mississippi ball clay with an absence of CDFs at comparable concentrations and the predominance of the 1,2,3,7,8,9-HxCDD among the toxic hexa-CDDs. The similarity in the congener profiles in ball clay mined in the United States and Germany suggests a common origin to the CDDs present in these clays (Ferrario, Byrne, and Cleverly, 2000).

In summary, no anthropogenic sources have been identified that explain the levels and profiles of CDD/CDFs present in the clay. On the other hand, no definitive scientific evidence has been brought forward that identifies the principal chemical and physical mechanism involved to cause the selective chemical synthesis of CDDs under the conditions inherent to the formation of ball clays some 40 million years ago. In order to further understand the origin of CDDs in these clays, EPA is currently planning systematic evaluation of the distribution of CDDs in these clay deposits and the surrounding area.

13.5 ENVIRONMENTAL RELEASES OF DIOXIN-LIKE COMPOUNDS FROM THE MINING AND PROCESSING OF BALL CLAY

In 1995, approximately 993 million kg ball clay was mined in the United States (Virta, 2000). Multiplication of the mean TEQ_{DF}-WHO_{98} concentration in mined ball clay by the total amount of ball clay mined in 1995 gives an estimate of 1,502 grams TEQ_{DF}-WHO_{98} contained in all the ball clay mined in 1995. It is unknown if any of these CDDs are released to the environment during the mining, initial refining and product handling. As discussed above, most ball clay is used to produce ceramics through a process of high temperature vitrification. The temperatures found in ceramic kilns are well above the levels needed for both volatilization and destruction of CDDs. Even though these high

temperatures exist, it is unclear whether some release occurs and no stack measurements have yet been made. Therefore, insufficient evidence is available to make even a preliminary estimate of releases and this activity is classified as a category "E" source.

Table 13-1. Concentrations of CDDs Determined in Eight (8) Ball Clay Samples in the U.S.

Congener	Concentrations (pg/g, dry weight)				
	Mean	Median	Minimum	Maximum	TEQ_{DF}-WHO_{98}
2,3,7,8-TCDD	711	617	253	1,259	711
1,2,3,7,8-PeCDD	508	492	254	924	508
1,2,3,4,7,8-HxCDD	131	134	62	193	13
1,2,3,6,7,8-HxCDD	456	421	254	752	46
1,2,3,7,8,9-HxCDD	2,093	1,880	1,252	3,683	209
1,2,3,4,6,7,8-HpCDD	2,383	2,073	1,493	3,346	24
OCDD	20,640	4,099	8,076	58,766	2
Total TEQ					1,513

Source: Ferrario et al. (2000).

Table 13-2. Comparison of the Mean CDD/CDF Congener Group Distribution in Ball Clay to the Mean Congener Group Distributions in Urban and Rural Soils in North America

Congener Group	Mean Concentration (pg/g, dry weight)		
	Raw Ball Clay	Urban Background Soil	Rural Background Soil
TCDD	3,729	36.1	2.3
TCDF	6	23.5	6.8
PeCDD	4,798	18.1	4.1
PeCDF	2	40.8	12.7
HxCDD	6,609	31.7	22.7
HxCDF	6	23.5	21.9
HpCDD	6,194	194.4	114.7
HpCDF	9	46.4	37.3
OCDD	11,222	2,596	565.1
OCDF	11	40.2	33.5
Total CDD/CDF	32,586	3,067.1	821.3

Sources: Adapted from U.S. EPA (2000a) and Ferrario, Byrne and Cleverly (2000).

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Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

Part I: Estimating Exposure to Dioxin-Like Compounds

Volume 2: Properties, Environmental Levels, and Background Exposures

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1.0. BACKGROUND AND SUMMARY

1.1. BACKGROUND

This reassessment is comprised of three reports:

Part 1. *Estimating Exposure to Dioxin-Like Compounds* (U.S. EPA, 2000a) (which expanded upon a 1988 draft exposure report titled, *Estimating Exposure to 2,3,7,8-TCDD* [U.S. EPA, 1988]);
Part 2. *Health Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 1994; U.S. EPA, 2000b); and
Part 3. *Dioxin: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA, 2000c).

Throughout the remainder of this document, these three parts as a whole will be abbreviated as the Reassessment Documents, and the individual parts will be referred to as the Exposure Reassessment Document, the Health Reassessment Document, and the Risk Characterization. The Exposure Reassessment Document has expanded to three volumes, as discussed below. Volumes 1 and 2 of the Exposure Reassessment Document are summarized in Section 4 of the Risk Characterization.

The process for developing the Reassessment Documents has been open and participatory. Each of the documents has been developed in collaboration with scientists from inside and outside the Federal Government. Each document has undergone extensive internal and external review, including review by EPA's Science Advisory Board (SAB). In September 1994, drafts of each document were made available for public review and comment. This included a 150-day comment period and 11 public meetings around the country to receive oral and written comments. These comments, along with those of the SAB (U.S. EPA, 1995), have been considered in the drafting of this final document. The Dose-Response Chapter of the Health Document underwent peer review in 1997 (U.S. EPA, 1997); an earlier version of the Integrated Summary and Risk Characterization underwent development and review in 1997 and 1998, and comments have been incorporated. In 1998, EPA released a workshop review version of the sources inventory (U.S. EPA, 1998), one of the three volumes of the Exposure Reassessment Document. In addition, as requested by the SAB, a chapter on Toxic Equivalency has been developed and underwent external peer review in parallel with the Integrated Summary and Risk Characterization in July 2000. The November 2000, review by the SAB of the Dose-Response Chapter, the Toxic Equivalency Chapter and the Integrated

Summary and Risk Characterization was the final step in this open and participatory process of reassessment. The full set of background documents and the integrative summary and risk characterization replace the previous dioxin assessments as the scientific basis for EPA decision-making.

The final Exposure Reassessment Document reflects changes made as a result of both review comments and analyses of a variety of other types of information that has come available. These include relevant information obtained from published peer-reviewed literature, EPA program offices, and other Federal agencies. This version of the Exposure Reassessment Document is current in this regard through 2000.

The purpose of the Exposure Reassessment Document is threefold: 1) to inventory the known sources of release of dioxins into the environment, 2) to develop an understanding of dioxins in the environment, including fate and transport properties, environmental and exposure media concentrations, background as well as elevated exposures, and temporal trends in exposure, and 3) provide site-specific procedures for evaluating the incremental exposures due to specific sources of dioxin-like compounds. Following this structure, the Exposure Reassessment Document is presented in three volumes:

Volume 1 - Sources of Dioxin-Like Compounds in the United States

This volume presents a comprehensive review of known sources of environmental releases of dioxin-like compounds in the United States. It includes an inventory of known source activity in terms of estimates of annual releases of dioxin-like compounds into the U.S. environment (i.e., air, water and land). This inventory is specific for two reference years, 1987 and 1995. From these data, it is possible to compare and contrast releases of dioxin-like compounds among the sources and between the reference years.

Volume 2 - Properties, Environmental Levels, and Background Exposures

This volume presents and evaluates information on the physical-chemical properties, environmental fate, environmental and exposure media levels, background and elevated human exposures, and temporal trends of dioxin-like compounds in the U.S. environment during the 20th century.

Volume 3 - Site-Specific Assessment Procedures

This volume presents procedures for evaluating the incremental impact from sources of dioxin release into the environment. The sources covered include contaminated soils, stack emissions, and point discharges into surface water. This volume includes sections on: exposure parameters and exposure scenario development; stack emissions and atmospheric transport modeling; aquatic and

terrestrial fate, and food chain modeling; demonstration of methodologies; and uncertainty evaluations including exercises on sensitivity analysis and model validation, review of Monte Carlo assessments conducted for dioxin-like compounds, and other discussions.

The primary technical resource supporting the development of the inventory of sources of dioxin-like compounds discussed in Volume I (above) is the Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States (EPA/600/C-01/012. March 2001). This database includes congener-specific CDD and CDF emissions data extracted from original engineering test reports. It has been published independently from the Reassessment and is available on Compact Disk-Read only Memory (CD-ROM), without cost, from EPA's National Service Center for Environmental Publications (NSCEP) in Cincinnati, Ohio (telephone: 1-800-490-9198, or 513-489-8190; fax: 513-489-8695). Summary files from the database will be available for downloading from the Web page of the National Center for Environmental Assessment, www.epa.gov/ncea/dioxin.htm. Instructions on how to order and obtain the CD-ROM will also be available on the Web page.

1.2. DEFINITION OF DIOXIN-LIKE COMPOUNDS

This assessment addresses specific compounds in the following chemical classes: polychlorinated dibenzo-*p*-dioxins (PCDDs or CDDs), polychlorinated dibenzofurans (PCDFs or CDFs), polybrominated dibenzo-*p*-dioxins (PBDDs or BDDs), polybrominated dibenzofurans (PBDFs or BDFs), and polychlorinated biphenyls (PCBs), and describes this subset of chemicals as "dioxin-like." Dioxin-like refers to the fact that these compounds have similar chemical structure, similar physical-chemical properties, and invoke a common battery of toxic responses. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. The CDDs include 75 individual compounds; CDFs include 135 different compounds. These individual compounds are referred to technically as congeners. Likewise, the BDDs include 75 different congeners and the BDFs include an additional 135 congeners. Only 7 of the 75 congeners of CDDs, or of BDDs, are thought to have dioxin-like toxicity; these are ones with chlorine/bromine substitutions in, at a minimum, the 2, 3, 7, and 8 positions. Only 10 of the 135 possible congeners of CDFs or of BDFs are thought to have dioxin-like toxicity; these also are ones with substitutions in the 2, 3, 7, and 8 positions. This suggests that 17 individual CDDs/CDFs, and an additional 17 BDDs/BDFs, exhibit dioxin-like toxicity. The database on many of the brominated

compounds regarding dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment.

There are 209 PCB congeners. Only 13 of the 209 congeners are thought to have dioxin-like toxicity; these are PCBs with 4 or more lateral chlorines with 1 or no substitution in the ortho position. These compounds are sometimes referred to as coplanar, meaning that they can assume a flat configuration with rings in the same plane. Similarly configured polybrominated biphenyls (PBBs) are likely to have similar properties. However, the database on these compounds with regard to dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment. Mixed chlorinated and brominated congeners of dioxins, furans, and biphenyls also exist, increasing the number of compounds potentially considered dioxin-like within the definitions of this assessment. The physical/chemical properties of each congener vary according to the degree and position of chlorine and/or bromine substitution. Very little is known about occurrence and toxicity of the mixed (chlorinated and brominated) dioxin, furan, and biphenyl congeners. Again, these compounds have not been explicitly considered in this assessment. Generally speaking, this assessment focuses on the 17 CDDs/CDFs and a few of the coplanar PCBs that are frequently encountered in source characterization or environmental samples. While recognizing that other "dioxin-like" compounds exist in the chemical classes discussed above (e.g., brominated or chlorinated/brominated congeners) or in other chemical classes (e.g., halogenated naphthalenes or benzenes, azo- or azoxybenzenes), the evaluation of less than two dozen chlorinated congeners is generally considered sufficient to characterize environmental "dioxin."

The chlorinated dibenzodioxins and dibenzofurans are tricyclic aromatic compounds with similar physical and chemical properties. Certain of the PCBs (the so-called coplanar or mono-ortho coplanar congeners) are also structurally and conformationally similar. The most widely studied of this general class of compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This compound, often called simply "dioxin," represents the reference compound for this class of compounds. The structure of TCDD and several related compounds is shown in Figure 1-1. Although sometimes confusing, the term "dioxin" is often also used to refer to the complex mixtures of TCDD and related compounds emitted from sources, or found in the environment or in biological samples. It can also be used to refer to the total TCDD "equivalents" found in a sample. This concept of toxic equivalency is discussed below.

1.3. TOXIC EQUIVALENCY FACTORS

CDDs, CDFs, and PCBs are commonly found as complex mixtures when detected in environmental media and biological tissues, or when measured as environmental releases from specific sources. Humans are likely to be exposed to variable distributions of CDDs, CDFs, and dioxin-like PCB congeners that vary by source and pathway of exposures. This complicates the human health risk assessment that may be associated with exposures to variable mixtures of dioxin-like compounds. In order to address this problem, the concept of toxic equivalency has been considered and discussed by the scientific community, and TEFs have been developed and introduced to facilitate risk assessment of exposure to these chemical mixtures.

On the most basic level, TEFs compare the potential toxicity of each dioxin-like compound comprising the mixture to the well-studied and understood toxicity of TCDD, the most toxic member of the group. The background and historical perspective regarding this procedure is described in detail in Part II, Chapter 9, Section 9.1, 9.2, and in Agency documents (U.S. EPA, 1987; 1989a,b; 1991). This procedure involves assigning individual TEFs to the 2,3,7,8-substituted CDD/CDF congeners and "dioxin-like" PCBs. To accomplish this, scientists have reviewed the toxicological databases along with considerations of chemical structure, persistence, and resistance to metabolism, and have agreed to ascribe specific, "order of magnitude" TEFs for each dioxin-like congener relative to TCDD, which is assigned a TEF of 1.0. The other congeners have TEF values ranging from 1.0 to 0.00001. Thus, these TEFs are the result of scientific judgment of a panel of experts using all of the available data and are selected to account for uncertainties in the available data and to avoid underestimating risk. In this sense, they can be described as

$$\text{TEQ} \cong \sum_{i=n}\left(\text{Congener}_i \times \text{TEF}_i\right) + \left(\text{Congener}_j \times \text{TEF}_j\right) + \ldots\ldots \left(\text{Congener}_n \times \text{TEF}_n\right) \quad (1\text{-}1)$$

"public health conservative" values. To apply this TEF concept, the TEF of each congener present in a mixture is multiplied by the respective mass concentration and the products are summed to represent the 2,3,7,8-TCDD Toxic Equivalence (TEQ) of the mixture, as determined by Equation (1-1):

The TEF values for PCDDs and PCDFs were originally adopted by international convention (U.S. EPA, 1989a). Subsequent to the development of the first international TEFs for CDD/CDFs, these values were further reviewed and/or revised and TEFs were also developed for PCBs (Ahlborg et al., 1994; van den Berg et al., 1998). A problem arises in that past and present quantitative exposure and risk assessments may not have clearly identified which of three TEF schemes was used to estimate the TEQ. This reassessment introduces a new uniform TEQ nomenclature that clearly distinguishes between the

different TEF schemes and identifies the congener groups included in specific TEQ calculations. The nomenclature uses the following abbreviations to designate which TEF scheme was used in the TEQ calculation:

1. I-TEQ refers to the International TEF scheme adopted by EPA in 1989 (U.S. EPA, 1989a). See Table 1-1.
2. TEQ-WHO_{94} refers to the 1994 WHO extension of the I-TEF scheme to include 13 dioxin-like PCBs (Ahlborg et al., 1994). See Table 1-2.
3. TEQ-WHO_{98} refers to the 1998 WHO update to the previously established TEFs for dioxins, furans, and dioxin-like PCBs (van den Berg et al., 1998). See Table 1-3.

The nomenclature also uses subscripts to indicate which family of compounds is included in any specific TEQ calculation. Under this convention, the subscript D is used to designate dioxins, the subscript F to designate furans and the subscript P to designate PCBs. As an example, "TEQ_{DF}-WHO_{98}" would be used to describe a mixture for which only dioxin and furan congeners were determined and where the TEQ was calculated using the WHO_{98} scheme. If PCBs had also been determined, the nomenclature would be "TEQ_{DFP}-WHO_{98}." Note that the designations TEQ_{DF}-WHO_{94} and I-TEQ_{DF} are interchangeable, as the TEFs for dioxins and furans are the same in each scheme. Note also that in this document, I-TEQ sometimes appears without the D and F subscripts. This indicates that the TEQ calculation includes both dioxins and furans.

This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxic equivalency to complex environmental mixtures for assessment and regulatory purposes. Sections in the Health Reassessment Document, and summarized in the Risk Characterization, describe the mode(s) of action by which dioxin-like chemicals mediate biochemical and toxicological actions. These data provide the scientific basis for the TEF/TEQ methodology. In its 20-year history, the approach has evolved, and decision criteria supporting the scientific judgment and expert opinion used in assigning TEFs has become more transparent. Numerous states, countries, and several international organizations have evaluated and adopted this approach to evaluating complex mixtures of dioxin and related compounds. It has become the accepted methodology, although the need for research to explore alternative approaches is widely endorsed. Clearly, basing risk on TCDD alone or assuming all chemicals are equally potent to TCDD is inappropriate on the basis of available data. Although uncertainties in the use of the TEF methodology have been identified (which are described in detail in the Health Reassessment Document, Chapter 9, Section 9.5), one must examine the use of this method in the broader context of the need to evaluate the potential public health impact of complex mixtures of

persistent, bioaccumulative chemicals. It can be generally concluded that the use of TEF methodology for evaluating complex mixtures of dioxin-like compounds decreases the overall uncertainties in the risk assessment process as compared to alternative approaches. Use of the latest consensus values for TEFs assures that the most recent scientific information informs this "useful, interim approach" (U.S. EPA, 1989a; Kutz et al., 1990) to dealing with complex environmental mixtures of dioxin-like compounds. As stated by the U.S. EPA Science Advisory Board (U.S. EPA, 1995), "The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the TEFs and the availability of representative and reliable exposure data." EPA will continue to work with the international scientific community to update these TEF values to assure that the most up-to-date and reliable data are used in their derivation and to evaluate their use on a periodic basis.

A chemical is assigned a TEF value based on all the available data comparing the chemical to either TCDD or PCB 126. In addition, there are weighting criteria that place more emphasis on chronic and subchronic studies examining toxic endpoints (van den Berg et al., 1998). There is a broad range in the quantity and quality of the data available for individual congeners. For example, the TEF for PCB 126 is based on over 60 in vivo endpoints examining responses as diverse as enzyme induction, developmental toxicity, immunotoxicity, hepatic toxicity, alterations in hormones and tumor promotion, while the TEF for 3,4,4',5-tetrachlorobiphenyl (PCB 81) is based on in vitro CYP1A induction and QSAR calculations. Fortunately, PCB 81 does not significantly contribute to human TEQ exposures. There are 5 congeners that contribute approximately 80% of the total TEQ in humans: 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PCDF, and PCB 126 (See Part I, Volume 2 and Section 4.4.3 of this document). With the exception of 1,2,3,6,7,8-HxCDD, the TEFs for these chemicals are based on a number of different endpoints from multiple studies performed in different laboratories. The TEF for 1,2,3,6,7,8-HxCDD is based on a two-year bioassay in which rats were exposed to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD. The TEFs for 2,3,4,7,8-PCDF and PCB 126 are similar to the mean REP value for all in vivo endpoints and are similar to their REPs for tumor promotion. The TEF for 12378-PCDD is based largely on its REP for tumor promotion in rats. From these data, it is clear that the chemicals that contribute approximately 80% to the total human TEQ are well studied and the assigned TEFs provide reasonable estimates of the relative potency of these chemicals. In contrast, while there are some chemicals in the TEF methodology which have minimal data sets to reliably assess their relative potency, these chemicals do not contribute substantially to the human blood TEQ.

The ability of the TEF methodology to predict the biological effects of mixtures containing dioxin-like chemicals has been evaluated in a number of experimental systems. These studies generally demonstrate that the assumption of additivity provides a reasonable estimate of the dioxin-like potential of a mixture (described in the Health Reassessment Document, Chapter 9, Section 9.4). In addition, there are examples of non-additive interactions between dioxins and non-dioxins. Both greater than additive and less than additive interactions have been observed in these studies. In general the non-additive interactions between the dioxins and non-dioxins have been observed at doses that are considerably higher than present background human exposures.

There are a number of natural chemicals that bind and activate the AhR and induce some dioxin-like effects. It has been proposed by some scientists that these chemicals contribute significantly to the total TEQ exposures and that these exposures far out weigh those from PCDDs, PCDFs and PCBs (Safe, 1995). While this hypothesis is intriguing, there are several limitations to these analyses. The in vivo data on the natural aromatic hydrocarbon receptor (AhR) ligands is limited to enzyme induction and a single developmental study. Few, if any, toxicology studies demonstrating clear dioxin-like toxicities have been published. The natural AhR ligands are rapidly metabolized and result in both transient tissue concentrations and transient effects. The natural ligands also have significant biological effects that are independent of the AhR and it is not clear as to the role of the AhR in the biological effects of these chemicals. Clearly this issue requires further research in order to better understand the relative potential health effect of dioxin and related chemicals as compared to natural AhR ligands.

One of the limitations of the use of the TEF methodology in risk assessment of complex environmental mixtures is that the risk from non-dioxin-like chemicals is not evaluated in concert with that of dioxin-like chemicals. Another limition of the TEF methodology is their application to non-biological samples. The fate and distribution of PCDDs, PCDFs and PCBs are not necessarily related to their TEF. Thus, the use of the TEF for non-biological media must be done cautiously. Future approaches to the assessment of environmental mixtures should focus on the development of methods that will allow risks to be predicted when multiple mechanisms are present from a variety of contaminants.

1.4. CONTENTS OF THIS VOLUME

The purpose of this volume is to: (1) summarize information on the physical and chemical properties of dioxin-like compounds; (2) provide an overview of the levels of dioxin-like compounds found in environmental media and food; (3) estimate background

exposures to dioxin-like compounds for the general population of the United States; (4) provide information on the potential for elevated exposures among certain subpopulations of the United States; and (5) summarize the evidence that suggests a downward trend in dioxin-like concentrations in the environment, as well as trends in exposure. These topics are organized in this volume as follows:

Chapter 2 - Physical and Chemical Properties and Fate

This chapter summarizes available information regarding the physical and chemical properties and fate of the dioxin-like compounds. Physical/ chemical properties addressed in Chapter 2 include melting point, water solubility, vapor pressure, Henry's Law constant, octanol/water partition coefficient, organic carbon partition coefficient, and photochemical quantum yield. Fate and transport processes addressed include photolysis, oxidation, hydrolysis, biodegradation, volatilization, and sorption. Biologically-mediated transport properties (i.e., bioconcentration, plant uptake, etc.) are also addressed in this volume. (These properties are also addressed in Volume 3: Site-Specific Assessment Procedures.) These data were compiled from a review of the current scientific literature on dioxin-like compounds.

Chapter 3 - Levels of CDD, CDF, and PCB Congeners

This chapter provides an overview of the concentrations at which dioxin-like compounds have been found in the environment and food based on data presented in the recent published literature. Data are presented for air, soil, sediment, water, and foods. For foods, the general focus is on foods with relatively high fat content (i.e., beef, pork, poultry and eggs, milk and dairy products, fish, and vegetable fats) because these items are most likely to contain dioxins and related compounds. Data from Government-sponsored monitoring studies and studies reported in the peer-reviewed literature are used in this chapter to estimate U.S. background concentrations of dioxin-like compounds in the various environmental media and foods. In order to represent current exposure concentrations, data used for the calculation of background media levels are based on studies published in the late 1980s and 1990s, but primarily in the 1990s. The studies used for the estimation of background concentrations were also chosen on the basis of credibility and representativeness. CDD/CDF profiles for environmental media are also presented in this chapter.

Chapter 4 - Human Exposures to CDD/CDF, and PCB Congeners

This chapter assesses background exposures to the dioxin-like compounds among the general population of the United States. Recent assessments of background exposures cited in the scientific literature are summarized, and background exposure estimates, based on the data presented in Chapter 3, are presented. Data on the concentrations of dioxin-like compounds in human tissue (i.e., adipose tissue, blood, and human breast milk) are also presented. Two methods are used in to estimate background daily intake of dioxin-like compounds. One method estimates background exposures based on pharmacokinetic modeling using the human tissue data. The other derives background exposure estimates from dietary intake and contact with other media containing dioxin-like compounds. The primary focus of this chapter is background exposure among the general population.

Chapter 5 - Potentially Elevated Populations

This chapter focuses on elevated exposures that may occur among the general population from dietary habits such as breast feeding or high rates of fish ingestion, increased environmental levels of dioxin-like compounds from localized sources, or cigarette smoking. This chapter does not, however, address occupational or accidental exposure. Epidemiological studies that have evaluated whether elevated dioxin exposure has occurred to certain workers in the chemical industry, members of the Air Force who worked with Agent Orange, and residents of Seveso, Italy, who were exposed as a result of a pesticide plant explosion are fully discussed in the Epidemiology Chapter of the Dioxin Health Reassessment Document.

Chapter 6 - Temporal Trends

This chapter describes trends in the levels of dioxin-like compounds that have been observed in various environmental media and foods, as well as evidence of downward trends in exposure to dioxin-like compounds in humans. The downward trend in human exposure is supported by a modeling exercise that reconstructs the most likely past doses of dioxin-like compounds contributing to observed body burdens. Reviews of several studies and the modeling exercise are followed by several key observations with regard to temporal trends of dioxin-like compounds.

1.5. SUMMARY OF FINDINGS IN THIS VOLUME

1.5.1. Physical and Chemical Properties and Fate

The physical/chemical properties of individual dioxin congeners vary and the various congeners behave differently in the environment. For example, the relative mix of congeners released from a stack cannot be assumed to remain constant during transport through the atmosphere and deposition to various media. Therefore, for purposes of environmental fate modeling, it is important to use the individual CDD/CDF and PCB congeners values, rather than TEQs. Estimates of environmental releases are presented in Volume 1. Full congener-specific release rates for most sources are provided in an electronic database which is available as a companion to this document (Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States (EPA/600/C-01/012). In Volume 3, site-specific procedures are provided for estimating the impact of emissions on local populations and this section emphasizes that congener specific emission values should be used in modeling their environmental fate. The following paragraphs provide a summary of the fate of dioxin-like compounds.

Dioxin-like compounds are widely distributed in the environment as a result of a number of physical and biological processes. The dioxin-like compounds are essentially insoluble in water, generally classified as semivolatile, and tend to bioaccumulate in animals. Some evidence has shown that these compounds can degrade in the environment, but in general they are considered very persistent and relatively immobile in soils and sediments. These compounds are transported through the atmosphere as vapors or attached to airborne particulates and can be deposited on soils, plants, or other surfaces (by wet or dry deposition). The dioxin-like compounds enter water bodies primarily via direct deposition from the atmosphere, or by surface runoff and erosion. From soils, these compounds can reenter the atmosphere either as resuspended soil particles or as vapors. In water, they can be resuspended into the water column from sediments, volatilized out of the surface waters into the atmosphere or become buried in deeper sediments. Immobile sediments appear to serve as permanent sinks for the dioxin-like compounds. Though not always considered an environmental compartment, these compounds are also found in anthropogenic materials (such as PCP) and have the potential to be released from these materials into the broader environment.

Atmospheric transport and deposition of the dioxin-like compounds are a primary means of dispersal of these compounds throughout the environment. The dioxin-like compounds can be measured in wet and dry deposition in most locations including remote areas. Numerous studies have shown that they are commonly found in soils throughout the world. Industrialized countries tend to show similar elevated concentrations in soil,

and detectable levels have been found in nonindustrialized countries. The only satisfactory explanation available for this distribution is air transport and deposition. Finally, by analogy these compounds would be expected to behave similarly to other compounds with similar properties, and this mechanism of global distribution is becoming widely accepted for a variety of persistent organic compounds.

The two primary pathways for the dioxin-like compounds to enter the ecological food chains and human diet are air-to-plant-to-animal and water/sediment-to-fish. Vegetation receives these compounds via atmospheric deposition in the vapor and particle phases. The compounds are retained on plant surfaces and bioaccumulated in the fatty tissues of animals that feed on these plants. Vapor phase transfers onto vegetation have been experimentally shown to dominate the air-to-plant pathway for the dioxin-like compounds, particularly for the lower chlorinated congeners. In the aquatic food chain, dioxins enter water systems via direct discharge or deposition and runoff from watersheds. Fish accumulate these compounds through their direct contact with water, suspended particles, bottom sediments, and through their consumption of aquatic organisms. Although these two pathways are thought to normally dominate contribution to the commercial food supply, others can also be important. Elevated dioxin levels in cattle resulting from animal contact with PCP-treated wood have been documented by the U.S. Department of Agriculture. Animal feed contamination episodes have led to elevations of dioxins in poultry in the United States, milk in Germany, and meat/dairy products in Belgium.

1.5.2. Environmental Media and Food Concentrations

Background levels of dioxin-like compounds in various environmental media including food are presented in Table 1-4 in terms of means, variability and sample sizes used to support the background estimates.

Estimates for background levels of dioxin-like compounds in environmental media are based on a variety of studies conducted at different locations in North America. Of the studies available for this compilation, only those conducted in locations representing "background" were selected. The amount and representativeness of the data vary, but in general these data were derived from studies that were not designed to estimate national background means. The environmental media concentrations were similar to studies in Western Europe. These data are the best available for comparing with site-specific values. Because of the limited number of locations examined, it is not known if these estimates adequately capture the full national variability. As new data are collected, these ranges are likely to be expanded and refined. The limited data on dioxin-like PCBs in environmental media are summarized in this document (Chapter 3).

Estimates for levels of dioxin-like compounds in food are based on data from a variety of studies conducted in North America. Beef, pork, and poultry were derived from statistically based national surveys. Milk estimates were derived from a survey of a nationwide milk sampling network. Dairy estimates were derived from milk fat concentrations, coupled with appropriate assumptions for the amount of milk fat in dairy products. The background egg concentrations were based on an analysis of 15 egg samples collected from retail stores in 8 states (CA, OH, GA, NY, PA, OR, MN, WS; 2 samples/state except one in OR), where each sample was a composite of 24 individual eggs (i.e., 15 samples represented 360 eggs). The fish data, as discussed below, were derived from multiple studies with samples collected both directly from water bodies and from retail outlets. All fish concentrations were expressed on the basis of fresh weight in edible tissue. As with other environmental media, food levels found in the United States are similar to levels found in Europe.

The procedure to evaluate background fish exposures emphasizes the use of both species-specific consumption rates and species-specific concentrations. EPA's National Bioaccumulation Study (U.S. EPA, 1992) provides some species-specific information on freshwater/estuarine fish caught in the wild at various locations in the United States. Additional species-specific data on store bought fish are available from studies conducted by the Food and Drug Administration during the mid to latter1990s (Jensen and Bolger, 2000; Jensen et al., 2000). An important aspect of the U.S. Food and Drug Administration (FDA) studies is that they include data on store-bought catfish, tuna, shellfish, and salmon which are some of the most highly consumed species. Accordingly, the data used to characterize CDD/CDF fish levels are much improved over previous estimates with over 300 individual samples and good representation of the most highly consumed species. However, the levels of dioxins in fish remain more uncertain than the other foods. The compilation of data from different studies still lacks the geographic coverage and statistical power of the other food surveys. The EPA and FDA studies did not address dioxin-like PCBs, rather these are based on a much smaller data set derived from the open literature. Also, the estimates of dioxin intake resulting from fish consumption do not include consumption of fish oils. Currently insufficient data are available to support estimates of dioxin intake from direct fish oil consumption.

The general population dioxin intake calculations used in this document are a function of both consumption rate and dioxin concentration in food. The concentration data used in this document were measured in raw foods. Therefore, if cooking significantly alters the dioxin concentration in consumed portions it must be accounted for in estimating dioxin intake. This issue has been examined in a number of studies which measured the effects of cooking on the levels of CDDs, CDFs and PCBs in foods (see

Chapter 3, Section 3.7.5). These studies have a range of results depending on food type and cooking method. Most of the cooking experiments suggested that cooking reduces the total amount of dioxins in food but causes relatively little change in its concentration. Although some cooking experiments have shown increases and others have shown decreases in dioxin concentrations, the relative prevalence of these impacts have not been established. Therefore given that most experiments show little change and that others show change in both directions, the most reasonable assumption that can be made from the existing data is that dioxin concentration in uncooked food is a reasonable surrogate for dioxin concentration in cooked food.

Some evidence from Europe suggests that during the 1990s a decline has occurred in concentrations of dioxins and furans in food products, particularly dairy products (see Chapter 6, Section 6.5). For example, the United Kingdom's Ministry of Agriculture, Fisheries, and Food (MAFF) collected milk samples in 1990 and again from similar locations in 1995. In 1990, the I-TEQ_{DF} ranged from 1.1 to 3.3 ppt, while the 1995 I-TEQ_{DF} ranged from 0.7 to 1.4. In Germany, a sampling of 120 dairy products in 1994 found I-TEQ_{DF} concentrations that were 25% lower than a similar sampling program in 1990. Liem et al. (2000) reports on a European cooperative study coordinated by the National Institute of Public Health and the Environment in the Netherlands, and the Swedish National Food Administration. Ten countries supplied data on food concentrations, food consumption patterns, and other data used to evaluate exposure to dioxins in Europe. Some of the data suggested reductions in concentrations over time, but the available information was insufficient to draw general conclusions. No systematic study of temporal trends in dioxin levels in food has been conducted in the United States. Although not statistically based, one U.S. study examined dioxin levels in 14 preserved food samples from various decades in the twentieth century (Winters et al., 1998). It was found that meat samples of the 1950s through the 1970s had concentrations that were 2-3 times higher for the CDD/CDF TEQs and about 10 times higher for the PCB TEQs, as compared to current meat concentrations.

1.5.3. Background Exposures

The average CDD/CDF/PCB tissue level for the general adult U.S. population appears to be declining, and the best estimate of current (late 1990s) levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis).

The tissue samples collected in North America in the late 1980s and early 1990s showed an average TEQ_{DFP}-WHO_{98} level of about 55 pg/g lipid. This finding is supported by a number of studies which measured dioxin levels in adipose, blood, and human milk, all conducted in North America. The number of people in most of these studies, however,

is relatively small and the participants were not statistically selected in ways that assure their representativeness of the general U.S. adult population. One study, the 1987 National Human Adipose Tissue Survey (NHATS), involved over 800 individuals and provided broad geographic coverage, but did not address coplanar PCBs. Similar tissue levels of these compounds have been measured in Europe and Japan during similar time periods.

Because dioxin levels in the environment have been declining since the 1970s (see trends discussion in Chapter 6), it is reasonable to expect that levels in food, human intake, and ultimately human tissue have also declined over this period. The changes in tissue levels are likely to lag the decline seen in environmental levels, and the changes in tissue levels cannot be assumed to occur proportionally with declines in environmental levels. CDC (2000) summarized levels of CDDs, CDFs, and PCBs in human blood collected during the time period 1995 to 1997. The individuals sampled were all U.S. residents with no known exposures to dioxin other than normal background. The blood was collected from 316 individuals in six different locations with an age range of 20 to 70 years. While the samples in this data set were not collected in a manner that can be considered statistically representative of the national population and lack wide geographic coverage, they are judged to provide a better indication of current tissue levels in the United States than the earlier data. PCBs 105, 118, and 156 are missing from the blood data for the comparison populations reported by CDC (2000). These congeners account for 62% of the total PCB TEQ estimated in the early 1990s. Assuming that the missing congeners from the CDC study data contribute the same proportion to the total PCB TEQ as in earlier data, they would increase our estimate of current body burdens by another 3.3 pg TEQ/g lipid for a total PCB TEQ of 5.3 pg/g lipid and a total of 25.4 pg TEQ_{DFP}-WHO_{98} /g lipid. A summary of the CDC (2000) data is shown in Table 1-5.

This finding regarding a current tissue level of 25.4 pg/g lipid TEQ_{DFP}-WHO_{98} is further supported by the observation that this mean tissue level is consistent with our best estimate of current adult intake, i.e., 66 pg WHO_{98}-TEQ_{DFP}/d. Using this intake in a one-compartment, steady-state pharmacokinetic model yields a tissue level estimate of about 11.2 pg TEQ/g lipid (assumes TEQ_{DFP} has an effective half-life of 7.1 yr, 80% of ingested dioxin is absorbed into the body, and lipid weight is 25% of the adult assumed body weight of 70 kg, or 17.5 kg). Because intake rates appear to have declined in recent years and steady-state is not likely to have been achieved, it is reasonable to observe higher measured tissue levels, such as the 25.4 pg TEQ/g lipid that was observed, than predicted by the model.

Characterizing national background levels of dioxins in tissues is uncertain because the current data cannot be considered statistically representative of the general

population. It is also complicated by the fact that tissue levels are a function of both age and birth year. Because intake levels have varied over time, the accumulation of dioxins in a person who turned 50 years old in 1990 is different than in a person who turned 50 in 2000. Future studies should help address these uncertainties. The National Health and Nutrition Examination Survey (NHANES) began a new national survey in 1999 that will measure blood levels of CDDs, CDFs, and PCBs 126, 77, 169, and 81 in about 1,700 people per year (see http:www.cdc.gov/nchs/nhanes.htm). The survey is conducted at 15 different locations per year and is designed to select individuals statistically representative of the civilian U.S. population in terms of age, race, and ethnicity. These new data should provide a much better basis for estimating national background tissue levels and evaluating trends than the currently available data.

Intake Estimates

Adult daily intakes of CDD/CDFs and dioxin-like PCBs are estimated to average 43 and 23 pg TEQ_{DFP}-WHO_{98}/day, respectively, for a total intake of 66 pg/day TEQ_{DFP}-WHO_{98}. Daily intake is estimated by combining exposure media concentrations (food, soil, air) with contact rates (ingestion, inhalation). Table 1-6 summarizes the media concentrations, contact rates and resulting intake estimates.

The intake estimate is supported by an extensive database on food consumption rates and estimates of dioxin-like compounds in food (as discussed above). Pharmacokinetic (PK) modeling provides further support for the intake estimates. Applying a simple steady-state PK model to an adult average blood level of 25 ppt TEQ_{DFP}-WHO_{98} (on a lipid basis) yields a daily intake of 146 pg TEQ_{DFP}-WHO_{98}/day (assumes TEQ_{DFP} has an effective half-life of 7.1 yr, 80% of ingested dioxin is absorbed into the body, and lipid weight is 25% of the adult assumed body weight of 70 kg, or 17.5 kg). This PK-modeled CDD/CDF/PCB intake estimate is about 2.2 times higher than the direct intake estimate of 66 pg TEQ_{DFP}-WHO_{98}/day. This difference is to be expected with this application of a simple steady-state PK model to current average adipose tissue concentrations. Current adult tissue levels reflect intakes from past exposure levels that are thought to be higher than current levels (see Chapter 6). Because the direction and magnitude of the difference in intake estimates between the two approaches are understood, the PK-derived value is judged supportive of the pathway-derived estimate. It should be recognized, however, that the pathway-derived value will underestimate exposure if it has failed to capture all significant exposure pathways.

Variability in Intake Levels

CDD/CDF and dioxin-like PCB intakes for the general population may extend to levels at least three times higher than the mean. Variability in general population exposure is primarily the result of the differences in dietary choices that individuals make. These are differences in both quantity and types of food consumed. An increased background exposure can result from either a diet that favors consumption of foods high in dioxin content or a diet that is disproportionately high in overall consumption of animal fats.

The best data available to determine the variability of total fat consumption comes from several analyses of the Bogalusa Heart Study (Cresanta et al., 1988; Nicklas et al., 1993; Nicklas et al., 1995; Nicklas et al., 1995; Frank et al., 1986). These data show that the 95th percentile of total fat consumption is about twice the mean and the 99th percentile is approximately three times the mean. For a diet which has a broad distribution of animal fats (as does the typical U.S. diet), this same distribution can be assumed for dioxin intake.

Although body burden data cannot be assumed to be perfectly representative of current intakes (because they reflect past exposures as well as current ones), they also provide some support for this finding. This is based on the observation that the 95th percentile blood level in the CDC (2000) study was almost twice the mean level.

Intakes of CDD/CDFs and dioxin-like PCBs are over three times higher for a young child as compared to that of an adult, on a body weight basis. This is based on combining age-specific food consumption rate and average food concentrations, as was done above for adult intake estimates (see Table 1-7).

Only four of the 17 toxic CDD/CDF congeners and one of the 11 toxic PCBs account for most of the toxicity in human tissue concentrations: 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PCDF, and PCB 126. This finding is derived directly from the data described earlier on human tissue levels and is supported by intake estimations indicating that these congeners are also the primary contributors to dietary dose. These five compounds make up about 80% of the total WHO_{98}-TEQ tissue level.

1.5.4. Potentially Highly Exposed Populations or Developmental Stages

As discussed earlier, background exposures to dioxin-like compounds may extend to levels at least three times higher than the mean. This upper range is assumed to result from the normal variability of diet and human behaviors. Exposures from local elevated sources or exposures resulting from unique diets would be in addition to this background variability. Such elevated exposures may occur in small segments of the population such as individuals living near discrete local sources. Nursing infants represent a special case:

for a limited portion of their lives, these individuals may have elevated exposures on a body weight basis when compared with non-nursing infants and adults.

CDD/CDF contamination incidents involving the commercial food supply have occurred in the United States and other countries. For example, in the United States, contaminated ball clay was used as an anti-caking agent in soybean meal and resulted in elevated dioxin levels in some poultry and catfish. This incident, which occurred in 1998, involved less than 5% of the national poultry production and has since been eliminated. Elevated dioxin levels have also been observed in a few beef and dairy animals where the contamination was associated with contact with pentachlorophenol-treated wood. Evidence of this kind of elevated exposure was not detected in the national beef survey. Consequently its occurrence is likely to be low, but it has not been determined. These incidents may have led to small increases in dioxin exposure to the general population. However, it is unlikely that such incidents have led to disproportionate exposures to populations living near where these incidents have occurred, because in the United States, meat and dairy products are highly distributed on a national scale. If contamination events were to occur in foods that are predominantly distributed on a local or regional scale, then such events could lead to highly exposed local populations.

Elevated exposures associated with the workplace or industrial accidents have also been documented. U.S. workers in certain segments of the chemical industry had elevated levels of TCDD exposure, with some tissue measurements in the thousands of ppt TCDD. There is no clear evidence that elevated exposures are currently occurring among United States workers. Documented examples of past exposures for other groups include certain Air Force personnel exposed to Agent Orange during the Vietnam War and people exposed as a result of industrial accidents in Europe and Asia.

Consumption of breast milk by nursing infants leads to higher levels of exposure and higher body burdens of dioxins during early years of life as compared with non-nursing infants. Three German studies have compared dioxin levels in infants who have been breast-fed with those who have been formula-fed. All have shown elevations in the concentrations of dioxins in infants being breast-fed. Collectively these studies included 99 infants and found that blood levels (in units of pg TEQ_{DF}-WHO_{98}/g lipid - i.e., dioxin-like PCBs not included) in infants aged 4-12 months were generally more than 20 in nursing infants and less than 5 in formula fed infants. The most comprehensive of these studies was by Abraham et al. (2000) who reported on 80 breast-fed infants. In that study, the median concentration was 25.3 pg/g TEQ_{DF}-WHO_{98}. Six of the nursing infants in the Abraham et al. (2000) study had lipid levels greater than 50 pg/g TEQ_{DF}-WHO_{98} and the maximum was 107 pg/g TEQ_{DF}-WHO_{98}. Five of these six children were from a region where mother's milk was found to be elevated due to regional contamination by a copper

recycling plant. These data suggest that breast-fed infants could have body burdens more than five times higher than formula-fed infants, depending on length of breast-feeding, dioxin concentrations in mother's milk, and other factors.

U.S. dioxin intakes from nursing were calculated using time dependent values for breast milk concentrations, consumption rates and body weights. These calculations estimated an intake immediately after birth of 242 pg TEQ_{DFP}-WHO_{98}/kg/day. This dropped to 22 pg TEQ_{DFP}-WHO_{98}/kg/day after 12 months of nursing. The average intake over one year of nursing was calculated to be 92 pg TEQ_{DFP}-WHO_{98}/kg/day. The cumulative intake for a one year nursing scenario represented about 12% of the total lifetime cumulative intake (see Chapter 5, Section 5.2 for details on these calculations).

The CDC (1997) reported that in 1995, 55% of all babies experience some breast feeding, with about half of those breast feeding beyond 5 months. The average duration of breast feeding was 28.7 weeks. In a policy statement, the American Academy of Pediatrics (1997) stated that exclusive breast feeding is ideal nutrition and sufficient to support optimal growth and development for 6 months after birth. They recommended that breast feeding continue for at least 12 months, and thereafter for as long as mutually desired.

To better evaluate the impact of nursing on infants, changes in body burden were calculated using a one-compartment, first-order pharmacokinetic model. Changes in TEQ tissue concentration over time were modeled for a variety of nursing scenarios: formula only, 6 weeks nursing, 6 months nursing, and one year. These scenarios reasonably capture the range of current nursing practice. This modeling effort required using the intake assumptions described earlier and a variety of additional assumptions including: the fraction of the oral dose which is absorbed into the body, changes in body weight over time, and changes in body fat fraction over time. Assumptions were also made about changes in the biological half-life of dioxins as a function of body fat fraction. For the infant, the half-life was less than one year, and during adulthood the half-life increased as the fraction of body fat increased. The short half-life at birth was based on a study by Kreuzer et al. (1997) and the longer half-life during the later years of life, when body fat fraction increased, was based on a model presented in Michalek et al. (1996). The complete set of input values are listed in Chapter 5, Section 5.2.

The modeling results in terms of changes in lipid concentrations and body burdens as a function of age are shown in Figure 1-2. Some key observations include:

- For the 6 and 12 month nursing scenarios, lipid concentrations peaked at around 4 months at about 46 ppt TEQ_{DFP}-WHO_{98}. The formula-fed infants peaked at less than 10 ppt after the first year.

- In all four scenarios, the lipid concentrations merged at about 10 years of age, at a concentration of about 13 ppt TEQ_{DFP}-WHO_{98}. Lipid and body burdens declined slightly from age 10 to about age 20, and then rose gradually through adulthood. This rise was due to the increase in half-life with age. At age 70, the modeled lipid and body burden concentrations were 13 ppt TEQ_{DFP}-WHO_{98} lipid and 5 ppt TEQ_{DFP}-WHO_{98}.whole body weight.

A sensitivity analysis was performed to test the assumptions about changes in breast milk concentrations during lactation and changes in half-life over time. In this analysis, breast milk concentrations were held steady at 25 pg TEQ_{DFP}-WHO_{98}/g lipid for a 6-month nursing scenario, and the half-life of dioxins in the body remained steady at 7.1 years from birth until 70 years of age. With these two changes, the maximum infant lipid concentration increased from 46 to 70 pg TEQ_{DFP}-WHO_{98}/g lipid. The major impact of a steady half-life assumption, instead of one which increased with increasing body lipid fractions in the aging adult, was that the lipid concentrations stabilized at about 8 pg TEQ_{DFP}-WHO_{98}/g lipid in the adult, instead of rising to 13 pg TEQ_{DFP}-WHO_{98}/g lipid at age 70.

The above analysis indicates that the average annual infant intake resulting from one year of nursing, 92 pg TEQ_{DFP}-WHO_{98}/kg/day, significantly exceeds the currently estimated adult intake of 1 pg TEQ_{DFP}-WHO_{98}/kg/day. The impact of nursing on infant body burdens, however, is much less, i.e. infant body burdens will not exceed adult body burdens by 92 times. Rather, the modeling suggests that peak infant body burdens are only about 2 times current adult body burdens (46 vs 25 pg TEQ_{DFP}-WHO_{98}/g lipid). The reduced body burden impacts in nursing infants (relative to the intake) is thought to be due to the rapidly expanding infant body weight and lipid volume and the possibly faster elimination rate in infants. Impacts to nursing infants should decline in the future if, as discussed earlier, general population exposures decline.

Consumption of fish, meat, or dairy products containing elevated levels of dioxins and dioxin-like PCBs can lead to elevated exposures in comparison with the general population. Most people eat some fish from multiple sources, both fresh and salt water. The estimated dioxin concentrations in these fish and the typical rates of consumption are included in the mean background calculation of exposure. People who consume large quantities of fish at estimated contamination levels may have elevated exposures. These kinds of exposures are addressed within the estimates of variability of background and are not considered to result in highly exposed populations. If individuals obtain their fish from areas where the concentration of dioxin-like chemicals in the fish is elevated, they may constitute a highly exposed subpopulation. Although this scenario seems reasonable, very

little supporting data could be found for such a highly exposed subpopulation in the United States. One study measuring dioxin-like compounds in the blood of sport fishers in the Great Lakes area showed elevations over mean background, but within the range of normal variability. Another study measuring 90 PCB congeners (seven of which were dioxin-like PCBs, although PCB 126 was not measured) in the blood of sport fishers consuming high amounts of fish caught from Lake Michigan (>26 pounds of sport fish/yr) did, however, show significant elevations of PCBs in their blood as compared to a control population (individuals consuming < 6 pounds of sport fish/yr). The average total concentration of PCBs in the blood of these sport fishers was over three times higher than that of the control population. Similarly, elevated levels of coplanar PCBs have been measured in the blood of fishers on the north shore of the Gulf of the St. Lawrence River who consume large amounts of seafood. Elevated CDD/CDF levels in human blood have been measured in Baltic fishermen. For further details on these studies see Chapter 5.

High exposures to dioxin-like compounds as a result of consuming meat and dairy products would most likely occur in situations where individuals consume large quantities of these foods and the level of these compounds is elevated. Most people eat meat and dairy products from multiple sources and, even if large quantities are consumed, they are not likely to have unusually high exposures. Individuals who raise their own livestock for basic subsistence have the potential for higher exposures if local levels of dioxin-like compounds are high. One study in the United States showed elevated levels in chicken eggs near a contaminated soil site. European studies at several sites have shown elevated CDD/CDF levels in milk and other animal products near combustion sources, and some of these have also documented elevations in the levels of dioxin-like compounds in blood from the families consuming their home products.

1.5.5. Temporal Trends Information

Some general observations can be made about changes in levels of dioxin-like compounds in the environment over time. These are discussed below and summarized in Table 1-8.

Concentrations of CDD/CDFs and PCBs in the U.S. environment were consistently low prior to the 1930s. Then, concentrations rose steadily until about 1970. At that time, the trend reversed and the concentrations began to decline. That trend has continued to the present. The most compelling supportive evidence of this trend for the CDD/Fs and PCBs comes from dated sediment core studies. Sediment concentrations in these studies are generally assumed to be an indicator of the rate of atmospheric deposition. CDD/F and PCB concentrations in sediments began to increase around the 1930s, and continued to increase until about 1970. Decreases began in 1970 and have

continued to the time of the most recent sediment samples (about 1990). Sediment data from 20 U.S. lakes and rivers from seven separate research efforts consistently support this trend. Additionally, sediment studies in lakes located in several European countries have shown similar trends.

It is reasonable to assume that sediment core trends should be driven by a similar trend in emissions to the environment. The period of increase generally matches the time when a variety of industrial activities began rising and the period of decline appears to correspond with growth in pollution abatement. Many of these abatement efforts should have resulted in decreases in dioxin emissions, i.e. elimination of most open burning, particulate controls on combustors, phase out of leaded gas, and bans on PCBs, 2,4,5-T, hexachlorophene, and restrictions on use of pentachlorophenol. Also, the national source inventory of this assessment documented a significant decline in emissions from the late 1980s to the mid-1990s. Further evidence of a decline in CDD/F levels in recent years is emerging from data, primarily from Europe, showing declines in foods and human tissues.

In addition to the congener specific PCB data discussed earlier, a wealth of data on total PCBs and aroclor mixtures exist which also supports these trends. It is reasonable to assume that the trends for dioxin-like PCBs are similar to those for PCBs as a class because the predominant source of dioxin-like PCBs is the general production of PCBs in aroclor mixtures. PCBs were intentionally manufactured in large quantities from 1929 until production was banned in 1977. U.S. production peaked in 1970, with a volume of 39,000 metric tons. Further support is derived from data showing declining levels of total PCBs in Great Lakes sediments and biota during the 1970s and 1980s. These studies indicate, however, that during the 1990s the decline is slowing and may be leveling off.

Past human exposures to dioxins were most likely higher than current estimates. This is supported by a study which applied a non-steady state pharmacokinetic model to data on background U.S. tissue levels of 2,3,7,8-TCDD from the 1970s and 80s. Various possible intake histories (pg/kg-day over time) were tested to see which best-fit the data. An assumption of a constant dose over time resulted in a poor fit to the data. The "best-fit" (statistically derived) to the data was found when the dose, like the sediment core trends, rose through the 60s into the 70s, and declined to low current levels. Some additional support for this finding comes from a limited study of preserved meat samples from several decades in the twentieth century. One sample, from before 1910, showed very low concentrations of dioxins and coplanar PCBs. Thirteen other samples, from the 1940s until the early 1980s, consistently showed elevated levels of all dioxin-like compounds as compared to food surveys conducted during the 1990s.

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Table 1-1. The TEF Scheme for I-TEQ_{DF}

Dioxin (D) Congener	TEF	Furan (F) Congener	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		OCDF	0.001

Table 1-2. The TEF Scheme for dioxin-like coplanar PCBs, as determined by the World Health Organization in 1994

Chemical Structure	IUPAC Number	TEF
3,3',4,4'-TeCB	PCB-77	0.0005
2,3,3',4,4'-PeCB	PCB-105	0.0001
2,3,4,4',5-PeCB	PCB-114	0.0005
2,3',4,4',5-PeCB	PCB-118	0.0001
2',3,4,4',5-PeCB	PCB-123	0.0001
3,3',4,4',5-PeCB	PCB-126	0.1
2,3,3',4,4',5-HxCB	PCB-156	0.0005
2,3,3',4,4',5'-HxCB	PCB-157	0.0005
2,3',4,4',5,5'-HxCB	PCB-167	0.00001
3,3',4,4',5,5'-HxCB	PCB-169	0.01
2,2',3,3',4,4',5-HpCB	PCB-170	0.0001
2,2',3,4,4',5,5'-HpCB	PCB-180	0.00001
2,3,3',4,4',5,5'-HpCB	PCB-189	0.0001

Table 1-3. The TEF Scheme for TEQ_{DFP}-WHO_{98}

Dioxin Congeners	TEF	Furan Congeners	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	1.0	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
OCDD	0.0001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		OCDF	0.0001

Chemical Structure	IUPAC Number	TEF
3,3',4,4'-TeCB	PCB-77	0.0001
3,4,4',5-TCB	PCB-81	0.0001
2,3,3',4,4'-PeCB	PCB-105	0.0001
2,3,4,4',5-PeCB	PCB-114	0.0005
2,3',4,4',5-PeCB	PCB-118	0.0001
2',3,4,4',5-PeCB	PCB-123	0.0001
3,3',4,4',5-PeCB	PCB-126	0.1
2,3,3',4,4',5-HxCB	PCB-156	0.0005
2,3,3',4,4',5'-HxCB	PCB-157	0.0005
2,3',4,4',5,5'-HxCB	PCB-167	0.00001
3,3',4,4',5,5'-HxCB	PCB-169	0.01
2,3,3',4,4',5,5'-HpCB	PCB-189	0.0001

Table 1-4. Summary of North American CDD/CDF and PCB TEQ-WHO_{98} Levels in Environmental Media and Food (whole weight basis; concentrations provided in parenthesis for food products are calculated at ND = 0).

Media	CDD/CDFs[a]	PCBs[a]
Urban Soil, ppt	n=270 9.3 ± 10.2[d] Range = 2 - 21	n=99 2.3[d]
Rural Soil, ppt	n = 354 2.7[d] Range = 0.1 - 6	n=62 0.59[d]
Sediment, ppt	n=11 5.3 ± 5.8 Range = <1 - 20	n = 11 0.53 ± 0.69
Urban Air, pg/m^3	n=106 0.12 ± 0.094 Range = 0.03 - 0.2	0.0009
Rural Air, pg/m^3	n=60 0.013 Range = 0.004 - 0.02	n=53 0.00071
Freshwater Fish and Shellfish, ppt	n=289 1.0 (NA[b])	n = 1 composite of 10 samples plus 6 composites 1.2[c] (NA[b])
Marine Fish and Shellfish, ppt	n=158 0.26 (NA[b])	n = 1 composite of 13 samples plus 5 composites 0.25[e] (NA[b])
Water, ppq	n=236 0.00056 ± 0.00079 (NA[b])	Nab
Milk, ppt (Note: each composite for CDD/F/PCB comprised of 40+ U.S. regional samples)	n=8 composites 0.018 ± 0.0012 (0.017)	n = 8 composites 0.0088 (0.0088)
Dairy, ppt[e]	n = 8 composites 0.12 ± 0.22 (0.12)	n = 8 composites 0.058 (0.058)
Eggs, ppt (Note: each composite for CDD/F data comprised of 24 eggs)	n=15 composites 0.081[c] (0.013)	n = 18 plus 6 composites 0.10[c] (NA[b])
Beef ppt	n=63 0.18 ± 0.11 (0.061) Range = 0.11 - 0.95	n = 63 0.084 (0.084)
Pork, ppt	n=78 0.28 ± 0.28 (0.080) Range = 0.15 - 1.8	n = 78 0.0093 (0.006)
Poultry, ppt	n=78 0.068 ± 0.070 (0.043) Range = 0.03 - 0.43	n = 78 0.026 (0.026)
Vegetable Fats, ppt	n=30 0.056 ± 0.24[d] (NA[b])	n = 5 composites 0.037[c]

[a] Values are the arithmetic mean TEQs, in ppt, and standard deviations. Nondetects were set to one-half the limit of detection, except for soil and CDD/CDFs in vegetable fats for which nondetects were set to zero.

[b] NA = not available; Congener-specific PCB data, and data to calculate TEQ concentrations at ND = 0, are limited.

[c] Standard deviations could not be calculated due to limitations associated with the data (i.e., composite analyses).

[d] TEQ calculated by setting nondetects to zero.

[e] Dairy concentration calculated from milk lipid concentrations and then assuming a fat fraction for dairy.

Table 1-5. Background Serum Levels in the United States 1995 - 1997

	TEQ_{DFP}-WHO_{98} (pg/g lipid)	2,3,7,8-TCDD (pg/g lipid)
Median	18.7	1.9
Mean	22.1*	2.1
95th Percentile	38.8	4.2

* After adjusting to account for missing PCBs, the mean is 25.4 pg/g lipid.

Source: CDC (2000).

Table 1-6. Adult Contact Rates and Background Intakes of Dioxin-like Compounds

Exposure Route	Contact Rate	Dioxins and Furans		Dioxin-like PCBS		Total intake (pg TEQ_{DFP}-WHO_{98}/kg-d)
		Concentration TEQ_{DF}-WHO_{98}	Intake (pg TEQ_{DF}-WHO_{98}/kg-d)	Concentration TEQ_{P}-WHO_{98}	Intake (pg TEQ_{P}-WHO_{98}/kg-d)	
Soil ingestion	50 mg/d	9.3 pg/g	0.0066	2.3	0.0016	0.0082
Soil dermal	12 g/d	9.3 pg/g	0.0016	2.3	0.00034	0.0019
Freshwater fish and shellfish	5.9 g/d	1.0 pg/g	0.084	1.2 pg/g	0.1	0.18
Marine fish and shellfish	9.6 g/d	0.26 pg/g	0.036	0.25 pg/g	0.045	0.070
Inhalation	13.3 m^3/d	0.12 pg/m^3	0.023	NA	NA	0.023
Milk	175 g/d	0.018 pg/g	0.045	0.0088 pg/g	0.022	0.067
Dairy	55 g/d	0.12 pg/g	0.094	0.058 pg/g	0.046	0.14
Eggs	0.24 g/kg-d	0.081 pg/g	0.019	0.10 pg/g	0.024	0.043
Beef	0.71 g/kg-d	0.18 pg/g	0.13	0.084 pg/g	0.060	0.19
Pork	0.22 g/kg-d	0.28 pg/g	0.062	0.012 pg/g	0.0026	0.065
Poultry	0.50 g/kg-d	0.068 pg/g	0.034	0.026 pg/g	0.013	0.047
Other Meats	0.35 g/kg-d	0.18 pg/g	0.062	0.041 pg/g	0.014	0.076
Vegetable fat	17 g/d	0.056 pg/g	0.014	0.037 pg/g	0.0090	0.023
Water	1.4 L/d	0.0005 pg/L	0.000011	NA	NA	0.000011
Total			**0.61 (43 pg/d)**		**0.33 (23 pg/d)**	**0.94 (66 pg/d)**

Table 1-7. Variability in Average Daily TEQ Intake as a Function of Age

Age range	Intake, mass basis pg TEQ_{DFP}-WHO_{98}/d	Intake, body weight basis pg TEQ_{DFP}-WHO_{98}/kg-d
1-5 yr	50	3.3
6-11 yr	54	1.9
12-19 yr	61	1.1
Adult	66	0.94

Table 1-8. Summary of Findings with Regard to Trends in Dioxin Levels in the Environment and in Humans

Finding	Support	Uncertainty
Concentrations of CDD/CDFs in the environment were consistently low for centuries until the 1930s. Then, concentrations rose steadily until about the 1960s, at which point concentrations began to drop. Evidence suggests that the drop in concentrations is continuing to the present.	***Sediment core studies show a trend of rising concentrations in 1930s and 1940s through the 1960s and 1970s and a subsequent decline to the present.*** - 11 lakes/reservoirs in the U.S.: Cleverly et al., 1996; Versar, 1996 - Lake Huron: Czuczwa et al., 1985 - Green Lake, NY: Smith et al., 1992, 1993 - Hudson River: Smith et al., 1995 - Lakes Superior, Michigan, and Ontario: Pearson et al., 1995 - Straight of Georgia, British Columbia: MacDonald et al., 1992 - A remote arctic lake: Tan et al., 1993; Vartiainen et al., 1995	The assumption of nondegradation of CDD/CDFs in sediment cores.
	Analogous trends in environmental loadings - Rise of the manufacture and use of chlorinated phenolic intermediates and products - Banning of leaded gasoline, certain phenoxy herbicides, PCBs - Reductions in pulp and paper mill discharges - EPA National Source Inventory showing 60% reduction in CDD/CDF TEQ emissions between 1987 and 1995 (see Volume 1)	Indirect measure of environmental levels.
	Limited trend for other environmental concentrations - Rises and declines in historical food products in the U.S.: Winters et al., 1998 - Rises and declines in herbage, soil, and air measured in archived samples in UK: Kjeller et al., 1991, 1996; Harner et al., 1995 - Reductions in the past two decades in herring gull eggs in the Great Lakes and the Gulf of St. Lawrence River (Hebert et al., 1994); pike in Sweden (DeWit et al., 1994); pike in Finland (Korhonen et al., 1995); air in Germany (Hiester et al., 1995); German dairy products and human milk between 1990 and 1994 (Fürst and Wilmers, 1995; 1997)	Very few archived environmental measurements to ascertain trends beyond the past decade or so. More recent data showing a decline in trends is limited.
	Suggestive evidence of declines in human body burdens in recent decade - National Human Adipose Tissue Survey: U.S. EPA, 1991 - Ministry of Agriculture, Fisheries, and Food's calculations of declines in dose based on market basket surveys showing reductions in levels in combination with reductions in consumption of key food items: MAFF (1995)	Long half-lives in humans impede responses in body burdens to changes in environmental levels.
Environmental levels of coplanar PCBs began increasing in the 1920s, peaking in the 1970s, and decreasing after that	***PCB production data*** - Rise in the manufacture from the latter 1920s to the early 1970s; complete ban in 1977	Nearly all trends data are specific to PCBs or Aroclors, and not to coplanar PCBs.
	PCB declining environmental levels - Evidence of declines in biota and sediment levels in the Great Lakes	

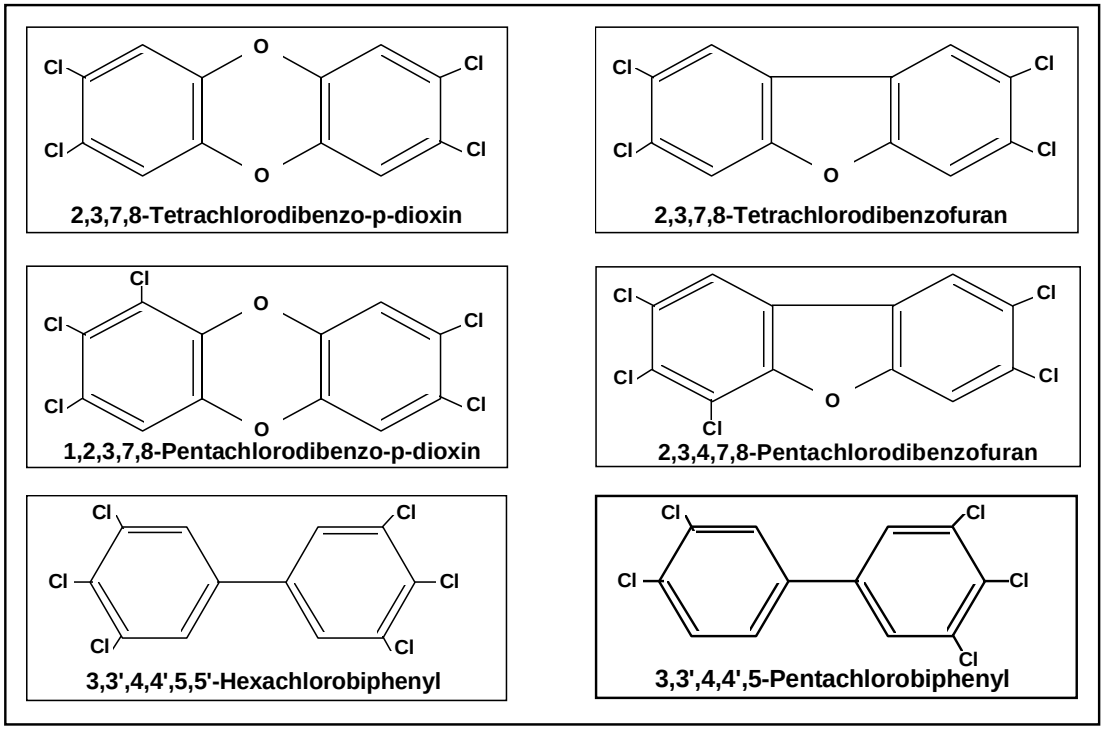
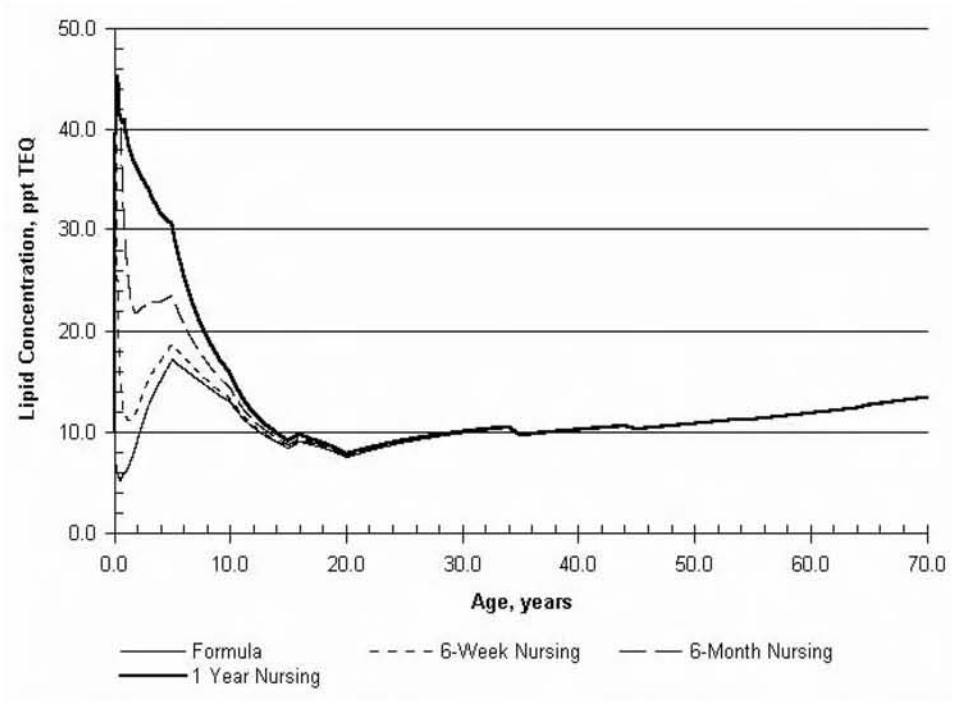


Figure 1-1. Chemical Structure of 2,3,7,8-TCDD and Related Compounds

(a)



(b)

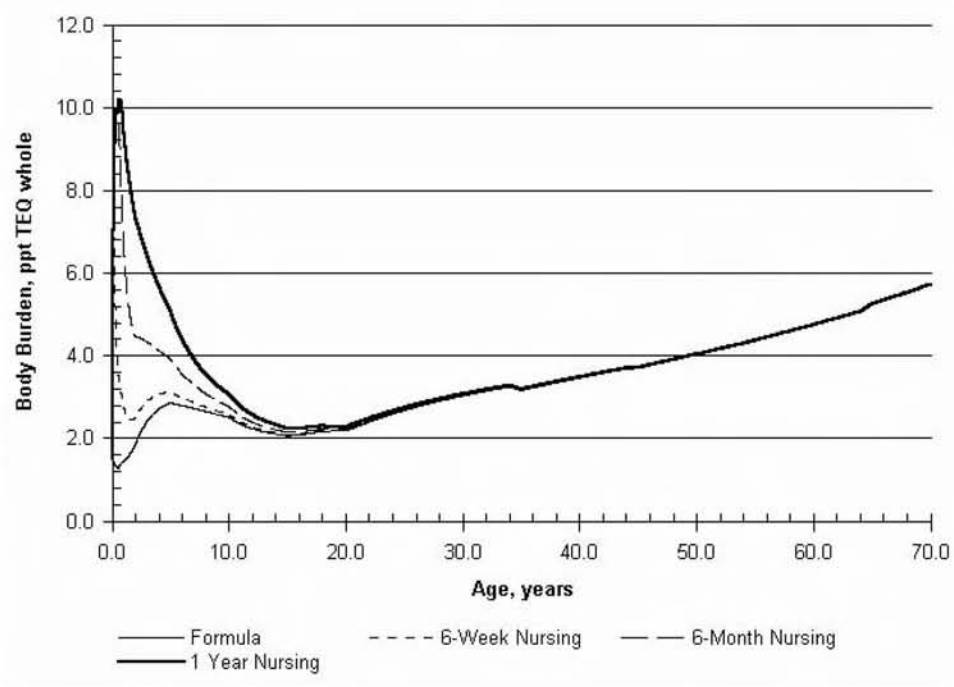


Figure 1-2. Lipid (a) and Body Burden (b) Concentrations in a Hypothethical Female Until Age 70 Under Four Nursing Scenarios: Formula Only, and 6-week, 6-month, and 1 year Nursing

2. PHYSICAL AND CHEMICAL PROPERTIES AND FATE

2.1. INTRODUCTION

This chapter summarizes available information regarding the physical and chemical properties and fate of the dioxin-like CDDs, CDFs, BDDs, BDFs, and PCBs. Physical/ chemical properties addressed in this chapter include melting point, water solubility, vapor pressure, Henry's Law constant, octanol/water partition coefficient, organic carbon partition coefficient, and photochemical quantum yield. Fate and transport processes addressed include photolysis, oxidation, hydrolysis, biodegradation, volatilization, and sorption. Biologically-mediated transport properties (i.e., bioconcentration, plant uptake, etc.) are also addressed in this volume, but are also addressed in the companion volume to this report, Volume 3: Site-Specific Assessment Procedures.

Knowledge of physical and chemical properties is essential to understanding and modeling the environmental transport and transformation of organic compounds such as the dioxin-like compounds. The properties most important for understanding the environmental behavior of the dioxin and dioxin-like compounds appear to be water solubility (WS), vapor pressure (VP), octanol/water partition coefficient (K_{ow}), organic carbon partition coefficient (K_{oc}), and photochemical quantum yield. The ratio of VP to WS (VP/WS) can be used to calculate the Henry's Law constant (H_c) for dilute solutions of organic compounds when the VP and WS are measured at the same temperature and for the same physical state. Henry's Law constant is an index of partitioning for a compound between the atmospheric and the aqueous phase (Mackay et al., 1982).

To maximize and optimize the identification of information on the physical/chemical properties of these compounds, a thorough search of the recent literature was conducted. A computer literature search was conducted using the on-line Chemical Abstracts (CA) data base maintained by the Scientific Technical Network (STN). Printed abstracts were obtained and screened, and selected literature were retrieved and critically evaluated. The most definitive value for each physical/ chemical property for each congener was selected. The evaluation method used to select the most definitive physical/chemical property values is detailed in Section 2.3. The property values obtained from the scientific literature are summarized in Appendix A. Sections 2.4 and 2.5 present the property values for the dioxin-like compounds that are considered to be the most definitive. These

values are utilized in the modeling equations in the companion volume to this report, Volume 3 Site-Specific Assessment Procedures. Appendix A lists reported chemical property values for the CDDs, CDFs, and dioxin-like PCBs. Where technically feasible and appropriate, estimation procedures have been used to provide values where measured data are not available. For those compounds for which data could not be found and estimates are not appropriate, the field is left blank, and a congener group average is presented as the property value for that congener group. The congener group average was calculated by averaging the selected (i.e., most definitive) property values listed for the congeners in that group.

The values suggested in this document as most definitive are, in the authors' opinion, the best values derivable from current data. Because the document has undergone extensive review inside the Agency, by scientific community outside the Agency, and by the Science Advisory Board, the values can be interpreted as generally representative of the Agency and scientific community. The authors recommend that document users consider the values as defaults in the sense that users are encouraged to accept them as a starting point but should feel free to modify them as new data become available.

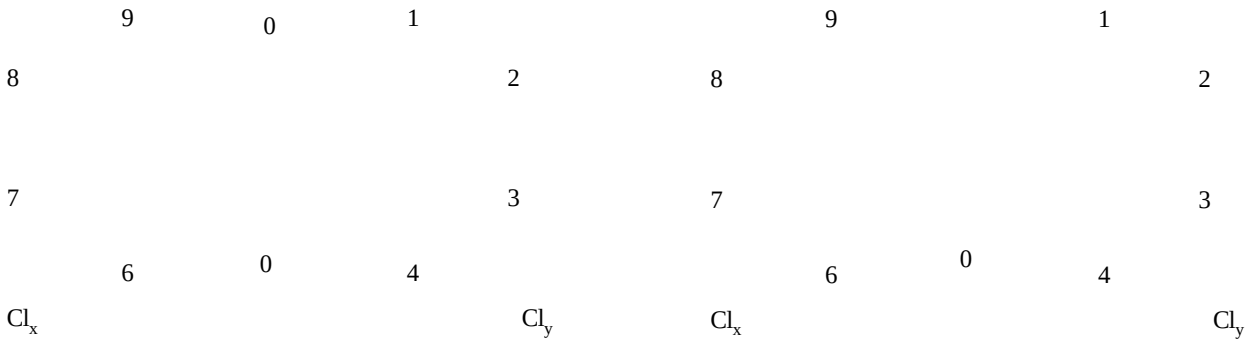
Brief summaries of the recent and relevant scientific literature on the environmental fate of the polychlorinated and polybrominated dibenzodioxins, dibenzofurans, and biphenyls are provided in Sections 2.6 and 2.7.

2.2. GENERAL INFORMATION

Polychlorinated dibenzo-p-dioxins (CDDs), polychlorinated dibenzofurans (CDFs), and polychlorinated biphenyls (PCBs) are chemically classified as halogenated aromatic hydrocarbons. CDDs and CDFs can be formed as unintentional by-products through a variety of chemical reactions and combustion processes. Both compound classes have a triple-ring structure that consists of two benzene rings connected by a third oxygenated ring. For CDDs, the benzene rings are connected by a pair of oxygen atoms. CDFs are connected via a single oxygen atom. (See structures below.) PCBs are a class of compounds formed by the chlorination of a biphenyl molecule.

There are 75 possible different positional congeners of CDDs and 135 different congeners of CDFs. Likewise, there are 75 possible different positional congeners of

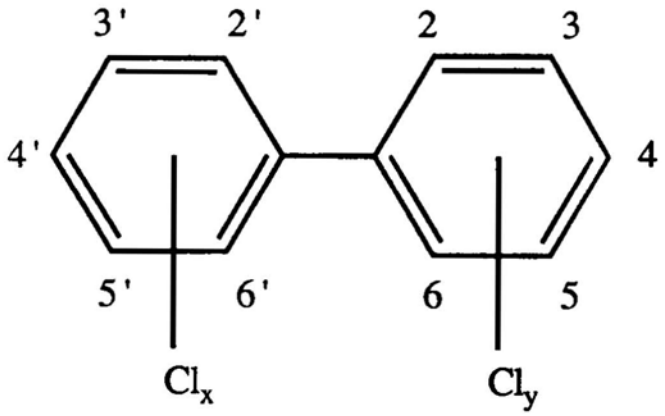
BDDs and 135 different congeners of BDFs. (See Table 2-1.) The basic structure and numbering of each chemical class is shown below.



PCDDs **PCDFs**

X = 0 to 4, Y = 0 to 4, X + Y > 1

There are 209 possible PCB congeners. (See Table 2-1.) The physical/ chemical properties of each congener vary according to the degree and position of chlorine substitution. The list of dioxin-like PCBs can be found in Table 1-2. The PCBs assume a dioxin-like structure when the substituent chlorines occupy: (a) usually no more than one of the ortho positions; (b) both para positions; and (c) at least two meta positions; and (d) the structure is not hindered from assuming the preferred planar configuration. The basic structure and numbering scheme for PCBs is shown below.



X = 1 to 5, Y = 1 to 5, X + Y > 1

2.3. PHYSICAL/CHEMICAL PROPERTY EVALUATION METHODOLOGY

As discussed above, a thorough search of the recent published scientific literature was conducted to maximize and optimize the identification of measured physical/chemical properties. For the purpose of identifying the most definitive of two or more physical/chemical property values reported in the literature for a given dioxin-like compound, a ranking methodology was developed to evaluate the degree of confidence in the reported values. A property value with a ranking of 1 is considered to have the highest level of confidence; a property value with a ranking of 5 is considered to have the lowest level of confidence. The ranking scheme assumes that measured values are more definitive than estimated values. The ranking scheme is based on five ranking criteria or factors. These factors are described below:

Factor 1: *Confirmation.* Value, measured or derived, confirmed by at least one other laboratory, or different experimental technique. Confirmation was assumed if the reported values were within 50 percent of the highest value (within 5 percent for values reported in logarithmic units).

Factor 2: *Measurement Technique.* Direct measurement technique used. No measurements reported less than 10 times the method detection limit.

Factor 3: *GLP Followed.* Good Laboratory Practice was followed in the experimental work. This includes the use of traceable, pure standards; sensitive, selective detection technique was employed; repeatability of measurements demonstrated; all experimental details sufficiently documented so others could reproduce experiments; and sources of determinate error considered - error analysis conducted.

Factor 4: *Derived Value.* Value derived from other directly measured physical/chemical properties by use of known physical/chemical relationships developed for structurally similar chemicals (e.g., other dioxin, furan, and PCB congeners, multiple-ring halogenated compounds). The input value (i.e., the independent variable) used to derive the property value of interest from the equation (i.e., the physical/chemical relationship) is a directly measured value.

Factor 5: *Estimated Value.* Value estimated using a physical/chemical relationship that was developed using estimated values or a combination of

estimated and measured values; this includes QSAR (Quantitative Structure Activity Relationship) methods. Also includes values derived from other directly measured physical/chemical properties by use of known physical/chemical relationships developed, in large part, for structurally dissimilar compounds.

Although this ranking scheme is subjective in nature, it is a reasonable method for identifying the most definitive physical/chemical property value. The ranking scheme has several advantages. First, it identifies where more work is needed to obtain a more definitive p-chem property value. Second, it allows for later adjustments in these values when more definitive studies are conducted. A low ranking for a study does not mean that a particular reported value is incorrect - only that insufficient evidence exists to determine its accuracy. The ranking scheme is as follows:

Rank 1: Confirmed Measured Values. The reported value has met Factors 1, 2, and 3. (See Table 2-2.) This value is considered definitive.
Rank 2: Unconfirmed Measured Values. The reported value has met Factors 2 and 3. The value is considered accurate; it could be definitive subject to confirmation.
Rank 3: Confirmed Derived Values. The reported value has met Factors 1, 3, and 4. The value is considered to be a close approximation.
Rank 4: Unconfirmed Derived Value. The reported value has met Factors 3 and 4. The value is considered to be an approximation.
Rank 5: Estimated Value. The reported value has met Factor 5 only. The value is considered to be an "order-of-magnitude" estimate.

If two or more values have the same ranking, then the value that has been selected as most definitive by Mackay et al. (1992a, 1992b), by other EPA offices, other government agencies, or scientific data bases (e.g., the Syracuse Research Corporation (SRC) Chemfate Data Base) was deemed to be the most definitive value for this document. If two or more values with the same ranking have not been peer reviewed as above, typically the most current value was chosen as the most definitive value. This

decision was made on the assumption that the most current value would have been developed by the latest scientific method; however, an evaluation of the techniques used to derive the values was also considered in choosing the more definitive value. The ranking of the literature can be found in Table A-2 in Appendix A. Table 2-3 lists the property values for the dioxin-like compounds that are considered to be most definitive.

2.4. PHYSICAL/CHEMICAL PROPERTIES - CHLORINATED COMPOUNDS

Limited research has been conducted to determine physical and chemical properties of CDFs, CDDs, and the dioxin-like PCBs. The CDD/CDF congeners having 2,3,7,8-chlorination have received the most research attention, with 2,3,7,8,-TCDD being the most intensely studied compound. All 2,3,7,8-substituted CDD/CDF congeners are now available commercially, but many of these congeners have not been prepared in pure form. Another factor that is likely to have limited research on these compounds is the high toxicity of these compounds, which necessitates extreme precautions to prevent potential adverse effects.

2.4.1. Water Solubility

Although water solubility data are not directly used in the exposure scenario equations in Volume 3, water solubility data can be used to estimate Henry's Law constants (using the VP/WS ratio technique) that are used in the equations in Volume 2. Very few measured water solubility values are available in the literature. Marple et al. (1986a) reported the water solubility of 2,3,7,8-TCDD as 19.3 $\pm$ 3.7 parts per trillion (nanograms per liter, ng/L) at 22°C. Marple et al. (1986a) used a procedure of equilibrating thin films of resublimed 2,3,7,8-TCDD with a small volume of water followed by gas chromatography (GC) analysis with 63Ni electron capture detection. Other water solubility values for 2,3,7,8-TCDD have been reported in the literature and are summarized in U.S. EPA (1990) and Mackay et al. (1992a). Values ranging from 7.9 ng/L to 483 ng/L are reported in U.S. EPA (1990) and Mackay et al. (1992a) with 19.3 ng/L selected as the recommended value. The value of 19.3 ng/L was confirmed by Marple et al. (1987) using both radio-labeled and unlabeled 2,3,7,8-TCDD. Marple et al. (1987) reported values of 10.6 ng/L and 10.4 ng/L for the labeled and unlabeled compounds respectively. Because

the value of 19.3 ng/L was confirmed by other techniques and was recommended by U.S. EPA (1990), it was chosen as the most definitive value.

Friesen et al. (1985) and Shiu et al. (1988) used high-performance liquid chromatography (HPLC) generator column techniques to measure the water solubilities of a series of chlorinated dioxins including the following dioxin-like congeners: 1,2,3,4,7,8-HxCDD; 1,2,3,4,6,7,8-HpCDD; and OCDD. Reported water solubilities ranged from 4.42 ng/L to 0.074 ng/L for the 1,2,3,4,7,8-HxCDD and OCDD congeners, respectively. Friesen et al. (1990b) used a gas chromatography/mass spectrometry detection (GC/MSD) generator column technique to measure the water solubilities of a series of 2,3,7,8-substituted CDFs (2,3,7,8-TCDF; 2,3,4,7,8-PeCDF; 1,2,3,6,7,8- and 1,2,3,4,7,8-HxCDF; and 1,2,3,4,6,7,8-HpCDF) and reported a decrease in water solubility with an increase in the number of chlorine substituents. The reported water solubility values ranged from 419 ng/L for 2,3,7,8-TCDF to 1.35 ng/L for 1,2,3,4,6,7,8-HpCDF.

Few measured data have been reported for the dioxin-like PCB compounds. The selected water solubility values for the dioxin-like PCB compounds are typically one to two orders of magnitude greater than the similarly chlorinated CDD and CDF congeners. For example, the selected value for 3,3',4,4'-TCB is 1 μg/l whereas the selected water solubility values averages for 2,3,7,8-TCDD and 2,3,7,8-TCDF are 0.019 and 0.42 μg/l, respectively.

For those compounds without reported measured water solubility values, estimations were calculated by the congener group-average method. For example, for the tetra-chlorinated dioxins, values reported in the literature were averaged to yield an estimated water solubility value for the tetra-chlorinated dioxin congener group. A similar procedure was used to develop the average value for each of the other CDD and CDF congener groups. The most definitive value for each isomer was used to derive the congener group average.

2.4.2. Vapor Pressure

Vapor pressure data are not directly used in the exposure scenario equations in Volume 3. However, vapor pressure data can be used to estimate Henry's Law constant using the VP/WS ratio technique. Very few measured vapor pressure values are available

in the literature for the CDDs and CDFs, but the majority of the measured vapor pressures are for the 2,3,7,8-substituted congeners.

Mackay et al. (1992a) reviewed the published vapor pressure data for 2,3,7,8-TCDD and selected a recommended value of 1.50×10^{-9} mm Hg at 25°C. This value had been measured by Rordorf (1987, 1989) using a gas-flow method in a saturation oven. SRC (1991) reported this same value by extrapolating the vapor pressures measured by Schroy et al. (1985) at four higher temperatures, 30°, 55°, 62°, and 71°C. Rordorf (1987, 1989) also reported experimental vapor pressure values for OCDD (8.25×10^{-13}mm Hg) and OCDF (3.75×10^{-12} mm Hg). These values were chosen as the most definitive because they were the most current directly measured values and also because they were selected by Mackay et al. (1992a) as the most definitive values.

Eitzer and Hites (1988) reported experimental vapor pressure values for several dioxin-like compounds utilizing GC capillary column retention time data. The values were reported as subcooled liquids and then converted to solid-phase vapor pressures. The solid-phase vapor pressures ranged from 2.16×10^{-12} mm Hg to 9.48×10^{-10} mm Hg for the CDDs and from 1.07×10^{-10} mm Hg to 8.96×10^{-9} for the CDFs. Rordorf (1987, 1989) used a vapor pressure correlation method to predict the vapor pressures of 15 CDDs and 55 CDFs (including most of the 2,3,7,8-substituted CDDs and CDFs) based on the measured vapor pressures for 10 CDDs, 4 CDFs, and the deduced boiling point and enthalpy data for the larger series of CDDs and CDFs. Measured boiling point and enthalpy data are in good agreement with the deduced data used in the correlation method. The values from Rordorf (1987, 1989) were considered the more definitive based on the review of the data from these two studies by Mackay et al. (1992a).

The ranges of selected values reported within various congener groups are as follows:

Congener Group	Vapor Pressure Range (mm Hg)		
TCDD	1.5×10^{-9}	to	4.80×10^{-8}
PeCDD	4.4×10^{-10}	to	6.6×10^{-10}
HxCDD	3.6×10^{-11}	to	5.1×10^{-11}
HpCDD	5.6×10^{-12}		
OCDD	8.2×10^{-13}		
TCDF	1.5×10^{-8}	to	4.0×10^{-8}
PeCDF	1.5×10^{-9}	to	4.3×10^{-9}
HxCDF	1.80×10^{-10}	to	5.70×10^{-10}
HpCDF	3.53×10^{-11}	to	5.8×10^{-11}
OCDF	3.75×10^{-12}		

The selected vapor pressure values reported for the dioxin-like PCBs are typically one to two orders of magnitude greater than the similarly chlorinated CDD and CDF congeners. (See Table 2-3.) The directly measured values of Murphy et al. (1987) and the derived values of Foreman and Bidleman (1985) were considered the most definitive. As with the CDDs and CDFs, the vapor pressures of the PCBs decrease with an increase in the number of chlorine substituents. The highest selected value for the dioxin-like PCBs is 1.09×10^{-6} mm Hg for 2,3,3',4,4'-PeCB, and the lowest value selected is 1.46×10^{-8} mm Hg for 2,3,3',4,4',5,5'-HpCB.

Estimated vapor pressure values for those CDDs and CDFs for which measured values were not found in the literature were calculated by the congener group-average method using the literature-reported values within a congener group. For example, the literature values for the TCDDs were averaged to obtain an estimated vapor pressure assumed to apply to the TCDD congeners that did not have literature values. A similar procedure was used to develop a congener-average for each of the other congener groups. The most definitive value for each isomer was used to derive the congener group average. Compounds with vapor pressures in the ranges reported for these compounds are considered to have very low vapor pressures.

2.4.3. Henry's Law Constant

Henry's Law constants are used in Volume 3 to estimate the volatilization of the dioxin-like compounds from soil. They are also utilized in estimating the vapor-phase bioconcentration factor from air to plant leaves. Directly measured Henry's Law constants

have been reported for only three compounds. Measured values have been reported for 1,2,3,4-TCDD, 1.99 x 10^{-5} atm-m^3/mol (Santl et al., 1994); 1,3,6,8-TCDD, 6.81 x 10^{-5} atm-m^3/mol (Webster et al., 1985); and for 3,3',4,4'-PCB, 9.4 x 10^{-5} atm-m^3/mol (Dunnivant and Elzerman, 1988). These three values were considered the most definitive. Other values reported in the literature for CDDs, CDFs, and PCBs were calculated by the vapor pressure/water solubility (VP/WS) ratio technique or by structure-activity relationship techniques. A derived VP/WS ratio value, Rank 4, was determined to be more definitive than an estimated value, Rank 5.

Congener group-average Henry's Law constants were estimated for each congener group based on the selected congener values within that group. The Henry's Law constant values for the PCBs are similar to those for the CDDs and CDFs.

Lyman et al. (1982) offers guidelines, though not specific to these compounds, for comparing the degree to which organic compounds volatilize from water. These guidelines suggest that volatilization of polycyclic aromatic hydrocarbons and halogenated aromatics (which includes all the dioxin-like compounds) from water represents a significant transfer mechanism from the aqueous to the atmospheric phase.

2.4.4. Octanol/Water Partition Coefficient

The octanol/water partition coefficient (K_{ow}) is used in several exposure estimation procedures in Volume 3. The log K_{ow} is used to estimate log K_{oc} when measured data are not available, and it is utilized in estimating the root concentration factor (RCF). RCF is used to estimate the uptake of contaminants by plant roots. Log K_{ow} is also used to estimate the vapor-phase bioconcentration factor from air to plant leaves.

Marple et al. (1986b) reported the octanol/water partition coefficient of 2,3,7,8-TCDD as 4.24 ($\pm$ 2.73) x 10^6 at 22 $\pm$ 1°C, yielding a log K_{ow} of 6.64 (Table A-1). Two similar experimental techniques were used, but the more reliable method involved equilibration of water-saturated octanol, containing the 2,3,7,8-TCDD, with octanol-saturated water, over 6 to 31 days. U.S. EPA (1990) reported that the available low K_{ow} data ranged from 6.15 to approximately 8.5. The 6.64 value reported by Marple et al. (1986b) was the value recommended in U.S. EPA (1990). More recently, Mackay et al. (1992a) evaluated all published measured and estimated log K_{ow} values for 2,3,7,8-TCDD and recommended a value of 6.80.

Burkhard and Kuehl (1986) used reverse-phase High Pressure Liquid Chromatography (HPLC) and Liquid Chromatography/Mass Spectrometry (LCMS) detection to determine octanol/water partition coefficients for 2,3,7,8-TCDD and a series of seven other tetrachlorinated planar molecules, including three other TCDD isomers (1,2,3,4-TCDD; 1,3,7,9-TCDD; 1,3,6,8-TCDD), 2,3,7,8-TCDF, and 3,3',4,4'-tetrachlorobiphenyl. The log K_{ow} values for the four TCDD isomers ranged from 7.02 to 7.20. The log K_{ow} for 2,3,7,8-TCDF was 5.82, and the log K_{ow} for 3,3',4,4'-TCB was 5.81.

Burkhard and Kuehl (1986) also re-evaluated data on 13 CDDs and CDFs previously reported by Sarna et al. (1984) under similar experimental techniques. In the re-evaluation, Burkhard and Kuehl (1986) used experimental rather than estimated log K_{ow} values in correlations with gas chromatographic retention times. This approach yielded log octanol-water partition coefficients ranging from about 4.0 for the nonchlorinated parent molecules to about 8.78 for the octa-chlorinated compounds, much lower than the values originally reported by Sarna et al. (1984).

Sijm et al. (1989) used a slow stirring method to obtain log K_{ow} values for 73 CDD and CDF congeners; values ranged from 6.10 to 7.92. Mackay et al. (1992a) reviewed all published measured and estimated log K_{ow} values for eight tetra- through octa-substituted CDDs and seven tetra- through octa-substituted CDFs; recommended values were selected by Mackay et al. (1992a) for the eight CDDs and for five of the CDFs. The most definitive values chosen were either those selected by Mackay et al. (1992a), a directly measured value, or the most current derived value. Selected values reported for congeners within the various congener groups ranged as follows:

Congener Group	Log K_{ow}
TCDD	6.1 to 7.1
PeCDD	6.2 to 7.4
HxCDD	6.85 to 7.8
HpCDD	8.0
OCDD	8.2
TCDF	5.6 to 6.79
PeCDF	6.19 to 6.92
HxCDF	7.0
HpCDF	7.4
OCDF	8.0

The selected log K_{ow} values for the PCBs are similar to those reported for the CDDs and CDFs. The values range from 6.5 (measured) for 3,3',4,4'-TeCB to 7.71 (literature-estimate) for 2,3,3',4,4',5,5'-HpCB. The log K_{ow} values increase with an increase in the number of chlorine substituents.

Partition coefficient values were calculated for those compounds for which no measured data were reported in the literature by averaging the literature values within congener groups, as were done for vapor pressure and water solubility. Partition coefficients in the ranges of these reported values indicate that the substances tend to adsorb strongly to organic components in the soil and may bioconcentrate in those organisms exposed to the compounds.

2.4.5. Organic Carbon Partition Coefficient

The organic carbon partition coefficient (K_{oc}) is used in several exposure estimations in Volume 3. K_{oc} is used in the estimation of the adsorption partition coefficient, which describes the partitioning of contaminants between suspended sediment and the water column. K_{oc} is also used in estimating the concentration of contaminants in below ground vegetables grown in contaminated soil.

Log K_{oc} values for 2,3,7,8-TCDD have been measured in several studies. Lodge and Cook (1989) used contaminated sediments from Lake Ontario and distilled water in glass cylinders to measure the log K_{oc} of 2,3,7,8-TCDD. Log K_{oc} values ranged from 7.25 to 7.59. Jackson et al. (1986) used 10 contaminated soil samples in a batch extraction procedure to measure log K_{oc}. The average log K_{oc} of the 10 soils was reported as 7.39. Marple et al. (1987) used two uncontaminated soils spiked by two different methods with 2,3,7,8-TCDD to obtain the log K_{oc} value. The soil was stirred with water in 2-liter flasks. The log K_{oc} values ranged from 5.96 to 6.54 for both soils, with an average value of 6.40 for the red clay soil and 6.02 for the alluvial soil.

Puri et al., (1989) studied log K_{oc} of 2,3,7,8-TCDD with several other co-contaminants such as crankcase oils and surfactants. An average log K_{oc} value of 5.68 was reported for 2,3,7,8-TCDD in the presence of 0.01 percent surfactant. Walters and Guiseppi-Elie (1988) used several soils and water/methanol mixtures in a batch shake testing procedure to determine the log K_{oc} of 2,3,7,8-TCDD. The study resulted in a log K_{oc} value of 6.6.

Five studies for log K_{oc} of 2,3,7,8-TCDD were ranked number 1. The studies by Jackson et al. (1986) and Lodge and Cook (1989) had confirming values of 7.39 and 7.42, respectively. The studies by Walters and Guiseppi-Elie (1988), Walters et al. (1989), and Marple et al. (1987) had confirming values of 6.6, 6.66, and 6.4, respectively. The 6.6 value reported by Walters and Guiseppi-Elie (1988) was chosen by Syracuse Research Corporation (SRC) in the CHEMFATE Database (SRC, 1991) as the most definitive. This value was determined in a mixed solvent system, water and methanol; therefore, it is not considered as appropriate as a pure water equilibration system determined value. The values reported by Marple et al. (1987) and Walters et al. (1989) were determined in uncontaminated soil and with pure water; therefore, these values are selected as the most definitive for this document.

Definitive values were not selected for other congeners because of few measured data points and, oftentimes, considerable differences in the reported values for those congeners with reported values. The ranges of reported values are presented in Table A-1 in Appendix A.

2.4.6. Photo Quantum Yields

Photo quantum yields, good semi-quantitative measures of phototransformation efficiency (Yan et al., 1995), have been reported for several CDD/CDF congeners. No values were located for the dioxin-like PCBs.

Congener	Photo Quantum Yield (mole/einstein)	Reference
1,2,3,7-TCDD	5.42×10^{-4}	(Choudhry and Webster, 1989)
1,3,6,8-TCDD	2.17×10^{-3}	(Choudhry and Webster, 1989)
2,3,7,8-TCDD	2.2×10^{-3}	(Dulin et al., 1986)
2,3,7,8-TCDD	3.3×10^{-2}	(Rapaport and Eisenreich, 1984)
2,3,7,8-TCDD	1.62×10^{-2}	(Yan et al., 1995)
1,2,3,4,7-PeCDD	9.78×10^{-5}	(Choudhry and Webster, 1987)
1,2,3,4,7,8-HxCDD	1.10×10^{-4}	(Choudhry and Webster, 1987)
1,2,3,4,7,8-HxCDD	1.58×10^{-3}	(Yan et al., 1995)
1,2,3,4,6,7,8-HpCDD	1.53×10^{-5}	(Choudhry and Webster, 1987)
OCDD	2.26×10^{-5}	(Choudhry and Webster, 1987)
OCDD	1.25×10^{-3}	(Yan et al., 1995)
1,2,4,7,8-PeCDF	1.29×10^{-2}	(Choudhry et al., 1990)
1,2,3,4,7,8-HxCDF	6.96×10^{-4}	(Choudhry et al., 1990)

All quantum yields were measured in a water-acetonitrile solution at 313 nm, except those reported by Rapaport and Eisenreich (1984) which were measured in the vapor phase and those reported by Yan et al. (1995) which were carried out in a butanol/decane mixture. Yan et al. (1995) also examined the effect of co-contaminants (pentachlorophenol, naphthalene, phenanthrene, and anthracene) on the photoquantum yield of OCDD and 2,3,7,8-TCDD. The presence of the co-contaminants decreased the photoquantum yield at a degree dependent upon both the concentration and extinction coefficient of the co-contaminants.

Congener group averages were not calculated because photo quantum yields are very sensitive to chlorine position and also to the physical medium (e.g., vapor or dilute solution) and conditions (e.g., the solvent system) used in the experiments (Yan et al, 1995).

2.5. PHYSICAL CHEMICAL PROPERTIES - BROMINATED COMPOUNDS

Information on the physical and chemical properties of the polybrominated dioxins and furans is very limited and has not been compiled for this report.

2.6. ENVIRONMENTAL FATE - CHLORINATED COMPOUNDS

CDD/CDFs and dioxin-like PCBs have been found throughout the world in practically all media including air, soil, water, sediment, and biota. The widespread occurrence observed is not unexpected considering the numerous sources that have emitted these compounds into the atmosphere and the overall resistance of these chemicals to abiotic and biotic transformation. Consequently, CDD/CDFs and PCBs emitted to the atmosphere can be transported long distances in the atmosphere before they are deposited onto vegetation, soil, and water via dry and wet deposition.

As depicted in Figure 2-1, deposition onto vegetation and subsequent ingestion of that plant material by animals is hypothesized to be the primary mechanism by which CDD/CDFs enter the terrestrial/agricultural food chain. Deposition onto soil with subsequent erosion and runoff into water bodies with subsequent bioaccumulation by aquatic biota is believed to be the major pathway by which CDD/CDFs enter the aquatic food chain in most freshwater bodies. These two pathways are also expected to be major pathways for entry of dioxin-like PCBs into the terrestrial and aquatic food chains.

However, because PCBs are more mobile in the environment (i.e., greater vapor pressures and water solubilities) than CDD/CDFs, there will be greater inter-media transport of PCBs (e.g., greater volatilization from soil and water to air). In addition, because of the previous widespread use and disposal of PCBs, localized sources of contamination may dominate aquatic food chain sources in more water bodies than is the case for CDD/CDFs.

The growing body of literature from laboratory, field, and monitoring studies examining the environmental transport, transformation, and distribution of CDD/CDFs and dioxin-like PCBs has increased the understanding of the fate of these environmentally ubiquitous compounds. The purpose of this section is to summarize the key findings from the growing body of literature dealing with the environmental fate of CDD/CDFs and PCBs.

Figure 2-2 presents a conceptual diagram of the intermedia movement of CDD/CDFs and PCBs among the five major environmental media: air, soil, water, sediment, and biota. As will be discussed in this section, the primary mechanism currently believed to be responsible for the widespread occurrence of CDD/CDFs and PCBs is long range atmospheric transport and deposition onto vegetation and soil.

2.6.1. Environmental Fate of CDDs and CDFs

2.6.1.1. Summary

Because of their high lipophilicity and low water solubility, CDD/CDFs are primarily associated with particulate and organic matter in soil, sediment, and the water column. Current understanding of CDD/CDF behavior on atmospheric particulate matter is that there is a partitioning between the particles and the gas phase. The two key parameters controlling the phase in which a particular congener is predominantly found are the congener's vapor pressure and the atmospheric temperature. Congeners with higher vapor pressures (i.e., the less chlorinated congeners) are found to a greater extent in the gas phase. CDD/CDFs sorbed to soil exhibit little potential for significant leaching or volatilization once sorbed to particulate matter.

The available evidence indicates that CDDs and CDFs, particularly the tetra- and higher chlorinated congeners, are extremely stable compounds under most environmental conditions. The only environmentally significant transformation processes for these congeners are believed to be atmospheric photooxidation and photolysis of nonsorbed

species in the gaseous phase or at the soil or water-air interface. Several studies have, however, indicated that certain ligninolytic fungi can degrade these higher-chlorinated congeners and that anaerobic degradation in sediment may occur at a slow rate. To a large extent, these degradation processes involve dechlorination to less-chlorinated (and possibly more toxic) congeners.

Burial in-place or erosion of soil to water bodies appears to be the predominant fate of CDD/CDFs sorbed to soil. CDD/CDFs entering the water column primarily undergo sedimentation and burial with some uptake by aquatic biota. The ultimate environmental sink of CDD/CDFs is believed to be aquatic sediments. CDD/CDFs entering the atmosphere are removed either by photodegradation or by dry or wet deposition.

Vapor-phase dry deposition of CDD/CDFs onto vegetation is hypothesized to be the primary route of entry of CDD/CDFs into the terrestrial/agricultural food chain. Atmospheric deposition of CDD/CDFs onto land followed by runoff/erosion to water bodies is hypothesized to be the major route of entry of CDD/CDFs into the aquatic food chain of most freshwater bodies.

2.6.1.2. Transport Mechanisms in Air

Once released into the atmosphere, CDDs and CDFs can become widely dispersed throughout the environment by atmospheric transport and deposition. In an assessment of the atmospheric transport and deposition of CDDs and CDFs for EPA, Hites and Harless (1991) generated data and analyses that support the contention that background environmental levels and congener profiles of CDDs and CDFs in soils and sediment (i.e., higher rather than lower chlorinated congener patterns predominate) can be attributed, in large part, to the atmospheric transport and transformation of CDDs and CDFs released from combustion sources. More recently, Tysklind et al. (1993) reported the results of measurements of CDD/CDFs in the ambient air from a rural site in Sweden collected during 1989 and 1990. The highest concentrations of total CDD/CDFs were measured during sampling events with air masses coming with westerly to southerly winds, thus indicating long range transport. The congener profiles were found to vary depending on wind trajectories implicating source influences from industrialized and urbanized areas of Europe.

Deposition is a broad term defining a number of atmospheric phenomena, including the wet and dry deposition of CDD/CDF-contaminated airborne particulate matter onto soils and vegetation, and the wet and dry deposition of vapor-phase CDD/CDFs onto soils and vegetation. Mass-balance studies have been conducted in several countries in an effort to establish the mechanisms associated with the generation, transport, and environmental fate of CDD/CDFs. A wide range of estimated deposition rates have been developed in these studies. The variation in estimates may be attributed, in part, to the likely differences in precision and accuracy of the various sampling methods used, as well as the inherent difficulty in comparing results from differing collection devices. Table 2-4 presents a summary of some of the deposition rates generated by investigators in Sweden, the United Kingdom, Belgium, Germany and the United States. As noted in Table 2-4, deposition fluxes appear to be greater in urban areas than in rural areas.

A variety of methods have been developed by researchers in several countries for measuring dry and wet deposition of CDD/CDFs. However, because of the complexity of deposition as it occurs in the natural environment, all of these methods, with the possible exception of wet deposition monitoring techniques, have major drawbacks which limit their utility for generating data that provide a reliable and accurate measure of deposition as it naturally occurs. Methods have also been developed for measurement of total CDD/CDF concentrations in air; modifications to these methods have been developed that can enable consistent and reproducible measurements of particulate and vapor-phase ambient air concentrations. Mathematical models have also been developed to estimate dry and wet deposition rates. [Volume 3 provides a detailed discussion of these modeling techniques]. Because the current state of knowledge concerning deposition mechanisms/rates and methods to accurately measure deposition is not well-developed, the most effective program that could be deployed today to better understand deposition would consist of ambient air measurements coupled with specific deposition studies designed to improve the accuracy of deposition modeling.

Because of the importance of atmospheric deposition as a pathway for contamination of the terrestrial/agricultural food chain, the remainder of this section (i.e., Section 2.6.1.2) presents an overview discussion of three areas: (1) vapor/particle partitioning; (2) dry deposition processes relevant for CDD/CDF; and (3) wet deposition processes relevant for CDD/CDF.

2.6.1.2.1. Vapor/Particle (V/P) Partitioning. The relative importance of the various deposition processes (and associated phases) is related to congener-specific vapor/particle partitioning. Hites and Harless (1991), Hippelein et al. (1996), and others have demonstrated that partitioning of CDD/CDFs between the vapor and particle-associated phases occurs in the atmosphere. The key parameters controlling the phase in which a particular congener is found are the congener's vapor pressure, the atmospheric temperature, and the particulate matter concentration in the atmosphere. Congeners with higher vapor pressures (i.e., the less-chlorinated compounds) are found to a greater extent in the vapor phase. For a given congener, the fraction in the vapor phase increases with increasing ambient temperature and decreases with increasing particle concentration. A portion of the particle-associated compound appears to be freely exchangeable between the particulate and vapor phases. A second portion may be irreversibly sorbed or occluded by the particles and not in equilibrium with the gas phase.

A comprehensive review of the published literature addressing vapor/particle (V/P) partitioning of CDD/CDFs in stack gases and ambient air is provided in Volume 3. The Volume 3 review includes an evaluation of the results of stack testing data, ambient air sampling data, and theory rooted in basic physical chemistry that either imply, directly deduce, or theoretically calculate V/P partitioning. Table 2-5 presents a summary of the Volume 3 review of the ambient air monitoring studies. The most comprehensive set of partitioning data were collected by Hippelein et al. (1996); data were collected continuously over the course of 48 weeks at six urban sites on the outskirts of Augsburg, Germany, during 1992 and 1993.

A theoretical approach developed by Bidleman (1988) for predicting V/P partitioning of CDD/CDFs is described in detail in the Volume 3 review. Table 2-6 presents, for each of the 2,3,7,8-substituted CDD/CDFs, the percentage of mass predicted in Volume 3 using this theoretical approach to be in the particle phase under four airshed conditions: "clean continental," "average background," "background plus local sources," and "urban." From the review in Volume 3, the following conclusions were made:

- The stack test methods in use today to monitor and measure the concentration of CDD/CDFs emitted to the air from combustion sources have given inconclusive and contradictory V/P partitioning results and thus do not provide a credible basis, at

present, for determining V/P partitioning at the point of release. There is no consistent pattern to the interpretation of V/P based on where the CDD/CDF segregate in the instrument (e.g., the glass fiber filter or the XAD resin). Factors that may contribute to this inconsistent pattern are: the relatively long residence time spent traversing the stack interior; the location of the probe to the instrument in a relatively hostile environment of the hot combustion gas; the static temperature of the particulate filter caused by heating the particulate filter housing; and the fact that located between the particulate trap and the vapor trap is a condensing section consisting of glass tubing surrounded by an ice bath.

- The use of a high-volume ambient air sampler consisting of a glass fiber particulate filter (GFF) and polyurethane foam adsorbent trap (PUF) is a reliable method for the collection and retention of CDD/CDFs in ambient air. Because the sampler is not artificially heated or cooled, but is allowed to operate at ambient air temperatures, the method can be used to imply the V/P partitioning of CDD/CDFs in ambient air. This is accomplished by separately extracting and analyzing the GFF and PUF. However, the method may only give an approximate indication of the V/P ratio since mass transfer of CDD/CDF from the particulate matter on the GFF to the PUF cannot be ruled out. For example, it is possible that a portion of the CDD/CDFs that are sorbed to particulate matter captured by the filter may be volatilized and carried with the air flow to the PUF sorbent trap (blow-off effect). If this were to occur, the observed V/P ratio would be overestimated. Also, the GFF will collect particles $\geq$0.1 microns in diameter and, therefore, it is possible that smaller particles will pass through the GFF and be trapped in the PUF. If this does occur, the observed V/P ratio will be overestimated.

  There are currently no empirical data that demonstrate the magnitude of these effects or that these effects actually occur. However, the potential impact of particle breakthrough may be ascertainable, if it is assumed that the CDD/CDF congener group pattern is the same on all particle size fractions. This assumption is supported by the findings of Kaupp et al. (1994) who demonstrated that CDD/CDF congener group profiles were nearly identical in four particle size ranges (1.35 to 4.05 um; 0.45 to 1.35 um; 0.15 to 0.45 um; and $<$0.15 um) collected in a rural area of Germany during the summer of 1992. Thus, if OCDD is, as is typical, the dominant congener in the collected material on the GFF, then the mass of any other CDD/CDF on the PUF that may be due to particle breakthrough can be estimated by multiplying: (1) the ratio of that congener's mass on the GFF to the mass of OCDD on the GFF by (2) the mass of OCDD in the PUF.

- Neither the currently available monitoring techniques nor the available models necessarily give the "correct" V/P partitions. Until the state of knowledge of CDD/CDF partitioning in air is improved through development of improved monitoring devices and laboratory investigations of the kinetics and thermodynamics of CDD/CDF sorption, the theoretical construct described in Chapter 3 of Volume 2 is the recommended approach for estimating V/P partitioning of CDD/CDFs at this time. Key advantages to the theoretical approach are that it relies on current adsorption theory, considers the molecular weight and the degree of halogenation of the congeners, uses the boiling points and vapor

pressures of the congeners, and uses the availability of surface area for adsorption of atmospheric particles that correspond to a variety of ambient air shed classifications having variable particulate matter densities.

2.6.1.2.2. Dry Deposition. Dry deposition can involve two phases, dry particulate deposition and vapor phase deposition, the relative importance of which for a given congener is dependent primarily on the V/P partitioning. First, dioxin-like compounds associated with particulate matter can deposit by gravitational settling or turbulent diffusion. Secondly, dioxin-like compounds can be deposited by vapor-phase diffusion into the soil, vegetation, and the surface layer of water bodies. The rate at which atmospheric chemicals are deposited is termed the "deposition flux". The deposition flux is derived as the product of the concentration of the chemical in the vapor phase or on/in the particulate and the deposition velocity of the contaminated particles. The downward motion represented by deposition velocity is controlled by the gravitational settling velocity, atmospheric resistance, surface resistance and the atmospheric surface friction layer. The factors that most influence deposition flux can be divided into two types: (1) meteorological influences and (2) the properties of the chemical influencing it's V/P partitioning. A detailed list of the many factors that can affect dry deposition is shown in Table 2-7.

Dry Particulate Deposition. Dry particulate deposition is the best characterized of the dry deposition processes. As noted in Table 2-5, the vast majority of the atmospheric burden of hepta- and octa-chlorinated CDD/CDF (and, to a lesser extent, the burden of hexa- and penta-chlorinated congeners) is associated with particulate matter. As such, dry particulate deposition is a major mechanism for removal of these congeners from the atmosphere. The major factors controlling the transfer of particulate from some height above the surface through the surface layer down to the immediate vicinity of the receptor surface are the forces of gravity and turbulent diffusion. As a general rule, very large particles (i.e., greater than 20 μm) will be removed from the atmosphere fairly rapidly by the force of gravity (Kaupp et al., 1994). Particles less than 20 μm will be removed at a slower rate primarily by atmospheric turbulence and Brownian diffusion through the laminar sub-layer which often has a thickness of 10^{-1} to 10^{-2} cm. The deposition flux for these smaller particles is influenced by many factors, including: the distribution of particles

by diameter and density; the atmospheric turbulence; and the friction and morphology of the impacted ground and vegetative surfaces.

Few studies have been published that have attempted to measure only dry particulate deposition of CDD/CDFs. Koester and Hites (1992a) used inverted frisbees and flat glass plates to collect dry particulate deposition. The collectors were coated with mineral oil and then deployed uncovered (except during precipitation events) for exposure periods of several weeks. The mineral oil is removed from the frisbees/plates after the exposure period and analyzed for CDD/CDF content. The extent to which these devices may also be acting as vapor phase collectors is not thought to be significant but has not been tested. Similarly, the extent of photodegradation of collected CDD/CDFs is not thought to be significant but has not been tested. Hall and Upton (1988) had previously conducted wind tunnel studies of the particle collection efficiency of inverted frisbees and had found an overall collection efficiency of approximately 50 percent with efficiencies decreasing as wind speed increased and particle diameter decreased.

The deposition velocity of particulate matter containing CDD/CDFs onto various surfaces has not been well characterized and is a major source of uncertainty in modeling particulate deposition. Bidleman (1988) estimated that particulates with diameters ranging from 0.08 to 2 μm have deposition velocities that vary from 0.003 to 0.036 cm/sec. Coarser particulates (i.e., >2 μm) were estimated to have much higher deposition velocities, 0.5 to 2.5 cm/sec (Bidleman, 1988). From the results of their study with inverted frisbees and glass plates, Koester and Hites (1992a) calculated an average deposition velocity for particulate-associated CDD/CDFs of 0.2 cm/sec; calculated deposition velocities for the tetra- through octa-chlorinated congener groups ranged from 0.086 to 0.6 cm/sec. Trapp and Matthies (1995) estimated that the fine particulates (i.e., diameters of 0.1 to 1.0 μm) that are responsible for the long range transport of atmospheric particle bound pollutants have deposition velocities of about 0.01 cm/sec.

Dry Vapor-Phase Deposition. Although not as well characterized, several studies have concluded that the transfer of all non-hepta- and non-octa-chlorinated dioxin-like compounds to leafy vegetation is dominated by vapor phase deposition which involves the movement of vapor-phase dioxin from ambient air into leafy vegetation (Bacci, et. al., 1990; Gaggi and Bacci, 1985; McLachlan, et. al., 1995; Rippen and Wesp, 1993; Simonich and Hites, 1995). Dry particulate and wet deposition are believed to be the

dominant mechanisms by which vegetation and soil are exposed to hepta- and octa-chlorinated congeners. Vapor phase deposition directly onto soil is not believed to be a dominant process in most settings because soil is usually covered by vegetation or detritus which are likely to serve as more important exchange sites.

Major factors governing vapor-phase deposition include the ambient air concentration of CDD/CDFs, the exposed surface area of vegetation, the plant morphology/canopy density, and the air side resistance (i.e., a function of air turbulence which is dependent on wind speed and canopy structure). The latter two factors control, to a large extent, the vapor phase deposition velocity. Bidleman (1988) reported that vapor phase deposition velocities calculated from the results of field studies with Aroclors, p,p'-DDT, and chlordane ranged from 0.01 to 1.0 cm/sec. The limited studies that have modeled deposition of CDD/CDFs onto vegetation have employed deposition velocities of 0.5 cm/sec or higher. Trapp and Matthies (1995) used a default vapor phase deposition velocity of 0.5 cm/sec for modeling vapor phase deposition of CDD onto meadow vegetation. Smith et al. (1995) used a deposition velocity of 0.78 cm/sec for deposition of 2,3,7,8-TCDD onto tall grass. A deposition velocity of 0.5 cm/sec (calculated from the data of a ryegrass experiment) was used by McLachlan et al. (1995) to predict gaseous uptake of semivolatile organic compounds (such as CDD/CDFs and PCBs) by grass.

There are two principal applications for vegetation monitoring of gas phase deposition of CDD/CDFs: (1) monitoring short-term trends (i.e., week, month or season), and (2) long-term temporal trends (i.e., over the course of a year). To date, three methods have been employed for each of these two principal applications. Each method has its own advantages and disadvantages and each measures different components of total deposition.

Short-term monitoring methods include collection of pasture grass, grass from grass cultures, and passive collectors (e.g., McLachlan et al., 1995; McLachlan, 1995). These three types of methods differ in their ability to serve as measures of "true" deposition onto natural vegetation. However, the methods can be appropriate monitoring tools depending upon the objective(s) of the monitoring task at hand. Collection of pasture grass is easy and inexpensive and represents "true" deposition onto native pasture grass. However, it cannot be standardized and is a function of uncontrollable factors (i.e., weather, species present, and growth rate). Collection of grass from a grass culture can

be semi-standardized but it may not accurately represent "true" deposition on native vegetation. Grass cultures can be elaborate and relatively costly, and it may be difficult to replicate rate of growth across sites and times. Passive collectors are easy to deploy, inexpensive, and easily standardized. However, there are no accepted, standardized passive methods available at present and the results obtained are not likely to be representative of "true" deposition on native vegetation.

The long-term methods include collection of conifer needles, canopy fall, and leaf fall. Collection of conifer needles is easy, inexpensive, and can integrate an entire year's deposition. Although the use of pine needles as CDD/CDF passive biomonitors has been extensively reported in Europe, few studies have been reported to date in the United States (Safe et al., 1992; Fiedler et al., 1995). Disadvantages of this method include potential loss of some CDD/CDFs because of wax erosion from needles over the year. Also, the method may not be an appropriate technique for a multi-year monitoring program because the canopy structure of a conifer forest will change over the course of many years. That is, the aerodynamic properties of a conifer forest, and consequently the extent and nature of deposition, will differ significantly over a 10 or 20 year period.

Collection of canopy fall using vessels to collect leaf fall, dry deposition, and wet deposition integrates the total deposition under the canopy for the entire exposure period. It is maintenance intensive and the canopy structure may change over the course of many years. The method captures most gas phase deposition, but not direct gaseous deposition to the forest floor; deposition onto the forest floor is likely to be much smaller than the deposition to the canopy. Collection of leaf fall in deciduous is easy, inexpensive, and can be easily standardized. In conifer forests, because only a small fraction of total annual deposition is reflected in fallen needles, the collection vessels must catch the eroded needle waxes as well as fallen needles. Leaf fall collection will also include measurement of some wet and dry particulate deposition that is retained on the leaves (personal communication with Dr. Michael McLachlan, University of Bayreuth, July 1996).

Investigations into the role of conifer forests in removing CDD/CDFs from the atmosphere and the consequences for accumulation in soil have recently been reported (Horstmann et al., 1995; Horstmann and McLachlan, 1996). These researchers measured bulk CDD/CDF deposition in a nature spruce forest and in an adjacent clearing over a 1-year period. Litter fall samples were also collected in the forest. The annual deposition

flux of hepta- and octa-chlorinated CDD/CDFs was approximately equal in the clearing and in the spruce forest. However, the deposition flux of the lower chlorinated congeners was up to five times higher in the forest. During the warmest month of the year, the bulk deposition flux of some congener groups in the forest was up to 16 times higher than in the clearing. However, litter fall accounted for only 16 percent (OCDF) to 48 percent (TCDD) of total deposition in the forest, and canopy throughfall of wet or dry particulate deposition was demonstrated not to be responsible for the large forest deposition rates observed. The researchers hypothesize that the high deposition rates are due to dry gaseous deposition onto conifer needles followed by shedding or erosion of needle waxes, which may be enhanced during hot weather.

2.6.1.2.3. Wet Deposition. In the case of wet deposition, dioxin-like compounds can enter the soil and water and impact on the vegetation in one of two phases: either dissolved in the precipitation or associated with particulate material scavenged by the precipitation. Over the long term, wet deposition processes are believed to dominate dry deposition in terms of total mass deposition of CDD/CDFs. Wet deposition is the primary mechanism responsible for removal of small particulates from the atmosphere. For removal of particulate-associated chemicals, wet deposition flux is the product of the particulate scavenging ratio and the chemical concentration on/in various particulate size fractions. The scavenging ratio is calculated as the product of the scavenging coefficient and precipitation rate. The scavenging coefficient depends on the size distribution of the particulates and the intensity and form of precipitation (i.e., liquid or frozen). Scavenging coefficients have been developed for varying types and intensities of precipitation relative to different particle diameters based on measurements of scavenging of aerosol particles during precipitation events.

CDDs and CDFs are removed physically from the atmosphere by wet deposition (i.e., scavenged by precipitation), particle dry deposition (i.e., gravitational settling of particles), and gas-phase dry deposition (i.e., sorption of CDD/CDFs in the vapor phase onto plant surfaces) (Marklund et al., 1990; Rippen and Wesp, 1993; Welsch-Pausch et al., 1993). Precipitation can be very effective in removing CDDs and CDFs from the atmosphere. Listed in Table 2-8 are the average precipitation scavenging ratios for congener groups reported by Hites and Harless (1991) and Koester and Hites (1992a) for

Bloomington, Indiana, and Indianapolis, Indiana, respectively. The scavenging ratio is the ratio of the concentration of a chemical in precipitation (rain in these studies) to the concentration in the atmosphere and is a measure of the effectiveness of rain in removing the chemical. Also listed in Table 2-8 are the percentages of congener groups scavenged as particles in rain rather than as dissolved solutes in rain. Total rain scavenging ratios ranged from 10,000 to 150,000; hepta- and octa- CDDs (i.e., the congeners most strongly associated with particulates) were scavenged most efficiently.

Wet deposition samplers have been used to collect both rainfall and snow samples. Several types are available, including those which are equipped with photovoltaic cells or moisture sensors, which selectively open and close the sampler in response to weather changes. Precipitation samplers not equipped with moisture sensors are uncovered at all times and thus are subject to bias (i.e., due to collection of dryfall particles as well as wet particulate deposition). Wet deposition collectors have been designed to measure total wet deposition (i.e., dissolved and particulate-associated deposition combined) and dissolved deposition and particulate deposition separately.

The Bergerhoff method is a standard method specified in the German Clean Air Act for monitoring CDD/CDF deposition. The method consists of deploying open-mouth jars for a one month exposure period. Ten Bergerhoff jars have a combined sample collection area of about 0.1 m^2. The Bergerhoff method was designed to collect wet and dry particulate deposition. The samplers have the potential for evaporative loss of CDD/CDFs both in the collected wet and dry deposition. The addition of a water/solvent solution to the jar is reported to minimize this potential problem. The samplers are not thought to be collecting gas phase CDD/CDFs but no confirmatory testing has been reported.

2.6.1.2.4. Mechanisms for Entry of CDD/CDFs into the Terrestrial Food Chain

Air to Plant to Animal Hypothesis. Based on information currently available, the primary mechanism by which CDD/CDFs appear to enter the terrestrial food chain is by vapor phase atmospheric deposition (and to a lesser extent, dry particulate deposition) onto plant surfaces which are subsequently ingested by animals (e.g., cattle). This hypothesis was originally advanced by McLachlan and Hutzinger (1990). Deposits onto the soil can enter the food chain via direct ingestion (e.g., soil ingestion by earthworms, fur preening by burrowing animals, incidental ingestion by grazing animals, etc).

CDD/CDFs in soil can also become available to plants and thus enter the food chain by volatilization and vapor sorption or particle resuspension and adherence to plant surfaces. Although CDD/CDFs in soil can adsorb directly to underground portions of plants, uptake from soil via the roots into above ground portions of plants is thought to be insignificant (McCrady et al., 1990).

Support for this air-to-food hypothesis is provided by Hites and Harless (1991) who concluded that "background environmental levels of PCD/F are caused by PCD/F entering the environment through the atmospheric pathway." Their conclusion was based on demonstrations that the congener profiles in lake sediments could be linked to congener profiles of combustion sources. Further argument supporting this hypothesis is offered below:

- Numerous studies have shown that CDD/CDFs are emitted into the air from a wide variety of sources and that CDD/CDFs can be commonly detected in air at low concentrations. (See Chapter 3 and Volume 1.)

- Studies have shown that CDD/CDFs can be measured in wet and dry deposition in most locations including remote areas (Koester and Hites, 1992a; Rappe, 1991).

- Numerous studies have shown that CDD/CDFs are commonly found in soils throughout the world. (See Chapter 3.) Atmospheric transport and deposition is the most plausible mechanism that could lead to this widespread distribution.

- Models of the air-to-plant-to-animal food chain have been constructed. Exercises with these models show that measured deposition rates and air concentrations can be used to predict food levels that are similar to levels actually measured in food (Travis and Hattemer-Frey, 1991; also Volume 3).

- Alternative mechanisms of uptake into food appear less plausible:

    - Uptake in food crops and livestock from water is minimal due to the hydrophobic nature of these compounds. Travis and Hattemer-Frey (1987, 1991) estimate water intake accounts for less than 0.01 percent of the total daily intake of 2,3,7,8-TCDD in cattle. Experiments by McCrady et al. (1990) show very little uptake in plants from aqueous solutions.

    - Relatively little impact on the general food supply is expected from soil residues that originate from site-specific sources such as sewage sludge and other waste disposal operations. Sewage sludge application onto agricultural fields is not currently a widespread practice in the United States. Waste disposal operations can be the dominant source of CDD/CDFs in soils

at isolated locations such as Times Beach, but are not sufficiently widespread to explain the ubiquitous nature of these compounds.

- The release of CDD/CDFs to the environment from the use of pesticides contaminated with CDD/CDFs is believed to have declined in recent years; however, the past and current impact of pesticide use on CDD/CDF levels in the food supply is uncertain. CDD/CDFs have been associated with certain phenoxy herbicides most of which are no longer produced or have restricted uses. EPA has issued data call-ins requiring certain pesticide manufacturers to test their products for CDD/CDF content. The responses, so far, indicate that current levels in these products are below or near the limit of quantitation. (See Volume 1.)

- Current CDD/CDF levels in food resulting from the use of bleached paper products containing CDD/CDFs appears to be minimal. In the early 1980s, testing showed that CDD/CDFs could migrate from paper containers into food. Current CDD/CDF levels in paper products are now much lower than in the early 1980s. Also, testing of products such as milk and beef prior to packaging has shown detectable levels which cannot be attributed to the packaging. (See Chapter 3.)

A related issue is whether the CDD/CDFs in food result more from current or past emissions. Sediment core sampling indicates that CDD/CDF levels in the environment began increasing around the turn of the century, but also that CDF levels have been declining since about 1980 (Smith et al., 1992). Thus, CDD/CDFs have been accumulating for many years and may have created reservoirs that continue to impact the food chain. Researchers in several countries have attempted to compare known emissions with deposition rates. All of these studies suggest that annual atmospheric depositions exceed annual emissions by a factor of 2 to 10. One possible explanation for this discrepancy between source emissions and deposition may be that volatilization or particle resuspension from these reservoir sources followed by atmospheric scavenging is responsible. These mass balance studies are highly uncertain, and it remains unknown how much of the food chain impact is due to current vs past emissions.

Plant Accumulation Models. McLachlan (1995) presents a simple "scavenging" approach for predicting grass concentrations from air concentrations. He suggests that grass scavenges the equivalent of 9 m^3 or air per gram of grass, and that corn scavenges 4.5 m^3 of air per gram of corn. These scavenging ratios were empirically derived from a set of monitoring data including air, pasture, and corn samples. CDD/CDF concentrations

in grass can be estimated by multiplying the air concentration by this scavenging coefficient of 9. McLachlan (1995) suggests that this simple scavenging coefficient would work with all CDD/CDF congeners since the deposition velocities of vapor and particle bound CDD/CDF appear to be similar.

EPA has developed an air-to-leaf transfer approach to estimate the concentration of CDD/CDFs in vegetation resulting from dry and wet deposition. The EPA approach, fully described in Volume 3, was developed from field test data. The approach is summarized below followed by a brief description of an alternative approach (the deposition velocity approach) recently applied to CDD/CDFs by Smith et al. (1995) and Trapp and Mattheis (1995).

EPA Empirical Air-to-Leaf Approach. Two processes, air-borne vapor phase absorption and air-borne particle deposition, are assumed to contribute to above ground vegetation concentrations:

$$C_{abv} = C_{vpa} + C_{ppa} \qquad \text{(Eqn. 2-1)}$$

where:

C_{abv} = concentration in above-ground vegetation, expressed on a dry weight basis (pg/g)
C_{vpa} = contribution of concentration due to vapor-phase absorption or airborne contaminants (pg/g)
C_{ppa} = contribution of concentration due to wet plus dry deposition of contaminated particulates onto plant matter (pg/g)

The algorithm estimating plant concentrations as a function of vapor-phase air concentrations, C_{vpa}, is:

$$C_{vpa} = \frac{B_{vpa} \; C_{va} \; VG_{ag}}{d_a} \qquad \text{(Eqn. 2-2)}$$

where:

C_{vpa} = contribution concentration due to vapor-phase absorption or airborne contaminants (pg/g)

B_{vpa} = mass-based air-to-leaf biotransfer factor, [(pg contaminant/g plant dry)/(pg contaminant/g air)]
C_{va} = vapor-phase concentration of contaminant in air (pg/m^3)
VG_{ag} = empirical correction factor which reduces vegetative concentrations considering that B_{vpa} was developed for transfer of air-borne contaminants into leaves rather than into bulky above ground vegetation
d_a = density of air (1,190 g/m^3)

The steady state solution for plant concentrations attributed to wet plus dry particle deposition, C_{ppa}, is:

$$C_{ppa} = \frac{F_p}{k_v Y_j} \quad \text{(Eqn. 2-3)}$$

where:

C_{ppa} = vegetative concentration due to settling of contaminated particulates onto plant matter (pg/g)
F_p = unit contaminant wet plus dry deposition rate onto plant surfaces (pg/m^2-yr)
k_v = first-order dissipation constant (1/yr)
Y_j = dry matter yield of crop j (g/m^2)

The non-steady state solution has an additional term in the numerator of Equation 2-3, $1\text{-}e^{(-kw\ t)}$, where t is the time to harvest or removal by grazing. Given that the k_v is relatively large (i.e., a relatively short half-life on the order of weeks), and the growing period for vegetation of concern can be weeks to months, this additional term reaches unity quickly, so a steady state solution is justified. The total deposition rate onto plants, F_p , is given as:

$$F_p = C_{pa} (V_d I_j + RN R_w W_p I_j) \quad \text{(Eqn. 2-4)}$$

where:

F_p = unit contaminant wet plus dry deposition rate onto plant surfaces (pg/m^2-yr)
C_{pa} = air-borne particulate phase contaminant concentration (pg/m^3)

V_d = deposition velocity (m/yr)
I_j = fraction of particulates intercepted by crop j during deposition
RN = annual rainfall (m/yr)
R_w = fraction of particles retained on vegetation after rainfall
W_p = scavenging coefficient (unitless)

The major uncertainties of this modeling approach are:

- Vapor/particle partitioning: The V/P partitioning modeling approach (i.e., Junge-Pankow model) yields different partitioning ratios than suggested by the results of some monitoring studies (i.e., monitoring suggests a greater percentage in the vapor phase). The model could be inaccurate or the monitoring data could be biased to vapor (i.e., blow-off potential).

- Vapor transfers to vegetation: The basis for the vapor-phase biotransfer factors (B_{vpa}) is the research performed Welsch-Pausch et al. (1995). There is some uncertainty that the Welsch-Pausch experiments may not be representative of field situations (e.g., pots were raised off the ground, and the grass was a dense monoculture) and that more typical field situations (e.g., at ground level with varied vegetation of lesser density) may lead to lower vapor-phase transfer factors. However, because the vapor phase transfer factor is also a function of the length of exposure, grass that is several months old may have higher levels than the grass used by Welsch-Pausch et al. (1995).

- Particle deposition: There is uncertainty surrounding the following factors: R_w (fraction retained on vegetation from wet deposition), the weathering half-life on vegetation, absorption of particulate-associated dioxin by vegetation, and the particle deposition velocity.

Deposition Velocity Approach for Vapor Phase CDD/CDFs. This alternative approach is based on a transfer velocity (or conductance) term, a plant dissipation term, and a plant yield term as shown in Equation 2-5. The approach is exactly analogous to the EPA approach for modeling particle phase deposition. This approach has been described and parameterized for vapor phase 2,3,7,8-TCDD impacts to grassy plants in two articles, Trapp and Matthies (1995) and Smith et al. (1995). The steady state solution for the transfer velocity approach is given as:

$$C_{vpa} = \frac{F_v}{k_v \, Y_j} \qquad \text{(Eqn. 2-5)}$$

where:

C_{vpa} = plant concentration due to vapor-phase transfer (pg/g dry weight)
F_v = deposition of vapor-phase congener (pg/m^2-day)
k_v = first-order dissipation constant (day^{-1})
Y_j = yield of crop j (g/m^2)

Like the solution for particle phase deposition to plants, the non-steady state solution for Equation (2-5) has an additional term in the numerator, $1\text{-}e^{(-kv\ t)}$, where t is the time to harvest or removal by grazing. Both authors who applied this approach assumed a half-life for vapor phase dioxins on plants on the order of days to weeks. Because the "time to harvest" for grasses is also on the order of days to weeks, the additional term reaches unity quickly and again a steady state solution is justified.

The two articles evaluated do diverge at this point. The Trapp and Matthies (1995) approach is actually a comprehensive approach involving particle phase impacts and soil to plant impacts. Their analysis suggests vapor phase impacts to foliar vegetation dominate for 2,3,7,8-TCDD. They also present their solution in a more generalized fashion by having a volume term in the denominator of Equation 2-5 instead of a plant yield term; the volume term is easily converted to a mass (or yield) term with a plant density factor. Their solution for F_v is:

$$F_v = A \; g \; C_{va} \; 86400 \qquad \text{(Eqn. 2-6)}$$

where:

F_v = deposition of vapor-phase congener (pg/m^2-day)
A = leaf area index (m^2 leaf area/m^2 ground area)
g = conductance (m/sec)
C_{va} = vapor phase air concentration (pg/m^3)
86400 = conversion factor (sec to days)

Trapp and Matthies (1995) used a default value of 0.1 cm/sec for the conductance term, g, when modeling the deposition of 2,3,7,8-TCDD onto meadow grass. The appropriate value to use for conductance for a given chemical depends upon the plant species, the

environmental conditions, and the lipophilicity of the vapor phase chemical. The possible range reported by Trapp and Matthies (1995) is 0.01 to 0.5 cm/sec with the appropriate value increasing as lipophilicity increases. Trapp and Matthies (1995) used a value of 5 for the leaf area index, A, in their TCDD modeling exercise. The product of the A term and the g term (i.e., 0.5 cm/sec) is analogous to a deposition velocity.

Smith et al. (1995) estimate the F_v as a multiplication of the vapor phase air concentration, C_{va} (pg/m^3), the transfer velocity, V_t, (cm/sec), and the plant interception fraction (unitless). They state that the transfer velocity is represented as the inverse of the sum of the resistances to transfer to the plant surface as:

$$V_t = \frac{1}{R_a + R_b + R_c} \qquad \text{(Eqn. 2-7)}$$

where:

V_t = transfer velocity (cm/sec)
R_a = atmospheric resistance (sec/cm) a function of vertical turbulent transport
R_b = surface boundary layer resistance (sec/cm) a function of molecular diffusivity
R_c = plant canopy/leaf resistance (sec/cm) a function of vegetative density, stomatal uptake, surface effects, and humidity

Smith et al. (1995) assumed the following reasonably conservative resistance values for deposition of 2,3,7,8-TCDD onto a flat open area with tall grass under neutral atmospheric stability conditions: R_a = 0.4 sec/cm; R_b = 0.38 sec/cm; and R_c = 0.5 sec/cm. The resulting transfer velocity is 0.78 cm/sec.

The deposition velocity approach is not uniform among researchers, and has the two key uncertain quantities: the velocity itself (termed V_t by Smith et al. (1995) and estimated as gA by Trapp and Matthies (1995)) and the plant degradation term - assigned values ranging by a factor of three by the two research efforts. The companion document to this report (i.e., Volume 3) provides a detailed comparison of the empirical EPA model, the Trapp and Matthies (1995) model, and the Smith et al. (1995) model.

2.6.1.3. Transport Mechanisms in Soil

Upon deposition of CDD/CDFs onto soil or plant surfaces, there can be an initial loss due to photodegradation and/or volatilization. The extent of initial loss due to volatilization and/or photodegradation is difficult to predict and is controlled by climatic factors, soil characteristics, and the concentration and physical form of the deposited CDD/CDFs (i.e., particulate-bound, dissolved in solvent, etc.) (Freeman and Schroy, 1989; Paustenbach et al., 1992; Nicholson et al., 1993). For example, observations from the Seveso incident indicated that the levels of 2,3,7,8-TCDD aerially deposited on the soil surface decreased substantially in the first six months (diDomenico et al., 1982) but that rate of disappearance then slowed by over two orders of magnitude (diDomenico et al., 1990). Nash and Beall (1980) reported that 12 percent of the 2,3,7,8-TCDD applied to bluegrass turf as a component (7.5 ppm concentration) of an emulsifiable Silvex concentrate volatilized over a period of 9 months. Schwarz and McLachlan (1993) observed no significant changes in CDD/CDF concentrations in sewage sludge amended soil that was exposed to natural sunlight for six weeks in the late summer/early fall in Germany. Similarly, Cousins et al. (1996) detected no volatilization from sludge-amended soils through which air was pumped for 30 days.

Although few studies have evaluated quantitatively the transport of soil-bound CDD/CDFs, the very low water solubilities, high K_{oc}s, and persistent nature of these chemicals indicate that erosion of soil to water bodies may be the dominant surface transport mechanism for CDD/CDFs sorbed to soil in settings where erosion is possible (Paustenbach et al., 1992; Nicholson et al., 1993). Because of their very low water solubilities and vapor pressures, CDD/CDFs below the soil surface (i.e., below the top few millimeters) are strongly adsorbed and show little upward or downward vertical migration, particularly in soils with a high organic carbon content (Yanders et al., 1989). Freeman et al. (1987) found no statistically meaningful changes in the concentration profile of 1,2,7,8-TCDD in the top 1 cm of Time Beach Soil over a 16-month period, with the exception of the top 3 mm of soil exposed to water and sunlight in which 50 percent reduction in 2,3,7,8-TCDD concentration was observed. In addition, the more chlorinated congeners do not show any significant degree of degradation below the soil surface.

Although for several years it was believed that near-surface (i.e., the top 1cm) CDD/CDFs could volatilize slowly to the surface (Freeman and Schroy, 1985), recent

research has indicated that CDD/CDFs, particularly the tetra and higher chlorinated congeners, show little or no movement upward or downward in the subsurface unless surfactants or a carrier such as waste oil or diesel fuel is present to act as a solvent (Kapila et al., 1989; Puri et al., 1989; Puri et al., 1990; Yanders et al., 1989; Schramm et al., 1995). For example, Palausky et al. (1986) injected 2,3,7,8-TCDD dissolved in various organic solvents into soil columns to determine the extent of vapor phase diffusion; little movement due to volatilization was observed unless the soil was incubated at 40°C. However, laboratory studies have shown that 2,3,7,8-TCDD moves readily through soil with waste oil components and that mobility can also be enhanced by the presence of surfactants such as sodium lauryl sulfate (Yanders et al., 1989; Puri et al., 1989; Schramm et al., 1995). Overcash et al. (1991) developed a model that considers diffusive transport of 2,3,7,8-TCDD in solvents and takes into account the rate of adsorption and desorption of 2,3,7,8-TCDD from the soil particles.

Paustenbach et al. (1992) reviewed many major published studies on dioxin persistence in soil and concluded that 2,3,7,8-TCDD probably has a half-life of 25 to 100 years in subsurface soil and 9 to 15 years at the soil surface (i.e., the top 0.1 cm). Several major studies reviewed by Paustenbach et al. (1992) and additional recent studies are summarized below. Some of these recent studies have concluded that the binding of dioxin-like compounds to soil approaches irreversibility over time due to the encapsulation of the compounds in soil organic and mineral matter (Puri et al., 1989; Puri et al., 1992; Adriaens and Grbic-Galic, 1992).

McLachlan et al. (1996) presented data on CDD/CDF persistence in a sludge-amended soil sampled from a long-term field experiment started in 1968. Over 50 percent of the CDD/CDFs present in the soil in 1972 were still present in 1990. The concentrations of all congeners were observed to decrease gradually and in the same manner over this time, indicating that either physical loss of material from the experimental plot had occurred or all congeners had undergone a uniform reduction in extractability over time. Half-lives for the disappearance of CDD/CDFs from the sludge-amended soil after 1972 were on the order of 20 years. These half-lives were believed by McLachlan et al. (1996) to principally reflect physical removal rather than degradation.

Young (1983) conducted field studies on the persistence and movement of 2,3,7,8-TCDD during 1973-1979 on a military test area that had been aerially sprayed

with 73,000 kg of 2,4,5-T during the period 1962-1970. TCDD levels of 10 to 1,500 ng/kg could be found in the top 15 cm of soil 14 years after the last application of herbicide at the site. Although actual data were not available on the amount of 2,3,7,8-TCDD originally applied as a contaminant of the 2,4,5-T, best estimates indicated that less than one percent of the applied 2,3,7,8-TCDD remained in the soil after 14 years. Photodegradation at the time of and immediately after aerial application was believed by Young (1983) to be responsible for most of the disappearance. However, once incorporated into the soil, the data indicated a half-life of 10 to 12 years.

Orazio et al. (1992) studied the persistence of di- to octa-chlorinated CDDs and CDFs in sandy loam soil held in laboratory columns under water-saturated soil conditions for a period of 15 months. Measurable upward movement was reported only for the dichlorofurans and dichlorodioxins. Downward movement was only noticeable for the dichloro- and trichloro-congeners. The mobility of the CDDs and CDFs was not significantly affected by co-contaminants (i.e., pentachlorophenol and creosote components) present at concentrations as high as 6,000 mg/kg. As much as 35 percent loss of the di- and trichloro-congeners due to degradation was observed; no significant degradation of the tetra- through octa-chlorinated congeners was reported (Orazio et al., 1992).

Hagenmaier et al. (1992) collected soil samples around two industrial plants in Germany in 1981, 1987, and 1989 at the same site and from the same depth, using the same sampling method. There was no indication (within the limits of analytical accuracy (+/- 20 percent)) of appreciable loss of CDDs and CDFs by vertical migration, volatilization, or degradation over the 8-year period. Also, there were no significant changes in the congener distribution pattern (i.e., tetra- through octa-) over this time period.

Yanders et al. (1989) reported that 12 years after oil containing 2,3,7,8-TCDD was sprayed on unpaved roads at Times Beach, Missouri, no dioxin was discovered deeper than 20 cm. However, these roads were paved about 1 year after the spraying episode, thus preventing volatilization to the atmosphere. Yanders et al. (1989) excavated this soil and placed the soil in bins located outdoors, subject to the natural conditions of sunlight and precipitation. They reported no appreciable loss nor vertical movement of 2,3,7,8-TCDD from the soil, even in the uppermost sections, during a 4-year study period. Puri et

al. (1992) reported no migration or loss of 1,2,3,4-TCDD, 1,2,3,7,8-PeCDD, OCDD, and OCDF from samples of this soil which were examined for 2 years in controlled laboratory column experiments.

Hallett and Kornelson (1992) reported finding 2,3,7,8-TCDD at levels as high as 20 pg/g in the upper 2 inches of soil obtained from areas of cleared forest in New Brunswick, Canada, where the pesticides 2,4-D and 2,4,5-T had been applied in one or more applications 24 to 33 years earlier.

Pereira et al. (1985) reported contamination by CDDs of the sand and gravel aquifer underlying unlined surface impoundments at a wood-treatment facility that had utilized creosote and pentachlorophenol. CDDs migrated both vertically and horizontally in the subsurface. Puri et al. (1992), using soil column experiments in the laboratory, demonstrated that pentachlorophenol and naphthalene and methylnaphthalene (components of creosote) readily transported CDD/CDFs through soil. Puri et al. (1989) and Kapila et al. (1989) demonstrated that application of waste oil and anionic surfactant solutions to field and laboratory columns of Times Beach soil can move 2,3,7,8-TCDD through soil. Walters and Guiseppe-Elie (1988) showed that methanol/water solutions (1g/L or higher) substantially increase the mobility of 2,3,7,8-TCDD in soils.

2.6.1.4. Transport Mechanisms in Water

The dominant transport mechanism for removal of CDD/CDFs from the water column is believed to be sedimentation and, ultimately, burial in sediments. Sediment resuspension and remobilization of CDD/CDFs will vary on a site-by-site basis depending on the nature and extent of physical processes (e.g., winds/waves/currents) and biological processes (disturbance by benthic organisms) (Fletcher and McKay, 1992).

Even though CDD/CDFs have very low vapor pressures, they can volatilize from water. However, volatilization is not expected to be a significant loss mechanism for the tetra- and higher chlorinated CDD/CDFs from the water column under most non-spill scenarios. Podoll et al. (1986) calculated volatilization half-lives of 15 days and 32 days for 2,3,7,8-TCDD in rivers and ponds/lakes, respectively. Broman et al. (1992) used measured concentrations of CDD/CDFs in ambient air (gaseous phase) and in Baltic Sea water (truly dissolved concentrations) to calculate the fugacity gradient over the air-water

interface. The fugacity ratios obtained indicated a net transport from air to water (ratios between 0.4 and 0.004).

Aquatic organisms can bioaccumulate significant levels of CDD/CDFs. Although the mass of CDD/CDFs in the biota in a given water body will account for only a small fraction of the total mass of CDD/CDFs in that water body (Mackay et al., 1992a), these bioaccumulated CDD/CDFs have entered the aquatic food chain and can lead to potentially significant human and wildlife exposures and cause sensitive fish species to be at increased risk (U.S. EPA, 1993).

2.6.1.4.1. Sorption to Particulates and Sedimentation

Most CDD/CDFs entering the aquatic environment are associated with particulate matter (i.e., dry and wet deposition of atmospheric particles, eroded soil/stormwater runoff solids, and solids in municipal and industrial discharges) and are likely to remain sorbed to the particulate matter once in the aquatic environment. Recent studies have demonstrated that dissolved CDD/CDFs entering the aquatic environment will, like other lipophilic, low water solubility organic compounds, partition to suspended solids or dissolved organic matter such as humic substances.

Muir et al. (1992) and Servos et al. (1992) recently reported that 48 hours after the addition of 2,3,7,8-TCDF, 1,3,6,8-TCDD, and OCDD in a sediment slurry to natural lake water/sediment limnocorrals, between 70 and 90 percent had partitioned to suspended particulates. The proportion freely dissolved in water ranged from <2 percent for 2,3,7,8-TCDF and OCDD to 10 to 15 percent for 1,3,6,8-TCDD. The remainder was associated with dissolved organic substances.

Broman et al. (1992) analyzed water collected from nine sampling points in the Baltic Sea selected to be representative of background levels. The concentration of particle-associated (>0.45mm) total CDD/CDFs varied between 0.170 and 0.390 pg/L with an average concentration of 0.230 pg/L (or 66 percent of total CDD/CDFs). The total CDD/CDF concentration of the "apparently" dissolved fraction varied between 0.036 and 0.260 pg/L with an average concentration of 0.120 pg/L (or 34 percent of the total). Subsequent calculations estimated that, on average, only 0.070 pg/L of the "apparently" dissolved CDD/CDFs were truly dissolved.

Servos et al. (1992) reported that the 1,3,6,8-TCDD and OCDD added as a sediment slurry to lake limnocorrals rapidly partitioned/settled to surficial sediments where they persisted over the 2 years of the study. The half-lives of 1,3,6,8-TCDD and OCDD in the water column were reported as 2.6 and 4.0 days, respectively. Based on sediment trap and mixed surface layer studies of the Baltic Sea, Broman et al. (1992) report that the mass of CDD/CDFs in the mixed surface layer at any moment represents about 1 percent of the total flux of CDD/CDFs to the sediment annually; this implies little recirculation of these compounds within the water column of the Baltic Sea. Broman et al. (1992) also reported that the concentration of CDD/CDFs in settling solids (i.e., sediment trap collected material) is approximately one order of magnitude greater than the concentration in suspended particulates. They attributed this elevated concentration to the capacity of settling solids to scavenge the dissolved fraction as the solids settle through the water column. Similar findings have been reported elsewhere (e.g., Baker et al., 1991) for PCBs and PAHs in the Great Lakes.

2.6.1.4.2. Bioaccumulation

Fish and invertebrates can strongly bioaccumulate 2,3,7,8-substituted CDD/CDFs, although the benthic and pelagic pathways by which the accumulation occurs are not well understood. Organisms have been shown to accumulate CDD/CDFs when exposed to contaminated sediments and also to bioconcentrate CDD/CDFs dissolved in water. However, because most CDD/CDFs in the water column and sediment are associated with particulate matter and dissolved organic matter, the accumulation observed in the environment may be primarily food chain-based starting with uptake by benthic organisms (e.g., mussels, chironomids) directly from sediment pore waters and/or by ingestion or filtering of contaminated particles. Those organisms consuming benthic organisms (e.g., crayfish, suckers) would then pass the contaminants up the food chain (Muir et al., 1992; Fletcher and McKay, 1992; U.S. EPA, 1993).

A thorough review of the concepts and available information on the bioaccumulation of 2,3,7,8-substituted CDD/CDFs is presented in U.S. EPA (1993) and U.S. EPA (1995). A brief overview of the material presented in these reports is provided in the remainder of this section.

Bioconcentration. For aquatic organisms, bioconcentration refers to the net accumulation (i.e., intake less elimination and metabolic transformation) of a chemical resulting from direct uptake from the water by gill membranes or other external body surfaces. A bioconcentration factor (BCF) is the ratio (in L/kg) of a chemical's concentration in the tissue of an aquatic organism to its concentration in the ambient water (U.S. EPA, 1993; 1995):

$$BCF = \frac{C_a}{C_w} \qquad \text{(Eqn. 2-8)}$$

where:

C_a = concentration of the chemical in the aquatic biota

C_w = concentration of the chemical in the ambient water

BCFs are measured in laboratory experiments. To be of most use in predicting bioaccumulation in natural settings, BCFs should be determined under steady-state conditions (i.e., conditions under which the concentrations in the biota and other ambient water are stable over a period of time). For highly hydrophobic chemicals like CDD/CDFs, steady-state takes a long time to reach and often may not be reached in laboratory experiments particularly with larger organisms which tend to have slower uptake rates and longer half-lives for elimination. Also, for highly hydrophobic compounds, a significant fraction of the chemical concentration in the water can be associated with suspended particles and dissolved organic matter and be less available for uptake by the organism.

In general, BCFs for a given species (particularly BCFs calculated using dissolved chemical concentrations rather than total water concentrations) are expected to be largely independent of site water characteristics (U.S. EPA, 1993). For hydrophobic compounds, the lipid component of an organism is believed to dominate partitioning of the chemical between the organism and water. Therefore, it is often useful to express BCFs on the basis of organism lipid content in order to reduce variability among whole weight BCFs reported for species differing in lipid content.

The expected equilibrium values for steady-state BCFs (lipid content basis) for 2,3,7,8-substituted CDD/CDFs are the corresponding K_{ow} values. However, because most reported BCFs for CDD/CDFs are calculated on the basis of total water concentrations, the

reported BCFs are significantly less than these values. U.S. EPA (1993) presents a compilation of measured steady-state BCFs for 2,3,7,8-TCDD. The log BCFs vary by more than an order of magnitude (4.91 to 6.63 on a lipid content basis; 3.97 to 5.20 on a whole body basis). This variability is likely due to incomplete characterization of exposure concentrations or experimental shortcomings, including partitioning onto organic matter in test systems, oversaturation of the chemical in water, and time-varying concentrations in static systems (U.S. EPA, 1993). Table 2-9 presents log BCF values reported by various researchers for CDD/CDFs.

Bioaccumulation. For aquatic organisms, bioaccumulation refers to the net accumulation of a chemical from exposure via food and sediments as well as water. A bioaccumulation factor (BAF) is the ratio (in L/kg) of a chemical's concentration in the tissue of an aquatic organism to its concentration in the ambient water, in situations where both the organism and its food are exposed and the ratio does not change substantially over time (U.S. EPA, 1993; 1995).

$$BAF = \frac{C_a}{C_w} \qquad \text{(Eqn. 2-9)}$$

where:

C_a = concentration of the chemical in the aquatic biota

C_w = concentration of the chemical in the ambient water

The difference between BAFs and BCFs is primarily in the routes of exposure involved and the levels of accumulation attained because of these exposure routes. BCFs are measured in laboratory experiments designed to measure the chemical uptake by the organism only from water. BAFs are usually determined from measurements of chemical concentration in water and organism tissue samples that are obtained in the field from aquatic systems at presumed steady-state exposure conditions. Thus, BAFs include both direct uptake from the water as well as uptake from intake of food and sediments. The previous discussion under "Bioconcentration" concerning the form of the chemical in the water (i.e., dissolved or total) and the value of lipid normalization also applies to BAFs.

Because reliable measurements of trace levels of CDD/CDFs in ambient water are generally not available, it is not practical to develop measured BAFs for these compounds.

However, detectable concentrations of CDD/CDFs are generally measurable in sediments. The relationship between chemical concentrations in organisms and sediments is defined as the biota-sediment accumulation factor (BSAF). BSAFs can be used to measure and predict bioaccumulation directly from measured concentrations of chemicals in surface sediments and biota. They may also be used to estimate BAFs. Because BSAFs are based on field measurements and incorporate uptake from water and food, and the effects of metabolism and growth, BAFs estimated from BSAFs will incorporate the net affect of all these factors (U.S. EPA, 1993; 1995).

BSAFs are measured by relating lipid-normalized concentrations of a chemical in an organism to the organic carbon-normalized concentration of the chemical in surface sediment samples associated with the average exposure of the organism (U.S. EPA, 1995). The BSAF equation is:

$$\mathbf{BSAF} = \frac{C_l}{C_s} \qquad \text{(Eqn. 2-10)}$$

where:

C_l = lipid-normalized concentration of the chemical in aquatic biota

C_s = organic carbon-normalized concentration of the chemical in surface sediment

The ratios of BSAFs of CDD/CDFs to a BSAF for 2,3,7,8-TCDD yield bioaccumulation equivalency factors (BEFs) which can be used to estimate the combined toxic potential of CDD/CDFs as a toxic equivalence concentration. Table 2-10 presents BSAFs and BEFs derived for CDD/CDFs from Lake Ontario lake trout and sediment. A compilation of additional BSAFs is presented in the companion document to this report (i.e., Volume 3). Chapter 3 of this report summarizes concentrations of CDD/CDFs in aquatic organisms that have been reported in the literature.

2.6.1.4.3. Mechanisms for Entry of CDD/CDFs Into the Aquatic Food Chain

Air to Land to Water to Animal Hypothesis. Based on information currently available, the primary mechanism by which CDD/CDFs enter the aquatic food chain in most freshwater bodies is by atmospheric deposition onto land followed by transport of the deposited material in stormwater runoff/erosion into water bodies. Once in the water

body, entry into the food chain starts with uptake by benthic organisms as described in Section 2.6.1.4.2.

CDD/CDFs can also enter aquatic systems directly from industrial and POTW effluent discharges, from deposition of CDD/CDFs in the atmosphere directly onto water bodies (of importance for the Great Lakes), and in erosion/stormwater runoff from areas where dioxin-containing material is present (e.g., a contaminated industrial or waste disposal site). Thus, for any given water body, the dominant transport mechanism will depend on site-specific conditions. For example, Pearson and Swackhammer (1997) report that atmospheric deposition is the dominant source of CDD/CDFs to Lake Superior, but not to Lake Michigan or Lake Ontario. However, for most freshwater bodies today, erosion/ stormwater runoff is the probable dominant mechanism for CDD/CDF input and the CDD/CDFs present in that runoff can be attributed to atmospheric deposition. Several studies support this hypothesis.

For example, Smith et al. (1995) analyzed CDD/CDF concentrations in sediment cores, air, precipitation, soil, and stormwater runoff in an effort to determine the contributing sources of these compounds to the lower Hudson River. The mass balance estimates developed from these data are, for the period 1990-1993: stormwater runoff entering tributaries (76 percent of total CDD/CDF input); anthropogenic wastes (19 percent); atmospheric deposition (4 percent); and shoreline erosion (less than 1 percent). Smith et al. (1995) also projected the percent contribution of these same sources for the year 1970 to be: anthropogenic wastes (70 percent); stormwater runoff into tributaries (15 percent); atmospheric deposition (15 percent); and shoreline erosion (0.1 percent).

Lebeuf et al. (1996) analyzed sediment cores from different locations in the lower St. Lawrence River Estuary and the Gulf of St. Lawrence. The congener group profiles found in the samples indicate that the input of CDD/CDFs is primarily from the atmosphere. Comparison of the CDD/CDF concentrations in sediments collected from areas where sediment accumulation is due primarily to fluvial transport with sediments from areas where sediment accumulation is due primarily to direct atmospheric deposition onto the water indicates that the contribution of CDD/CDF from direct atmospheric deposition represents less than 35 percent of the sediment burden. Thus, the primary source of CDD/CDFs was determined to be emissions to the atmosphere upwind of the

Estuary that are deposited within the watershed and subsequently transported downstream by fluvial waters.

Paustenbach et al. (1996) and Mathur et al. (1997) reported that stormwater runoff from 15 sites in the San Francisco area contained CDD/CDF I-TEQ_{DF} at levels ranging from 0.01 to 65 pg/L; most samples contained less than 15 pg/L. The sites differed widely in land use; the highest levels measured were obtained from an urban, but nonindustrialized area. A distinct variability was noted in the results obtained at the same sampling location during different rain events. However, the profiles of CDD/CDFs in the urban stormwater samples were similar at all sites, particularly in samples collected at the onset of rain events. Stowe (1996) reported similar findings from analyses of sediments from three stormwater basins collecting runoff from a military base, city street, and parking lots.

Further argument supporting this hypothesis is offered below:

- Much less data have been published on CDD/CDF discharges in wastewater than have been published on emissions to air. Nonetheless, the general scientific consensus is that because of their extremely low water solubilities and the restrictions on suspended particulate discharges in wastewater discharges, CDD/CDF emissions via wastewater are negligible compared to atmospheric emissions and land-disposed waste material. This is the conclusion drawn in the U.S. Inventory (see Volume 1), the European Dioxin Inventory (Quab and Fermann, 1997), and the recent United Nations compilation of national and regional CDD/CDF emissions inventories (UNEP, 1999).
- Studies have measured CDD/CDFs in wet and dry deposition in most locations, including remote areas (see Table 2-4).
- Studies have measured CDD/CDFs in soils in most locations, including remote areas (see Chapter 3). Volume 1 of this Reassessment presents preliminary rough estimates of the potential magnitude of soil erosion via rural runoff sources to be 2,700 grams of I-TEQ_{DF} annually.
- The Paustenbach et al. (1996) and Mather et al. (1997) studies cited above detected CDD/CDFs in all stormwater samples collected in the San Francisco area. However, CDD/CDFs were only rarely detected in discharges collected

from nine POTWs in the San Francisco area during the same approximate time period (California Regional Water Quality Control Board, 1996).

- Fisher et al. (1998) reported that urban runoff samples from eight sites (15 samples) in the Santa Monica Bay watershed contained CDD/CDF I-TEQ_{DF} at levels ranging from 0.7 to 53 pg/L (all but one sample were in the range of 0.7 to 10 pg/L). The samples were collected in 1988/1989 from continuously flowing storm drains during both dry and storm periods. Concentrations measured during storm events (mean = 18 pg/L) were higher than concentrations observed during dry periods (mean = 1 pg/L).

2.6.1.5. Transformation Processes

2.6.1.5.1. Photolysis. Photolysis appears to be one of the most environmentally significant degradation mechanisms for CDD/CDFs in water and soil, and possibly in the atmosphere. CDD/CDFs absorb electromagnetic radiation at wavelengths greater than 290 nm (i.e., the lower bound of the Sun's radiation reaching the Earth's surface) and, therefore, can be expected to be subject to photolysis by sunlight. Numerous studies have demonstrated that CDD/CDFs undergo relatively rapid photolysis in a variety of organic solvents and at much slower rates in water, typically following first order kinetics. Because of the difficulties inherent in controlling experimental variables for nonvolatile and highly lipophilic compounds like CDD/CDFs, few photolysis studies have been performed with natural waters, with CDD/CDFs sorbed to soil or particulate matrices, and with gas phase CDD/CDFs. The photochemistry of CDD/CDFs has been reviewed by Miller and Zepp (1987), Choudry and Webster (1987), Atkinson (1991; 1996), and others.

The major products from photolysis are complex and, in most studies, good mass balances have not been obtained. Although, the photolytic pathway(s) for CDD/CDFs has not been fully identified, a major photolysis pathway appears to be photodechlorination resulting in formation of lower chlorinated CDD/CDFs. Several researchers have reported that carbon-oxygen cleavage and other mechanisms may be similarly or more important pathways for CDD/CDFs containing four or fewer chlorines (Choudry and Webster, 1989; Dulin et al., 1986; Miller et al., 1989; Kieatiwong et al., 1990). Studies performed to date suggest that the photolytic degradation products from irradiation of CDD/CDFs in

organic solvents may be significantly different than those observed when surface-sorbed and gas-phase CDD/CDFs are irradiated. A preferential loss of chlorines from the lateral positions (i.e., chlorines at the 2, 3, 7, and 8 positions) rather than from the peri positions (i.e., chlorines at the 1, 4, 6, and 9 positions) has been reported for solution studies (Crosby et al., 1973; Dobbs and Grant, 1979; Tysklind and Rappe, 1991); the opposite trend is observed for some congener groups when irradiated as dry films, sorbed to soil, and as gas-phase CDD/CDFs (Choudry and Webster, 1989; Kieatiwong et al., 1990; Sivils et al., 1994; Sivils et al., 1995).

Most studies performed until recently have been conducted using artificial light, pure congeners, and reaction media consisting of homogenous solutions in aqueous-organic solvent mixtures, silica gel, or clean solid surfaces. Thus, although photolysis of CDD/CDFs at environmentally significant rates has been observed in laboratory studies, the results of these studies may not be representative of photolysis rates that occur under actual environmental conditions. The following subsections summarize the key findings of recent environmentally significant studies for the water, soil, and air media.

Photolysis in Solution. Numerous studies have demonstrated that CDD/CDFs will undergo photodechlorination following first order kinetics in solution with preferential loss of chlorine from the lateral positions. Photolysis is slow in pure water but increases dramatically when solvents serving as hydrogen donors are present such as hexane, benzene, methanol, acetonitrile, hexadecane, ethyl oleate, dioxane, and isooctane (Buser, 1976; Buser, 1988; Choudry and Webster, 1987; Choudry et al., 1990; Crosby et al., 1971; Crosby, 1978; Crosby, 1981; Dobbs and Grant, 1979; Dougherty et al., 1991; Dulin et al., 1986; Friesen et al., 1990a; Hutzinger, 1973; Koester and Hites, 1992b; Koshioka et al., 1990; Wagenaar et al., 1995; and others).

The photolytic behavior of CDD/CDFs in organic solvents or in pure water, however, is not expected to accurately reflect the photolytic behavior of these compounds in natural waters. Natural waters have differing quantities and types of suspended particulates and dissolved organic material that could either retard or enhance the photolysis of CDD/CDFs. However, only a few studies have been performed that have examined the photolysis of CDD/CDFs using natural waters and sunlight. Several other published studies have used a mixture of water and acetonitrile to enhance the solubility

of CDD/CDFs. The following paragraphs summarize the results of these studies. Table 2-11 presents selected results from these studies.

Dulin et al. (1986) studied the photolysis of 2,3,7,8-TCDD in a water:acetonitrile solution (1:1, v/v) under sunlight and artificial light (i.e., a mercury lamp). The quantum yield for photodegradation of 2,3,7,8-TCDD in water was three times greater under artificial light at 313 nm than under sunlight which suggests that the medium-pressure mercury lamp used was a more efficient light source than the sun (Koester and Hites, 1992b). Podoll et al. (1986) used the Dulin et al. (1986) reaction rate data from the artificial light experiment to calculate seasonal half-life values for 2,3,7,8-TCDD at 40 degrees north latitude in clear near-surface water. The calculated seasonal values for half-lives ranged from 0.9 days in summer to 4.9 days in winter. Using the Dulin et al. (1986) reaction rate data from the sunlight experiment yields calculated seasonal values for half-lives ranging from 2.7 days in summer to 16 days in winter.

Choudry and Webster (1989) studied the photolytic behavior of a series of CDDs in a water:acetonitrile solution (2:3, v/v) using a low-pressure mercury lamp. Choudry et al. (1990) investigated the photolytic behavior of two CDFs (1,2,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF) using a similar experimental setup but with a 1:1 water:acetonitrile solution. Assuming that the quantum yields observed in these studies are the same as would be observed in natural waters, Choudry and Webster (1989) and Choudry et al. (1990) estimated the mid-summer half-life values at 40 degrees north latitude in clear near-surface water to be as follows: 1,2,3,7-TCDD (1.8 days); 1,3,6,8-TCDD (0.3 days); 1,2,3,4,7-PeCDD (15 days); 1,2,3,4,7,8-HxCDD (6.3 days); 1,2,3,4,6,7,8-HpCDD (47 days); OCDD (18 days); 1,2,4,7,8-PeCDF (0.2 hours); and 1,2,3,4,7,8-HxCDF (6 hours). However, Choudry and Webster (1989) also experimentally determined the sunlight photolysis half-life of 1,3,6,8-TCDD in pond water to be 3.5 days (i.e., more than 10 times greater than the half-life predicted by laboratory experiments). The authors attributed this significant difference in photolysis rates to the light screening/quenching effects of dissolved organic matter.

Friesen et al. (1990a) examined the photolytic behavior of 1,2,3,4,7-PeCDD and 1,2,3,4,6,7,8-HpCDD in water:acetonitrile (2:3, v/v) and in pond water under sunlight at 50 degrees north latitude. The observed half-lives of these two compounds in the water:acetonitrile solution were 12 and 37 days, respectively, which are very similar to

the results observed by Choudry and Webster (1989) for these two congeners using artificial light. However, in contrast to the results observed by Choudry and Webster (1989) for 1,3,6,8-TCDD, Friesen et al. (1990a) found that the half-lives of 1,2,3,4,7-PeCDD and 1,2,3,4,6,7,8-HpCDD were much shorter in pond water (0.94 and 2.5 days, respectively) than in the water:acetonitrile solution. Similarly, Friesen et al. (1993) studied the photodegradation of 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF by sunlight using water:acetonitrile (2:3, v/v) and lake water. The observed half-lives of the 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF in the water:acetonitrile solution were 6.5 and 46 days, respectively, and 1.2 and 0.19 days in lake water, respectively. Friesen et al. (1990a) and Friesen et al (1993) attributed the significant differences between the natural water and water:acetonitrile solution results to indirect or sensitized photolysis due to the presence of naturally occurring components in the lake and pond water.

Dung and O'Keefe (1992), in their investigation of aqueous photolysis of 2,3,7,8-TCDF and 1,2,7,8-TCDF, reported findings similar to those of Friesen et al. (1993). Dung and O'Keefe prepared aqueous solutions by pumping water through "generator columns" containing particles coated with a thin film of the respective TCDF congener. Solutions in high purity HPLC water, distilled water, Hudson River water, and Saratoga Lake water were exposed to sunlight during September at approximately 42.5 degrees north latitude. The photolysis rates of the two TCDF congeners observed in the river and lake water (half-lives of about 4 to 6 hours) were double the rates observed in pure water (half-lives of about 8 to 11 hours). Dung and O'Keefe (1992) attribute the difference in rates to the presence of natural organics in the river and lake water that may be acting as sensitizers.

Kim and O'Keefe (1998) confirmed the results observed in Dung and O'Keefe (1992) by photolyzing 1,2,7,8-TCDD; 2,3,7,8-TCDF; OCDD; and OCDF in natural water from seven different locations. The values reported in Table 2-11 are the average values for the seven natural waters. The half-lives of TCDD and TCDF were at least two times shorter in all the natural waters than in pure water. However, the natural water half-lives of OCDD and OCDF showed greater variability with some half-lives greater than pure water and some less than pure water. Because there was no apparent relationship between the dissolved organic content of the water and the observed half-lives, it was hypothesized that certain waters may contain organic molecules which either act as photosensitizers or as photodesensitizers.

Photolysis on Soil. Photolysis of CDD/CDFs on soil has been reported but the factors affecting the rate and extent of photolysis have not been well characterized. Based on the data generated to date, photolysis is an operative degradation process only in the near-surface soil where UV light penetrates (i.e., the top few millimeters or less of soil) and dechlorination of peri-substituted chlorines appears to occur preferentially. Even within this near surface area, the rate of photolysis is substantially slower than the rate of photolysis that would be observed in a solution of same depth presumably as a result of the light-attenuating effects of soils. Below this near-surface level, photolysis is not a significant process, and CDD/CDFs present in soil at any greater depth are likely to persist (Miller et al., 1989; Puri et al., 1989; Yanders et al., 1989; Kieatiwong et al., 1990). The substantial research performed on the environmental persistence of 2,3,7,8-TCDD in the area around the ICMESA chemical plant in Seveso, Italy, demonstrates that photolysis in soils is a near-surface process. The Seveso area was contaminated when a trichloro-phenol reaction vessel overheated in 1976, blowing out the safety devices and spraying 2,3,7,8-TCDD-contaminated material into the environment. The levels of dioxin in the soil decreased substantially during the first 6 months following the accident before reaching a relatively steady state of 1/5 to 1/11 of the initial levels (DiDomenico et al., 1982).

Kieatiwong et al. (1990) investigated the photolysis of 2,3,7,8-TCDD added to two agricultural soils (350 ug/kg) of approximately 0.3 mm depth and irradiated for 15 days with a mercury lamp. A loss of approximately 15 percent of 2,3,7,8-TCDD was observed on the soil of higher organic carbon and clay content. A loss of approximately 45 percent of 2,3,7,8-TCDD was observed on the soil of lower organic carbon and clay content. There was no significant loss on either soil after the first 5 days.

Miller et al. (1989) studied the CDD degradation products resulting from irradiation of ^{13}C-labeled OCDD on two soil types using sunlamps. Approximately 38 to 42 percent of the OCDD were degraded by day five of the experiment; no significant further loss of OCDD was observed over the following 10 days. Although determined not to be the dominant photolysis pathway, photodechlorination was observed in both soils; approximately 10 to 30 percent of the lower chlorinated congeners were produced from the immediate higher chlorinated congeners. The HpCDD and HxCDD congeners observed as degradation products were present in approximately similar proportions to the number of congeners in each congener group. However, Miller et al. (1989) found that, unlike the

results reported for photolysis of OCDD in solution by Choudry and Webster (1989) and Dobbs and Grant (1979), 2,3,7,8-TCDD and 1,2,3,7,8-PeCDD were observed in greater yields than would be expected on the basis of the number of potential TCDD and PeCDD congeners. One-fifth to one-third of the total yield of PeCDDs was 1,2,3,7,8-PeCDD, and one-half of the total yield of TCDDs was 2,3,7,8-TCDD.

Kieatiwong et al. (1990) performed similar experiments to those of Miller et al. (1989) using natural sunlight rather than sunlamps for irradiation of ^{13}C-labeled OCDD on soils. Photodechlorination was estimated to account for approximately 10 percent of the loss of OCDD. One-third to one-half of the total yield of PeCDDs was 1,2,3,7,8-PeCDD, and one-half of the total yield of TCDDs was 2,3,7,8-TCDD. The findings of Miller et al. (1989) and Kieatiwong et al. (1990) indicate that the 2,3,7,8-substituted TCDD and PeCDD congeners were either preferentially formed or were photochemically less reactive than the other congeners that were formed.

Tysklind et al. (1992) also studied the sunlight photolysis of OCDD on soil and reported results in good agreement with those of Miller et al. (1989) and Kieatiwong et al. (1990). Photodechlorination was observed with production of HpCDDs, HxCDDs, PeCDDs, and TCDDs over the 16-day irradiation period. Photodechlorination at the peri-substituted positions was the preferred photodechlorination mechanism; the proportions of 2,3,7,8-substituted congeners present in the soils after 16 days for each congener group were as follows: HxCDD - 65 percent; PeCDD - 40 percent; and TCDD - 75 percent.

The sunlight photolysis of OCDF on soil was also studied by Tysklind et al. (1992). Photodechlorination was observed. However, unlike the case with OCDD, photodechlorination of the lateral-substituted positions was found to be the dominant photodechlorination mechanism resulting in a relative decreasing proportion of 2,3,7,8-substituted congeners during the irradiation period. 2,3,7,8-TCDF was not observed in any of the irradiated samples.

Schwarz and McLachlan (1993) studied the photolysis of CDD/CDFs in an experiment designed to simulate the application of sewage sludge to an agricultural field. No significant changes in CDD/CDF concentrations were observed during the 43-day exposure period to late summer/early fall natural sunlight. Although the OCDD concentration in the sludge had been increased by a factor of 1,000 through spiking, no increase in HpCDD concentrations were observed. The absence of any changes indicates

that neither photodegradation nor volatilization are important mechanisms in the fate of CDD/CDF in sewage sludge following agricultural applications.

The addition of solvents to soil can increase the rate and extent of photolysis. Botre et al. (1978) reported the destruction of 8 μg/mL of 2,3,7,8-TCDD in 0.02 M hexadecylpyridinium chloride (an aqueous surfactant) applied to soil in 4 hours. Kieatiwong et al. (1990) reported that addition of hexadecane to soil containing 2,3,7,8-TCDD resulted both in an increased rate of photolysis and continued photochemical loss of 2,3,7,8-TCDD beyond the point at which soil containing no hexadecane showed photochemical loss.

Although only minimally related to soil environmental conditions, Buser (1988) studied the photolytic decomposition rates of 2,3,7,8-TCDF, 1,2,3,4-TCDF, and 1,2,7,8-TCDF dried as thin films on quartz vials. When exposed to sunlight, the substances slowly degraded with reported half-lives of 5 days, 4 days, and 1.5 days, respectively. Similarly, Koester and Hites (1992b) studied the photodegradation of a series of tetra- through octa-chlorinated CDDs and CDFs on silica gel. In general, the CDFs degraded much more rapidly than the CDDs, and half-lives increased with increasing level of chlorination (1,2,7,8-TCDF excluded). The half-lives for CDDs ranged from 3.7 days for 1,2,3,4-TCDD to 11.2 days for OCDD. The half-lives for CDFs ranged from 0.1 day for 1,2,3,8,9-PeCDF to 0.4 days for OCDF.

Photolysis on Vegetation. Photolysis of CDD/CDFs sorbed on the surface of vegetation has not been well characterized and the findings to date are somewhat contradictory. McCrady and Maggard (1993) reported that 2,3,7,8-TCDD sorbed on the surface of reed canary grass (*Phalaris arundinacea L.*) undergoes photolytic degradation with a half-life of 44 hours in natural sunlight. In contrast, Welsch-Pausch et al. (1995) found little difference in the CDD/CDF congener patterns between grass (*Lolium multiflorum*) grown on an outdoor plot and grass grown in a greenhouse (i.e., UV-light transmission blocked). In an attempt to clarify this contradiction, Welsch-Pausch and McLachlan (1995) studied the photodegradation of CDD/CDFs on pasture grass (*Arrhenatherion elatioris*) during two growing cycles (summer and autumn) using two greenhouses. One greenhouse was constructed of glass which blocks UV transmission and the other was constructed of plexiglass (4 mm) with an UV-light transmission of greater than 50 percent in the 280-320 mm range. In both the summer and autumn

exposure periods, the concentrations of CDD/CDFs (on a congener group basis) were similar in the grass exposed to UV-light and the grass that was not exposed. Welsch-Pausch and McLachlan (1995) concluded that if photodegradation is occurring, it is a relatively insignificant factor in the accumulation of CDD/CDF in pasture grass.

Photolysis in Air. Photolysis of CDD/CDFs in the atmosphere has not been well-characterized. Based on the data generated to date, however, photolysis appears to be a significant mechanism for degradation (i.e., principally dechlorination of the peri-substituted chlorines) of those CDD/CDFs present in the atmosphere in the gas phase. For airborne CDD/CDFs sorbed to particulates, photolysis appears to proceed very slowly and may be influenced by the organic content of the particle. Because of the low volatility of CDD/CDFs, few studies have been attempted to measure actual rates of photodegradation of gaseous-phase CDD/CDF, and only recently have studies been undertaken to examine the relative importance of photolysis for particulate-bound CDD/CDFs.

Gas-Phase Photolysis - Podoll et al. (1986) estimated the photolysis rate of 2,3,7,8-TCDD vapors in the atmosphere based on the quantum yield for photolysis in hexane. The half-life in summer sunlight at 40 degrees north latitude was estimated to be 1 hour as an upper limit.

Mill et al. (1987) reported that photolysis of vapor phase 2,3,7,8-TCDD at 145°C in a flow system using a pulsed 308 nm laser light gave a photolysis quantum yield ranging from 0.013 to 0.03, equivalent to an atmospheric half-life of a few hours. However, the true gas phase quantum yield at 25°C is uncertain, and, therefore, the atmospheric lifetime in sunlight is uncertain.

Orth et al. (1989) conducted photolysis experiments with vapor-phase 2,3,7,8-TCDD under illumination with a Hg-Xe light source and filters to achieve radiation in the UV region from 250 nm to 340 nm. The temperature in the photolysis cell was approximately 150°C. Carrier gases included air and helium. No significant difference in the rate constants was observed in helium and air, 5.4×10^{-3} sec^{-1} and 5.9×10^{-3} sec^{-1}, respectively, which correspond to half-lives of a few minutes. The average quantum yield in air over the absorption band was found to be 0.033 ± 0.046. As with the results of Mill et al. (1987), the true gas phase quantum yield at 25°C is uncertain, and, therefore, the atmospheric lifetime in sunlight is uncertain.

Sivils et al. (1994; 1995) studied the gas phase photolysis of several CDDs (2,3,7-TrCDD; 2,3,7,8-TCDD; 1,2,3,4-TCDD; 1,2,3,7,8-PeCDD, and 1,2,4,7,8-PeCDD) by irradiating the effluent from a gas chromatograph with broadband radiation in the UV/visible region for periods of time up to 20 minutes. The irradiated sample was then introduced into a second gas chromatograph to measure the extent of dechlorination. The results showed that degradation followed first order kinetics and that there was an inverse relationship between the degree of chlorination and the rate of disappearance. Although the lack of photoproducts prevented an independent confirmation of the preferential loss mechanism, the results indicated that laterally-substituted congeners (i.e., chlorines at the 2, 3, 7, and 8 positions) degrade at a slower rate than the peri-substituted congeners (i.e., chlorines at the 1, 4, 6, and 9 positions). Although the rate constants were not presented in Sivils et al. (1994), the degradation rate for 2,3,7,8-TCDD (30 percent loss in 20 minutes) was reported to be slower than the rates for all other tested CDDs. Also, 1,2,4,7,8-PeCDD (with 2 peri-chlorines) degraded significantly faster than 1,2,3,7,8-PeCDD (with only 1 peri-chlorine).

Particulate Phase Photolysis - The photolysis of 2,3,7,8-TCDD sorbed onto small diameter fly ash particulates suspended in air was measured by Mill et al. (1987). The results indicated that fly ash appears to confer photostability on 2,3,7,8-TCDD. Little (8 percent) to no loss was observed on the two fly ash samples after 40 hours of illumination.

Koester and Hites (1992b) studied the photodegradation of CDD/CDFs naturally adsorbed to five fly ashes collected from electrostatic precipitators (one from a hospital incinerator, two from municipal incinerators, and two from coal-fired power plants) using a rotary reactor and a medium-pressure mercury lamp. Although they found that CDD/CDFs underwent photolysis in solution and when spiked onto silica gel, no significant degradation was observed in 11 photodegradation experiments performed on the ashes for periods ranging from 2 to 6 days. Three additional experiments were performed to determine what factors may have been inhibiting photolysis. From the results of these additional experiments, Koester and Hites (1992b) concluded that: (1) the absence of photodegradation was not due to the absence of a hydrogen-donor organic substance; (2) other molecules or the ash, as determined by a photolysis experiment with an ash extract, inhibit photodegradation either by absorbing light and dissipating energy or by quenching

the excited states of the CDD/CDFs; and (3) the surface of the ash itself may hinder photolysis by shielding the CDD/CDFs from light.

Pennise and Kamens (1996) injected the emissions from the combustion of wood chips treated with PCP, plastic PVC pipe shavings, and solid 2,4,6-trichlorophenol into 25-m^3 outdoor Teflon film chambers. The behavior of the eight congener groups was monitored for approximately one day. Experiments were performed during January, June, and October of 1994 in North Carolina. Experiments with combustion temperatures ranging from 350 to 380°C were categorized as low-temperature experiments, and those ranging from 760 to 800°C were categorized as high temperature experiments. Little or no reactivity was observed for CDD/CDFs sorbed to particles resulting from the high temperature experiments. Greater photochemical reactivity was observed for CDD/CDFs sorbed to particles resulting from the low combustion experiments, where photolysis appeared to compete with a CDD/CDF production mechanism believed to be associated with non-combusted PCP. Photolysis rates appeared to decrease with increasing levels of chlorination. On low temperature combustion particles, estimated TCDD half-lives (excluding the impact of the observed formation from PCP) increased from 0.4 hours under summer conditions to 17 hours under winter conditions. On high-temperature particles, estimated TCDD half-lives ranged from 6.8 to 62 hours. Estimated OCDD half-lives ranged from 5 to 38 hours in low combustion temperature experiments to 36 to 257 hours in high temperature combustion experiments.

2.6.1.5.2. Photooxidation. Until recently, the reaction rates of hydroxyl (OH) radicals, ozone (O_3), and nitrate (NO_3) radicals with CDDs and CDFs had not been measured because, in large part, the low vapor pressures of these compounds make direct measurements very difficult with currently available techniques. In the absence of experimental data, Podoll et al. (1986) and Atkinson (1987) estimated the half-life of 2,3,7,8-TCDD vapor via OH oxidation in the atmosphere to be 8.3 days and 3 days, respectively. In a subsequent study, Atkinson (1991) used published reaction rate data for other organic compounds to estimate the OH radical reaction rate constants for vapor-phase dibenzofuran and dibenzo-p-dioxin, and from these estimates, Atkinson (1991) estimated the OH radical reaction rate constants for the CDDs and CDFs. Based on these empirical estimates, Atkinson (1991) concluded that the OH radical reaction is

likely to be the dominant gas-phase transformation process for vapor phase CDDs and CDFs. The tropospheric lifetimes calculated by Atkinson (1991) from the rate constant estimates increased with increasing levels of chlorination from 2.0 days for 2,3,7,8-TCDD and 4.4 days for 2,3,7,8-TCDF to 9.6 days for OCDD and 39 days for OCDF.

Kwok et al. (1994) expanded the work of Atkinson (1991) by experimentally determining the room temperature gas-phase reaction rate constants of dibenzofuran and dibenzo-p-dioxin with hydroxyl radical to be 3.9E-12 cm^3 $molecule^{-1}$ s^{-1} and 1.48E-11 cm^3 $molecule^{-1}$ s^{-1}, respectively. These measured rate constants for dibenzo-p-dioxin and dibenzofuran are lower than those estimated by Atkinson (1991) by factors of 2.5 and 8. Assuming a 12-hour average daytime OH radical concentration of 8 x 10^5 molecule/cm^3, Kwok et al. (1994) estimated the atmospheric lifetimes for gas phase reactions of dibenzofuran and dibenzo-p-dioxin with OH radicals to be 3.7 days and 1.0 day, respectively. Also, based on experimental data, Kwok et al. (1994) calculated lifetimes for the gas phase reaction of dibenzofurans with NO_3 and O_3 to be greater than 7 years and greater than 205 days, respectively; the calculated lifetimes for the gas phase reaction of dibenzo-p-dioxin with NO_3 and O_3 were 4.9 days and greater than 330 days, respectively. The latter results indicate that reaction with the OH radical is the dominant photooxidation mechanism.

Kwok et al. (1995) extended the work of Kwok et al. (1994) by measuring the OH radical reaction rate constants for 1-chlorodibenzo-p-dioxin, diphenyl ether, and 1,2-dimethoxybenzene. These new reaction rate data when taken together with the measurements of Kwok et al. (1994) and the estimation method described in Atkinson (1991) were used to generate more reliable estimates of the reaction rate constants for the 2,3,7,8-substituted CDDs and CDFs (Atkinson, 1996). Table 2-12 presents these recalculated rate constants and tropospheric lifetimes and half-lives. As can be seen from Table 2-12, the persistence of CDD/CDFs increases with increasing degree of chlorination.

Recently, Brubaker and Hites (1997) measured the OH radical reaction rate constants for dibenzo-p-dioxin, dibenzofuran, 2,7-dichlorodibenzo-p-dioxin (2,7-D), 2,8-dichlorodibenzofuran (2,8-F), and 1,2,3,4-dibenzo-p-dioxin (1,2,3,4-D) over temperatures ranging from 72 to 159°C. From these results, OH reaction rate constants were estimated for each compound at 25°C. When these estimated values were compared to the previously measured rate constants reported by Kwok et al. (1994; 1995) and the

values predicted by Atkinson (1995; 1996), Brubaker and Hites (1997) concluded that Atkinson's structure activity method is reliable.

2.6.1.5.3. Hydrolysis. There is no available evidence indicating that hydrolysis would be an operative environmental process for degradation of CDDs or CDFs. The attachment of chlorines directly to the aromatic ring in CDDs and CDFs confers hydrolytic stability. Specifically, S_N1 and S_N2 reactions do not take place readily at sp2 hybridized carbons (Leifer et al., 1983; Miller and Zepp, 1987).

2.6.1.5.4. Biotransformation and Biodegradation. Most investigations examining the biodegradability of CDDs and CDFs have, until recently, focused on the microbial degradation of 2,3,7,8-TCDD. Arthur and Frea (1989) provided a comprehensive review of studies conducted during the 1970s and 1980s and concluded that 2,3,7,8-TCDD is recalcitrant to microbial degradation. Several major studies conducted during that time period as well as more recent studies are discussed below.

Matsumura and Benezet (1973) tested approximately 100 strains of micro-organisms that were shown previously to degrade persistent pesticides; only five strains showed any ability to metabolize 2,3,7,8-TCDD, based on autoradiographs of thin-layer chromatograms. Hutter and Philippi (1982) concluded that although it is possible that the less chlorinated dioxins are more susceptible to biodegradation, microbial action on 2,3,7,8-TCDD is very slow under optimum conditions; the long-term incubations of radiolabeled 2,3,7,8-TCDD yielded no radioactivity in carbon dioxide traps after 1 year, and analyses of the cultures showed that, at most, 1 to 2 percent of the initial 2,3,7,8-TCDD were recovered as a potential metabolite (assumed to be a hydroxylated derivative of 2,3,7,8-TCDD). Camoni et al. (1982) added organic compost to contaminated soil from the Seveso area to enrich the soil and enhance the 2,3,7,8-TCDD biodegradation rate; however, the soil amendment had no clear effect on degradation. Quensen and Matsumura (1983) reported that low concentrations (5 ppb) of radiolabeled 2,3,7,8-TCDD were metabolized by pure cultures of *Nocardiopsis* spp. and *Bacillus megaterium* that had been isolated from farm soil. The extent of metabolism after 1-week incubation was strongly dependent on the carrier solvent used to dissolve and introduce the 2,3,7,8-TCDD to the culture medium. The solvent ethyl acetate gave the best results; 52 percent

of ^{14}C were recovered as 2,3,7,8-TCDD out of a total of 77 percent ^{14}C recovered. However, incubation of 2,3,7,8-TCDD in farm soil, garden soil, and forest soil resulted in little, if any, metabolism of 2,3,7,8-TCDD.

Bumpus et al. (1985) tested the white rot fungus, *Phanerochaete chrysosporium*, which secretes a unique H_20_2-dependent extracellular lignin-degrading enzyme system capable of generating carbon-centered free radicals (Tien and Kirk, 1983; Tien and Kirk, 1984). Lignin is resistant to attack by all microorganisms except some species of fungi and a relatively small number of bacteria species. Radiolabeled 2,3,7,8-TCDD was oxidized to labeled $C0_2$ by nitrogen-deficient, ligninolytic cultures of *P. chrysosporium;* because the label was restricted to the ring, it was concluded that the strain was able to degrade halogenated aromatic rings. In 10 mL cultures containing 1,250 pmol of substrate, 27.9 pmol of 2,3,7,8-TCDD were converted to labeled-CO_2 during the 30-day incubation period; thus, only about 2 percent of the starting material were converted.

Hofmann et al. (1992) demonstrated that the fungi, *Fusarium redolens*, could degrade 3-chlorodibenzofuran and, to a lesser degree, mono- and di-CDDs. Hoffman et al. (1992) also identified 14 other strains of fungi that demonstrated the capability to degrade dibenzofuran (nonchlorinated). The strains are members of the following genera: *Mucor, Chaetomium, Phoma, Fusarium, Paecilomyces, Papulaspora, Inonotus, Lentinus, Phanerochaete, Polyporus, Pycnoporus, Schizophyllum*, and *Trametes*.

Takada et al. (1994; 1996) reported significant degradation of 2,3,7,8-substituted CDDs and CDFs by low-nitrogen medium cultures of the white rot fungus, *Phanerochaete sordida YK-624 strain*. Tetra- through octa- CDDs and CDFs were incubated for 14 days in glucose-amended cultures at 30°C. For both CDDs and CDFs, the 1,2,3,6,7,8-congeners showed the highest degradation values, 75 percent and 70 percent, respectively. The lowest degradation values were for 2,3,7,8-TCDD (40 percent), 1,2,3,7,8-TCDF (45 percent), and 1,2,3,7,8-PeCDF. Similar results were obtained under the same conditions for *P. chrysoporium IFO 31249 strain*.

Several recent reports indicate that CDDs and CDFs, like PCBs, may undergo microbial dechlorination in anaerobic sediments. Adriaens and Grbic-Galic (1992; 1993) and Adriaens et al. (1995) have reported the results of a series of microcosm studies utilizing Hudson River sediment (contaminated with Aroclor 1242) and aquifer material (contaminated with CDDs) from Pensacola, Florida. Both types of substrates were spiked

with several CDDs (1,2,3,4,6,7,8-HpCDD; 1,2,3,4,7,8-HxCDD; and 1,2,4,6,8,9-/1,2,4,6,7,9-HxCDD) and CDFs (1,2,3,4,6,7,8-HpCDF and 1,2,4,6,8-PeCDF) and monitored over a period of 16 months at an incubation temperature of 30°C. The Hudson River sediment was spiked with 144 μg/kg of each congener and the Pensacola aquifer material was spiked with 63 μg/kg of each congener. Recoveries of the CDD/CDF congeners from the control samples decreased with increasing incubation time indicating that these congeners are strongly sorbed to the substrates. For example, after 50 days of incubation, the fraction of CDD/CDF that could be recovered by manual extraction had already decreased to 20-40 percent.

All of the congeners, with the exception of HpCDF, showed a slow decrease in concentration over time attributed to biologically mediated reductive dechlorination with net disappearance rates ranging from 0.0031 wk^{-1} to 0.0175 wk^{-1} (i.e., half-lives of approximately 1 to 4 years). However, Adriaens et al. (1995) conclude that the actual half-lives may be orders of magnitude higher. If it is assumed that transformation/degradation occurs only for CDD/CDF in the aqueous phase, then the CDD/CDF that sorb to the sediments may never be biologically available because of the apparent very slow rates of desorption. The experiment with 1,2,3,4,6,7,8-HpCDD yielded formation of two HxCDD (1,2,3,4,7,8- and 1,2,3,6,7,8-). Thus, removal of the peri-substituted (1,4,6,9) chlorines was favored with enrichment of 2,3,7,8-substituted congeners. No lesser chlorinated congeners were identified from incubations with the other tested congeners. 1,2,4,6,8-PeCDF was also examined in dichlorophenol-enriched cultures. After 6 months incubation, several TCDFs were identified which also indicated that peri-dechlorination was the preferred route of reduction.

Barkovskii et al. (1994) expanded the testing of Adriaens and Grbic-Galic (1992; 1993) by spiking the sediments with higher doses to determine if faster rates could be achieved. Passaic River sediments (contaminated with CDD/CDFs) were spiked with 4,500 μg/kg of OCDD and incubated under anaerobic conditions for 6 months. Although no significant degradation of OCDD was observed, significant reductions in the concentrations of the hepta-, hexa-, penta-, and tetra-CDDs were observed.

Barkovskii and Adriaens (1995; 1996) reported that 2,3,7,8-TCDD (extracted from Passaic River sediments) was susceptible to reductive dechlorination when incubated at 30°C under methanogenic conditions in a mixture of aliphatic and organic acids inoculated

with microorganisms obtained from Passaic River sediments. The initial concentration of 2,3,7,8-TCDD (20 ± 4 μg/L) decreased by 30 percent to 14 ± 2 μg/L over a period of 7 months with the consecutive appearance and disappearance of tri-, di-, and mono-CDDs. Experiments were also conducted by spiking the sediment with HxCDDs, HpCDDs, and OCDD. Up to 10 percent of the spiked OCDD was converted to hepta-, hexa-, penta-, tetra-, tri-, di-, and monochlorinated isomers, but the reaction stoichiometry was not determined. Two distinct pathways of dechlorination were observed: the *peri*-dechlorination pathway of 2,3,7,8-substituted hepta- to penta-CDDs, resulting in the production of 2,3,7,8-TCDD, and the *peri*-lateral dechlorination pathway of non-2,3,7,8-substituted congeners. Direct evidence of further lateral dechlorination of 2,3,7,8-TCDD was obtained from the historically contaminated incubations. Pasteurized cells exhibited no *peri*-dechlorination pathway, and triCDDs were the least-chlorinated congeners produced in these treatments. These results demonstrate that: (I) both freshly spiked and aged CDDs are available to microbial reductive dechlorination; (ii) the *peri* and triCDD dechlorinations are attributed to activities of nonmethanogenic, non-spore-forming microbial subpopulations; and (iii) the 2,3,7,8-residue patterns in historically contaminated sediments are likely affected by microbial activity.

2.6.2. Environmental Fate of Dioxin-Like PCBs

2.6.2.1. Summary

Little specific information exists on the environmental transport and fate of the dioxin-like PCBs. However, the available information on the physical/chemical properties of dioxin-like PCBs coupled with the body of information available on the widespread occurrence and persistence of PCBs in the environment indicates that these dioxin-like PCBs are likely to be associated primarily with soils and sediments, and to be thermally and chemically stable. Soil erosion and sediment transport in waterbodies and volatilization from the surfaces of soils/water bodies with subsequent atmospheric transport and deposition are believed to be the dominant current transport mechanisms responsible for the widespread environmental occurrence of PCBs. Photodegradation and biologically-mediated reductive dechlorination to less chlorinated congeners followed by slow anaerobic and/or aerobic biodegradation in soils/sediments are believed to be the

principal paths for destruction of PCBs. Of note, however, is that the available photolysis studies to date indicate that the more toxic coplanar PCBs are more resistant to photolysis and are formed as products during the photolysis of more chlorinated less toxic congeners.

2.6.2.2. Transport Mechanisms

Based on their low vapor pressures, low water solubilities, and high K_{oc} values, dioxin-like PCBs are expected primarily to be associated with soils, sediments, and particulates. PCBs move from land to aquatic environments primarily associated with runoff sediments (Gan and Berthouex, 1994). However, due to the stability and persistence of dioxin-like PCBs via other transformation and transport pathways, volatilization is likely to be a significant transport mechanism from a global perspective. It should be noted that although dioxin-like PCBs have low vapor pressures and water solubilities, the Henry's Law constants for the similarly substituted CDDs and CDFs are expected to be one to two orders of magnitude lower. Therefore, it can be expected that volatilization of PCBs from soil and water into air is likely to be a more significant transport mechanism for PCBs than for CDDs and CDFs. For example, Cousins et al. (1996) recently demonstrated that PCBs with fewer than eight chlorines will volatilize but 2,3,7,8-substituted CDD/CDFs do not volatilize from sewage sludge amended soil. The rate of volatilization will be affected by soil characteristics (e.g., temperature, moisture content, and organic carbon content) and the concentration and physical form of the PCBs present (Ayris and Harrad, 1997).

Recent studies have shown that PCBs are cycling between the atmosphere and the terrestrial and aquatic environments. For example, Murray and Andren (1992) studied the precipitation scavenging of PCBs in the Great Lakes region. They reported that atmospheric PCBs are largely in the gas phase (typically >90 percent) rather than bound to particulate material. The results of their study support the hypothesis that precipitation provides episodic inputs of PCBs to the Great Lakes. However, several published studies indicate that, on an annual basis (and particularly during the summer and autumn), the Great Lakes are net sources of PCBs to the atmosphere through the process of volatilization. Shallow, warm, and impacted aquatic systems such as Green Bay, Lake Michigan and Chesapeake Bay exhibit the highest net volatilization fluxes due partially to

intimate contact with contaminated sediments (Baker and Eisenreich, 1990; Eisenreich, 1997). Gregor et al. (1992) reported similar findings in a study of PCB deposition in the Arctic during the winter of 1990/1991. The results of the study indicated that snowfall and ice crystal deposition were scavenging the full range of PCB congeners from the atmosphere. The daily deposition rate during winter was about 2 ng/m^2/day. Also, a comparison of the PCB content of snow/ice samples from collectors and end of season samples from the snowpack suggested that volatilization of the PCBs, particularly of the lower chlorinated congeners, was occurring.

Like CDD/CDFs, the dioxin-like PCBs have a high potential for bioaccumulation in aquatic organisms thereby leading to elevated exposures to humans and wildlife from ingestion of contaminated fish. Table 2-13 presents BAFs, BCFs, and BSAFs reported in the literature for dioxin-like PCBs. A compilation of additional reported BSAFs is provided in the companion document to this report (i.e., Volume 3). Chapter 3 of this report summarizes concentrations of dioxin-like PCBs in fish that have been reported in the literature.

2.6.2.3. Transformation Processes

2.6.2.3.1. Photolysis. Based on the data available in 1983, Leifer et al. (1983) concluded that all PCBs, especially the more highly chlorinated congeners and those that contain two or more chlorines in the ortho position, photodechlorinate. In general, as the chlorine content increases, the photolysis rate increases. The products of photolysis are predominantly lower chlorinated PCBs.

More recently, Lepine et al. (1992) exposed dilute solutions (4 ppm) of Aroclor 1254 in cyclohexane to sunlight for 55 days in December and January. Isomer-specific analysis indicated that the amounts of many higher chlorinated congeners decreased while those of some lower chlorinated congeners increased. These results are consistent with the studies reviewed in Leifer et al. (1983) that indicated photodegradation of PCBs proceeds through successive dechlorination of the biphenyl molecule. The results for the dioxin-like PCBs indicated a 43.5 percent decrease in the amount of 2,3,4,4',5-PeCB; a 73.5 percent decrease in the amount of 2,3,3',4,4',5-HxCB; and a 24.4 percent decrease in the amount of 2,3,3',4,4',5'-HxCB. However, the more toxic 3,3',4,4'-TeCB (PCB77)

and 3,3',4,4',5-PeCB (PCB126), which were not detected in unirradiated Aroclor 1254, represented 2.5 percent and 0.43 percent, respectively, of the irradiated mixture. The authors postulated that formation of these two congeners probably occurred, at least in part, from dechlorination at the ortho position of their mono-ortho-substituted precursors, considering the greater reactivity of PCB ortho chlorines toward photodechlorination. Dechlorination was reported to proceed by the loss of chlorine in the order of ortho > para > meta.

Brown et al. (1995) examined the changes in congener levels that occurred after exposing hexane solutions of various Aroclors and specific congeners in quartz tubes to direct summer sunlight (43°N). The reported disappearance rates and estimated half-lives for several of the dioxin-like PCBs are as follows:

PCB Congener	Substitution Pattern	Disappearance Rate (day^{-1})	Half-life (days)
105	234-34	0.11	6.3
156	2345-34	0.3	2.3
167	245-345	0.08	8.7
170	2345-234	0.006	115
180	2345-245	0.004	173
189	2345-345	0.08	8.7

Barr et al. (1997) irradiated several PCB congeners in solution on silica gel for up to 30 minutes. The results indicated that dechlorination in the ortho position is favored but also that steric congestion and structural symmetry are major factors in determining the relative reactivity of chlorines in the meta and para positions. The following conclusions were made:

- In all cases, the ring with the greatest degree of chlorination is the primary ring where the dechlorination occurs.
- Ortho-chlorine substituents and para-chlorine substituents that have two adjacent chlorines were preferentially lost in coplanar (non-ortho-substituted) PCBs.
- Chlorine substituents having neighboring chlorines are replaced more easily than isolated chlorines.
- Para-chlorine substituents were lost preferentially from coplanar hexa-, penta- or tetrachlorobiphenyls, while meta-chlorine was lost preferentially from trichlorobiphenyls.

- More symmetrical isomers tend to be formed more easily, and are more stable.

2.6.2.3.2. Oxidation. Reaction of PCBs with common environmental oxidants such as hydroperoxy radicals (HO_2) and ozone (O_3) has not been reported and is probably not very important because only very strong oxidant species can react with PCBs (Sedlak and Andren, 1991). However, reaction of gas-phase PCBs in the atmosphere and dissolved PCBs in certain surface waters with hydroxyl radicals (OH) (one of the strongest environmental oxidants known) may be an important degradation mechanism.

Oxidation in Air. Atkinson (1987) and Leifer, et al. (1983), using assumed steady-state atmospheric OH concentrations and measured oxidation rate constants for biphenyl and monochlorobiphenyl, estimated atmospheric decay rates and half-lives for gaseous-phase PCBs. Atmospheric transformation was estimated to proceed most rapidly for those PCB congeners containing either a small number of chlorines or those containing all or most of the chlorines on one ring. The predicted half-lives for the congener groups containing the 13 dioxin-like PCBs were as follows:

Congener Group	Half-Life in Air (days)
TeCBs	11 to 20
PeCBs	12 to 31
HxCBs	32 to 62
HpCBs	94+

Kwok et al. (1995) extended the work of Atkinson (1987) by measuring the OH radical reaction rate constants for 2,2'-, 3,3'-, and 3,5-dichlorobiphenyl. These reaction rate constants when taken together with the measurements of Atkinson (1987) for biphenyl and monochlorobiphenyl and the estimation method described in Atkinson (1991; 1995; 1996) have been used to generate more reliable estimates of the gas-phase OH radical reaction rate constants for the dioxin-like PCBs. Table 2-14 presents these estimated rate constants and the corresponding tropospheric lifetimes and half-lives. As can be seen from Table 2-14, the persistence of the PCB congeners increases with increasing degree of chlorination.

Oxidation in Water. Sedlak and Andren (1991) demonstrated in laboratory studies that OH radicals, generated with Fenton's reagent, rapidly oxidized PCBs (i.e., 2-mono-PCB and the DiCBs through PeCBs present in Aroclor 1242) in aqueous solutions. The

results indicated that the reaction occurs via addition of a hydroxyl group to one nonhalogenated site; reaction rates are inversely related to the degree of chlorination of the biphenyl. The results also indicated that meta and para sites are more reactive than ortho sites due to stearic hindrance effects. Based upon their kinetic measurements and reported steady-state aqueous system OH concentrations or estimates of OH radical production rates, Sedlak and Andren (1991) estimated environmental half-lives for dissolved PCBs (mono-through octa-PCB) in several water systems as listed below.

Water System	Half-Life in Water (days)
Fresh surface water	4 to 11
Marine surface water	1,000 to 10,000
Cloud water	0.1 to 10

Estimates for dissolved PCBs in marine surface water are in excess of 1,000 days due to the very low concentration of OH radicals in these waters (10^{-18}M or about two orders of magnitude lower than in freshwater systems). The results of studies to date indicate that OH oxidation of PCBs dissolved in cloud water may be an important, although not very fast, degradation mechanism for PCBs from a global perspective.

2.6.2.3.3. Hydrolysis. PCBs are unlikely to be affected by hydrolysis under environmental conditions because the attachment of chlorines directly to the aromatic ring in PCBs confers hydrolytic stability. Specifically, S_N1 and S_N2 reactions do not take place readily at sp2 hybridized carbons (U.S. EPA, 1988; Leifer et al., 1983).

2.6.2.3.4. Biotransformation and Biodegradation. Leifer et al. (1983), Brown and Wagner (1990), and Abramowicz (1990) summarized the available information on the degradation of PCBs by microorganisms. Laboratory studies (e.g., Bedard et al., 1986; Pardue et al., 1988; Larsson and Lemkemeier, 1989; Hickey, 1995; Schreiner et al., 1995; and Fukuda et al., 1997) have revealed that more than two dozen strains of aerobic bacteria and fungi are widely distributed in the environment that are capable of degrading most PCB congeners with five or fewer chlorines. Many of these organisms are members of the genus *Pseudomonas* or the genus *Alcaligenes*. Only a few strains have been demonstrated to have the ability to degrade higher chlorinated congeners. The major

metabolic pathway involves addition of O_2 at the 2,3-position by a dioxygenase enzyme with subsequent dehydrogenation to the catechol followed by ring cleavage. Several bacterial strains have been shown to possess a dioxygenase enzyme that attacks the 3,4-position.

In general, the rate of aerobic biodegradation decreases with increasing chlorination. Growth on biphenyl as the sole carbon source is required for optimal PCB degradative activity. Degradation in soil systems where numerous carbon sources are present is more than 50-fold slower compared to biphenyl assays. The half-lives for biodegradation of tetra-PCBs in fresh surface water and soil are 7 to 60+ days and 12 to 30 days, respectively. For penta-PCBs and higher chlorinated PCBs, the half-lives in fresh surface water and soil are likely to exceed 1 year. PCBs with all or most chlorines on one ring and PCBs with fewer than two chlorines in the ortho position tend to degrade more rapidly. For example, Gan and Berthouex (1994) monitored over a 5-year period the disappearance of PCB congeners applied to soil with sewage sludge. Three of the tetra- and penta-chlorinated dioxin-like PCBs (IUPAC Nos. 77, 105, and 118) followed a first-order disappearance model with half-lives ranging from 43 to 69 months. A hexa-substituted congener (IUPAC No. 167) and a hepta-substituted congener (IUPAC No. 180) showed no significant loss over the 5-year period.

Until recent years, little investigation focused on anaerobic microbial dechlorination or degradation of PCBs even though most PCBs eventually accumulate in anaerobic sediments (Abramowicz, 1990; Risatti, 1992). Environmental dechlorination of PCBs via losses of meta and para chlorines has been reported in field studies for freshwater, estuarine, and marine anaerobic sediments including those from the Acushnet Estuary, the Hudson River, the Sheboygan River, New Bedford Harbor, Escambia Bay, Waukegan Harbor, and the Housatonic River (Brown et al., 1987; Rhee et al., 1989; Van Dort and Bedard, 1991; Abramowicz, 1990; Bedard et al., 1995). The altered PCB congener distribution patterns found in these sediments (i.e., different patterns with increasing depth or distance from known sources of PCBs) have been interpreted as evidence that bacteria may dechlorinate PCBs in anaerobic sediment.

Results of laboratory studies have been reported recently that confirm anaerobic degradation of PCBs. Chen et al. (1988) found that "PCB-degrading" bacteria from the Hudson River could significantly degrade the mono-, di-, and tri-PCB components of a 20

ppm Aroclor 1221 solution within 105 days. These congeners make up 95 percent of Aroclor 1221. No degradation of higher chlorinated congeners (present at 30 ppb or less) was observed, and a separate 40-day experiment with tetra-PCB also showed no degradation.

Rhee et al. (1989) reported degradation of mono- to penta-substituted PCBs in contaminated Hudson River sediments held under anaerobic conditions in the laboratory (N_2 atmosphere) for 6 months at 25°C. Amendment of the test samples with biphenyl resulted in greater loss of PCB. No significant decreases in the concentrations of the more highly chlorinated (i.e., more than five chlorines) were observed. No evidence of degradation was observed in samples incubated in CO_2/H_2 atmospheres. Abramowicz (1990) hypothesized that this result could be an indication that, in the absence of CO_2, a selection is imposed favoring organisms capable of degrading PCBs to obtain CO_2 and/or low molecular weight metabolites as electron receptors.

VanDort and Bedard (1991) reported the first experimental demonstration of biologically-mediated ortho dechlorination of a PCB and stoichiometric conversion of that PCB congener (2,3,5,6-TeCB) to less-chlorinated forms. In that study, 2,3,5,6-TeCB was incubated under anaerobic conditions with unacclimated methanogenic pond sediment for 37 weeks with reported dechlorination to 2,5-DCB (21%); 2,6-DCB (63%); and 2,3,6-TrCB (16%).

Risatti (1992) examined the degradation of PCBs at varying concentrations (10,000 ppm, 1,500 ppm, and 500 ppm) in the laboratory with "PCB-degrading" bacteria from Waukegan Harbor. After 9 months of incubation at 22°C, the 500 ppm and 1,500 ppm samples showed no change in PCB congener distributions or concentrations, thus indicating a lack of degradation. Significant degradation was observed in the 10,000 ppm sediment with at least 20 congeners ranging from TrCBs to PeCBs showing decreases.

Quensen et al. (1988) also demonstrated that microorganisms from PCB-contaminated sediments (Hudson River) dechlorinated most PCBs in Aroclor 1242 under anaerobic laboratory conditions. Aroclor 1242 contains predominantly tri- and tetra-PCBs. Three concentrations of the Aroclor corresponding to 14, 140, and 700 ppm on a sediment dry-weight basis were used. Dechlorination was most extensive at the 700 ppm test concentration; 53 percent of the total chlorine were removed in 16 weeks, and the proportion of TeCBs through HxCBs decreased from 42 to 4 percent. Much less

degradation was observed in the 140 ppm sediment, and no observable degradation was found in the 14 ppm sediment. These results and those of Risatti (1992) suggest that the organism(s) responsible for this dechlorination may require relatively high levels of PCB as a terminal electron acceptor to maintain a growing population.

Quensen et al. (1990) reported that dechlorination of Aroclor 1242, 1254, and 1260 by microorganisms from PCB-contaminated sediments in the Hudson River and Silver Lake occurred primarily at the meta and para positions; ortho-substituted mono- and di-PCBs increased in concentration.

Nies and Vogel (1990) reported similar results with Hudson River sediments incubated anaerobically with acetone, methanol, or glucose. Approximately 300 μg/g of Aroclor 1242 was added to the sediments to increase the concentrations of higher chlorinated congeners in the sediments prior to incubation for 22 weeks under an N_2 atmosphere. Significant dechlorination over time was observed with dechlorination occurring primarily at the meta- and para-positions on the highly chlorinated congeners resulting in the accumulation of less-chlorinated, primarily ortho-substituted congeners. No significant dechlorination was observed in the control samples (i.e., samples containing no added organic chemical substrate and samples which had been autoclaved).

Bedard et al. (1995) demonstrated that it is possible to stimulate substantial microbial dechlorination of the highly chlorinated PCB mixture Aroclor 1260 *in situ* with a single addition of 2,6-dibromobiphenyl. Bedard et al. (1995) added 365 g of 2,6-dibromobiphenyl to 6-foot diameter submerged caissons containing 400 kg sediment (dry weight) and monitored the change in PCB congener concentrations for a period of 1 year. At the end of the observation period, the hexa- through mono-chlorinated PCBs had decreased by 74 percent in the top of the sediment and 69 percent in the bottom. The average number of chlorines per molecule dropped by 21 percent from 5.83 to 4.61 with the largest reduction observed in meta-chlorines (54 percent reduction) followed by para-chlorines (6 percent). The dechlorination stimulated by 2,6-dibromobiphenyl selectively removed meta-chlorines positioned next to other chlorines.

The findings of these latter studies are significant because removal of meta and para chlorines from the dioxin-like PCBs should reduce their toxicity and bioaccumulative potential and also form less chlorinated congeners that are more amenable to aerobic biodegradation. In support of the findings of these studies, Mousa et al. (1997)

demonstrated that the PCBs present in extracts from PCB-contaminated sediments (i.e., Aroclor 1242 and 1254) that had been incubated for nine months under anaerobic conditions had either reduced biological activities or did not manifest any significant change, depending upon the toxicological endpoint used.

2.7. ENVIRONMENTAL FATE - BROMINATED COMPOUNDS

2.7.1. Summary

Although there are few published studies documenting measured fate rate constants, relatively few studies with measured physical/chemical property data, and few relevant environmental monitoring studies, it is possible to estimate the environmental transport and transformation processes for the brominated dioxin-like compounds using the available published information and using structure activity and property estimation methods. Mill (1989) performed such an assessment, and much of the limited information published since 1989 supports the conclusions of Mill (1989).

Mill (1989) concluded that the estimated physical/chemical properties of these compounds indicate they will behave in a similar fashion to their chlorinated analogues. In general, these chemicals are expected to be stable under normal environmental conditions, relatively immobile in the environment, and primarily associated with particulate and organic materials. The only environmentally significant path for destruction is photodegradation. If discharged to the atmosphere, any vapor-phase compounds will probably be rapidly photolyzed. The higher brominated congeners, like their chlorinated counterparts, may be present primarily in a particle-bound rather than gaseous phase. If so, they likely will be more resistant to photolysis and become more widely dispersed in the environment.

Upon deposition onto surfaces, there can be an initial loss due to photodegradation and/or volatilization. Once sorbed onto soils or sediments, however, they are expected to be strongly sorbed with erosion and aquatic transport of sediment the dominant physical transport mechanism. If discharged to water, they are expected to preferentially sorb to solids. Volatilization may also be a significant transport mechanism for nonsorbed chemicals even though they have negligible estimate vapor pressures.

2.7.2. Transport Mechanisms

Little information exists on the environmental transport of brominated dioxin-like compounds. For example, Jacobs et al. (1978) reported that less than 0.2 percent of 2,2',4,4',5,5'-hexa-PBB (14μg PBB/g of soil) and 2,2',3,4,4',5,5'-hepta-PBB (7μg PBB/g of soil) volatilized from soil incubated for 1 year at 28°C. However, the available information on the physical/chemical properties of these compounds and their chlorinated analogs coupled with the body of information available on the widespread occurrence and persistence of the chlorinated analogs in the environment indicate that these compounds are likely to be strongly sorbed by soils, sediments, and other particulate material, and to be resistant to leaching and volatilization.

2.7.3. Transformation Processes

2.7.3.1. Photolysis. Photolysis appears to be a major potential pathway for loss of brominated dioxin-like compounds in water, air, and soil. The available data indicate that BDDs and BDFs undergo photolytic degradation more readily than their chlorinated analogs. Also, BCDDs and BCDFs appear to undergo debromination more readily than dechlorination. However, no photolysis studies have been published that used natural waters as the reaction medium or that measured gas-phase photolysis rates. Most studies have been conducted using reaction media consisting of homogenous solutions in organic solvent mixtures or clean solid surfaces. Thus, although photolysis of brominated dioxin-like compounds at environmentally significant rates has been observed in laboratory studies, the results of these studies may not be representative of photolysis rates that occur under actual environmental conditions. The following subsections summarize the key findings of recent environmentally significant studies for the water, soil, and air media.

Photolysis in Organic Solvents. Buser (1988) studied the photolytic decomposition rates of the following compounds in dilute isooctane solutions in quartz vials and as solid phases on quartz surfaces under sunlight (47 degrees north latitude): 1,2,3,4-TBDD; 2,3,7,8-TBDD; 2,3,7,8-TBDF; and mono- and dibrominated 2,3,7,8-TCDD and 2,3,7,8-TCDF. Estimated half-lives were very short, on the order of minutes for solution photolysis. Solid-phase photolysis was significantly slower with half-lives in the range of 7 to 35 hours. The major photolytic pathway was reductive dehalogenation with the

formation of lower halogenated or unsubstituted dibenzo-p-dioxins and dibenzofurans. The bromo-chlorodibenzofurans degraded faster than either the brominated or chlorinated congeners. The major pathway of photolysis was debromination to form a chlorinated dibenzofuran.

Lenoir et al. (1991) studied the photolysis in hexane and methanol of a series of mono-through octa-substituted BDD. Several BDFs (di-, tetra-, and hepta-BDF) were also studied as were a series of CDDs for comparison purposes. The results reported by Lenoir et al. (1991) were similar to those reported by Buser (1988) with half-lives on the order of minutes. Bromines at the lateral positions (i.e., 2, 3, 7, and 8 positions) reacted faster than bromines at the peri-positions (i.e., 1, 4, 6, and 9 positions). The bromine compounds reacted nearly an order of magnitude faster than the chlorine analogs. Photolysis in methanol was found to be nearly six times faster than in hexane.

Chatkittikunwong and Creaser (1994) studied the fate of a mixture of mono-through penta-substituted BDDs and BCDDs dissolved in dodecane in borosilicate glass vials exposed to sunlight through a laboratory window. The results indicated that for both the BDDs and the BCDDs the major mechanism of degradation was consecutive debromination from higher congeners to lower congeners. The half-lives calculated by Chatkittikunwong and Creaser (1994) for various congener groups (listed below) are much greater than those reported by Buser (1988). Chatkittikunwong and Creaser (1994) attribute the difference to the fact that borosilicate glass is more effective than quartz at absorbing those wavelengths most likely to cause degradation of these compounds.

Congener Group	Estimated Average Half-Life in Dodecane (hrs)
PeBDD	150
TBDD	480
Br_2Cl_2DD	580
Br_3Cl_1DD	650
Br_1Cl_4DD	480
Br_2Cl_3DD	995
Br_3Cl_2DD	300
Br_4Cl_1DD	520
Br_1Cl_5DD	520

Watanabe et al. (1994) extracted BDFs and BCDFs from the soil at a metal reclamation facility using hexane and exposed the hexane solution to natural sunlight. The half-lives calculated by Watanabe et al. (1994) for various congener groups are listed below. The half-lives decrease with increasing number of bromines.

Congener Group	Estimated Average Half-Life in Hexane (min)
Br_1Cl_3DF	43
Br_2Cl_2DF	11
Br_3Cl_1DF	6.5
TBDF	4.0
Br_1Cl_4DF	18
Br_2Cl_3DF	4.9
Br_3Cl_2DF	5.4
Br_4Cl_1DF	3.1
PeBDF	2.7
Br_1Cl_5DF	9.8
Br_2Cl_4DF	5.7
Br_1Cl_6DF	12

Photolysis in Water. No published studies were located that measured the photolysis rates of brominated dioxin-like compounds in water. Mill (1989) used the results obtained by Buser (1988) together with assumptions to overcome the lack of quantum yield data from Buser (1988) to estimate the photolysis half-lives of the three brominated-only compounds tested by Buser (1988). Mill (1989) estimated the following half-lives in water (top 1 meter) for clear-sky conditions in mid-summer at 40 degrees north latitude:

Congener	Estimated Half-Life in Water (hrs)
1,2,3,4-TBDD	7
2,3,7,8-TBDD	2
2,3,7,8-TBDF	1.7

Photolysis in Soil. Chatkittikunwong and Creaser (1994) studied the fate of a mixture of mono- through penta-substituted BDDs and BCDDs spiked onto soil (5 mm depth) exposed to full sun outdoors for a 3-month period. The pattern of degradation was

similar to that observed in solution (i.e., debromination of higher congeners with formation of lower congeners) although the rate of degradation was much slower (by a factor of about 4) than observed in solution. For example, the calculated average half-lives for PeBDDs and TBDDs were 600 hours and 2,330 hours, respectively.

Photolysis in Air. No published studies were located that measured the photolysis rates of brominated dioxin-like compounds in the gas phase in air. Mill (1989) used the results obtained by Buser (1988) together with assumptions to overcome the lack of quantum yield data from Buser (1988) to estimate the photolysis half-lives of the three brominated-only compounds tested by Buser (1988). Mill (1989) estimated the following gas-phase half-lives (first kilometer above surface) for clear-sky conditions in mid-summer at 40 degrees north latitude:

Congener	Estimated Half-Life in Air (min)
1,2,3,4-TBDD	<1
2,3,7,8-TBDD	0.3
2,3,7,8-TBDF	0.2

Lutes et al. (1992a, 1992b) studied the short-term photochemistry of tetra- and penta-BDDs and BDFs sorbed onto airborne soot particles in 25 m^3 outdoor Teflon film chambers. The emissions from high temperature (640 to 760°C) controlled burning of polyurethane foam containing polybrominated diphenyl ether flame retardants served as the source of the particulate-bound BDDs and BDFs. Initial experiments demonstrated that more than 95 percent of the BDDs/BDFs were associated with airborne particulate material; less than 5 percent were in the vapor phase. Particulate phase concentrations of tetra- and penta-CDD/CDFs were monitored for 3 to 6 hours after introduction of the emissions from the foam burn to the chamber under winter and spring temperatures and sunlight regimes in Pittsboro, North Carolina. No significant reduction in concentration was observed. The authors concluded that if photolytic degradation was occurring, then the half-lives are much greater than 3 to 6 hours.

Birla and Kamens (1994) expanded the research of Lutes et al. (1992a; 1992b) by examining the effect of combustion temperature on the atmospheric stability of BDDs and BDFs generated using the same polyurethane combustion apparatus. Both "high temperature" (745 to 780°C) and "low temperature" (400 to 470°C) combustion

temperatures were studied. The results obtained from the high temperature experiments were similar to those obtained by Lutes et al. (1992a; 1992b) in that there was little evidence of any decay in particulate-bound BDDs and BDFs. In the low temperature experiments, production of TBDFs and PeBDFs and decay of TBDDs were observed. Birla and Kamens (1994) attributed the increase in particulate-bound TBDF and PeBDF levels to photolysis of unburned polybrominated diphenyl ether flame retardants. The decay of TBDD was attributed to differences in physical and chemical properties of the particles generated from the high and low temperature experiments.

Watanabe et al. (1994) collected air dust on glass filters for a period of 24 hours in Osaka, Japan, and then exposed the glass filters to 24 hours of sunlight. More than 10 congener groups of BCDFs as well as TBDFs and PeBDFs were measured in the collected dust prior to irradiation. Although there was a reduction in the concentration of every congener group over the exposure period with the largest decrease observed for the lower halogenated congeners, Watanabe et al. (1994) concluded that most of the decrease was probably due to volatilization rather than photolysis.

2.7.3.2. Oxidation

No reaction rate data for OH radicals with gas-phase brominated dioxin-like compounds could be located. The low vapor pressures of these compounds make direct measurements very difficult with the current techniques. However, Mill (1989), using a structure activity relationship developed by Atkinson (1987), has estimated the half-lives of OH oxidation for the tetra- through octa- BDDs and BDFs. The estimated half-lives listed below indicate that OH oxidation is probably too slow to compete with photolysis.

Number of Bromines	BDD Half-Life in Air (hrs)	BDF Half-Life in Air (hrs)
4	50	420
5	50	430
6	100	960
7	200	1900
8	770	3800

2.7.3.3. Hydrolysis

No evidence is available indicating that hydrolysis would be a significant degradation process for these compounds.

2.7.3.4. Biotransformation and Biodegradation

Although no data are available concerning the biodegradability of the brominated dioxin-like compounds, it is expected that these brominated compounds, especially the more halogenated congeners, will be recalcitrant to biodegradation. The limited data available on PBBs (discussed below) indicate recalcitrance.

Jacobs et al. (1976) examined the distribution and fate of PBBs in the environment following the accidental contamination of livestock feed in Michigan in 1973 with the brominated flame retardant, FireMaster BPG. FireMaster BPG (a.k.a., PBB) was found by Jacobs et al. (1976) to be comprised of 2,2',4,4',5,5'-hexabromobiphenyl as the major component, two isomers of pentabromobiphenyl, three additional isomers of hexabromobiphenyl, and two isomers of heptabromobiphenyl. Jacobs et al. (1976) reported that PBBs are extremely persistent based on the results of aerobic and anaerobic soil incubation studies for 24 weeks with the flame retardant, PBB. Only one major PBB component, a pentabromobiphenyl isomer, showed any significant disappearance; however, Jacobs et al. (1976) were not certain whether the disappearance was due to microbial degradation, to poor soil extraction efficiency, or to sorption onto glassware. Jacobs et al. (1976) also detected components of PBB in soils from a field that had received manure from a PBB-contaminated dairy herd 10 months earlier (quantitative changes in PBB were not possible because no earlier soil samples had been obtained). Additional soil studies by Jacobs et al. (1978) found no degradation of 2,2',4,4',5,5'-hexa-PBB (14μg/25g soil) or 2,2',3,4,4',5,5'-hepta-PBB (7μg/25g soil) after incubation at 28°C for 1 year.

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Table 2-1. Possible Number of Positional CDD (or BDD) and CDF (or BDF) Congeners

Halogen Substitution	Number of Congeners		
	CDDs (or BDDs)	CDFs (or BDFs)	PCBs
Mono	2	4	3
Di	10	16	12
Tri	14	28	24
Tetra	22	38	42
Penta	14	28	46
Hexa	10	16	42
Hepta	2	4	24
Octa	1	1	12
Nona	0	0	3
Deca	0	0	1

Table 2-2. Ranking Scheme for P-Chem Property Evaluation

Ranking	Factors				
	1	2	3	4	5
1	✓	✓	✓	x	x
2	x	✓	✓	x	x
3	✓	x	✓	✓	x
4	x	x	✓	✓	x
5	x	x	x	x	✓

Notes:

✓ indicates all specifications of the Factor have been met.
x indicates the specifications of the Factor have not been met, or the Factor does not apply.

Table 2-3. Selected Physical-Chemical Property Values for the "Dioxin-Like" CDD, CDF, and PCB Congeners

Chemical	Melting Point		Water Solubility			Vapor Pressure			Henry's Constant		Log K_{ow}	
CAS No. (IUPAC No.)	**Value (°C)[a]**	**Ref.**	**Value (mg/l)[a,c]**	**Temp. (°C)**	**Ref. [R][b]**	**Value (mm Hg)[a,c]**	**Temp. (°C)**	**Ref. [R][b]**	**Value ($atm\text{-}m^3/mol$)[a]**	**Ref. [R][b]**	**Value**	**Ref. [R][b]**
Tetrachlorodibenzo-p-dioxins (MW = 321.98)												
2,3,7,8-TCDD 1746-01-6	305-306	9	1.93E-05	25	4,53 [1]	(1.50E-09)	25	9,53 [2]	(3.29E-05)	53 [4]	6.80	53 [1]
Congener Group Average			(3.3E-04)	25	20	(1.4E-08)	25	20	(1.7E-05)	20	(6.5)	20
Pentachlorodibenzo-p-dioxins (MW = 356.42)												
1,2,3,7,8-PeCDD 40321-76-4	240-241	9				(4.4E-10)	25	9 [4]			6.64	10 [2]
Congener Group Average			(1.18E-04)	20	20	(5.6E-10)	25	20	(2.6E-06)	20	(6.6)	20
Hexachlorodibenzo-p-dioxins (MW = 390.87)												
1,2,3,4,7,8-HxCDD 39227-28-6	273-275	9	4.42E-06	25	6,53 [2]	(3.8E-11)	25	53 [4]	(1.07E-05)	53 [4]	7.80	53 [4]
1,2,3,6,7,8-HxCDD 57653-85-7	285-286	9				(3.6E-11)	25	9 [5]				
1,2,3,7,8,9-HxCDD 19408-74-3	243-244	9				(4.9E-11)	25	9 [5]				
Congener Group Average			(4.4E-06)	25	20	(4.4E-11)	25	20	(1.1E-05)	20	(7.3)	20
Heptachlorodibenzo-p-dioxins (MW = 425.31)												
1,2,3,4,6,7,8-HpCDD 35822-46-9	264-265	9	2.40E-06	20	6,53 [2]	(5.6E-12)	25	9,53 [4]	(1.26E-05)	53 [4]	8.00	53 [4]
Congener Group Average			(2.4E-06)	20	20	(3.2E-11)	25	20	(1.26E-05)	20	(8.0)	20
Octachlorodibenzo-p-dioxins (MW = 460.76)												
1,2,3,4,6,7,8,9-OCDD 3268-87-9	325-326	6	7.4E-08	25	5,53 [2]	(8.25E-13)	25	9,53 [2]	(6.75E-06)	5,53 [4]	8.20	5,53 [2]

Table 2-3. P-Chem Properties for the Dioxin-Like Congeners (continued)

Chemical CAS No. (IUPAC No.)	Melting Point		Water Solubility			Vapor Pressure			Henry's Constant		Log K_{ow}	
	Value (°C)[a]	Ref.	Value (mg/l)[a,c]	Temp. (°C)	Ref. [R][b]	Value (mm Hg)[a,c]	Temp. (°C)	Ref. [R][b]	Value (atm-m^3/mol)[a]	Ref. [R][b]	Value	Ref. [R][b]
Tetrachlorodibenzofurans (MW = 305.98)												
2,3,7,8-TCDF 51207-31-9	227-228	21	4.19E-04	22.7	11 [2]	(1.5E-08)	25	21,53 [4]	(1.44E-05)	53 [4]	6.1	53 [2]
Congener Group Average			(4.2E-04)	22.7	20	(2.5E-08)	25	20	(1.4E-05)	20	(6.2)	20
Pentachlorodibenzofurans (MW = 340.42)												
1,2,3,7,8-PeCDF 57117-41-6	225-227	21				(1.7E-09)	25	21 [4]			6.79	10 [2]
2,3,4,7,8-PeCDF 57117-31-4	196- 196.5	21	2.36E-04	22.7	11 [2]	(2.6E-09)	25	21,53 [4]	(4.98E-06)	53 [4]	6.5	53 [2]
Congener Group Average			(2.4E-04)	22.7	20	(2.7E-09)	25	20	(5.0E-06)	20	(6.4)	20
Hexachlorodibenzofurans (MW = 374.87)												
1,2,3,4,7,8-HxCDF 70648-26-9	225.5- 226.5	21	8.25E-06	22.7	11 [2]	(2.4E-10)	25	21,53 [5]	(1.43E-05)	19 [5]	(7.0)	53
1,2,3,6,7,8-HxCDF 57117-44-9	232-234	21	1.77E-05	22.7	11 [2]	(2.2E-10)	25	21 [5]	(7.31E-06)	53 [5]		
1,2,3,7,8,9-HxCDF 72918-21-9	246-249[d]	21										
2,3,4,6,7,8-HxCDF 60851-34-5	239-240	21				(2.0E-10)	25	21 [5]				
Congener Group Average			(1.3E-05)	22.7	20	(2.8E-10)	25	20	(1.1E-05)	20	(7.0)	20
Heptachlorodibenzofurans (MW = 409.31)												
1,2,3,4,6,7,8-HpCDF 67562-39-4	236-237	21	1.35E-06	22.7	11 [2]	(3.5E-11)	25	21,53 [4]	(1.41E-05)	53 [4]	(7.4)	53 [2]

Table 2-3. P-Chem Properties for the Dioxin-Like Congeners (continued)

Chemical CAS No. (IUPAC No.)	Melting Point		Water Solubility			Vapor Pressure			Henry's Constant		Log K_{ow}	
	Value (°C)[a]	Ref.	Value (mg/l)[a,c]	Temp. (°C)	Ref. [R][b]	Value (mm Hg)[a,c]	Temp. (°C)	Ref. [R][b]	Value (atm-m^3/mol)[a]	Ref. [R][b]	Value	Ref. [R][b]
1,2,3,4,7,8,9-HpCDF 55673-89-7	221-223	21				1.07E-10 (4.7E-11)	25	21,53 [4]				
Congener Group Average			(1.4E-06)	22.7	20	(4.7E-11)	25	20	(1.4E-05)	20	(7.4)	20
Octachlorodibenzofurans (MW = 444.76)												
1,2,3,4,6,7,8,9-OCDF 39001-02-0	258-260	21	(1.16E-06)	25	11 [2]	3.75E-12	25	21 [2]	(1.88E-06)	19 [4]	8.0	53 [4]
Tetrachloro-PCB (MW = 291.99)												
3,3',4,4'-TCB 32598-13-3 (77)	180-181	58	1.0E-03	25	56 [2]	4.47E-07	25	56 [2]	1.70E-05	56 [2]	6.5	56 [2]
3,4,4',5-TCB 70362-60-4 (81)	160-163	58	2.92E-03	25	17 [5]	(7.85E-07)	25	18 [4]	1.28E-04	41 [4]	(6.36)	15 [5]
Pentachloro-PCB (MW = 326.44)												
2,3,3',4,4'-PeCB 32598-14-4 (105)	116.5- 117.5	56	(1.90E-03)	25	35 [5]	(8.28E-07)	25	18 [4]	(9.93E-05)	35 [5]	(6.0)	56 [2]
2,3,4,4',5-PeCB 74472-37-0 (114)	98-99	58	(2.58E-03)	20	41 [2]	(4.18E-07)	20	41 [2]	6.90E-05	41 [4]	(6.65)	15 [5]
2,3',4,4',5-PeCB 31508-00-6 (118)	111-113	58	(1.59E-03)	20	41 [2]	(3.14E-07)	20	41 [2]	8.50E-05	41 [4]	7.12	31 [4]
2',3,4,4',5-PeCB 65510-44-3(123)	134-135	58	(1.64E-03)	25	17 [5]	(8.78E-07)	25	18 [4]	1.74E-04	35 [5]	(6.74)	15 [5]
3,3',4,4',5-PeCB 57465-28-8 (126)	160-161	58	(1.03E-03)	25	17 [5]	(2.96E-07)	25	18 [4]	(5.40E-05)	35 [5]	(6.89)	15 [5]
Hexachloro-PCB (MW = 360.88)												

Table 2-3. P-Chem Properties for the Dioxin-Like Congeners (continued)

Chemical CAS No. (IUPAC No.)	Melting Point		Water Solubility			Vapor Pressure			Henry's Constant		Log K_{ow}	
	Value (°C)[a]	Ref.	Value (mg/l)[a,c]	Temp. (°C)	Ref. [R][b]	Value (mm Hg)[a,c]	Temp. (°C)	Ref. [R][b]	Value (atm-m^3/mol)[a]	Ref. [R][b]	Value	Ref. [R][b]
2,3,3',4,4',5-HxCB 38380-08-4 (156)	129.5-131	58	(4.10E-04)	20	41 [2]	(1.47E-07)	25	18 [2]	8.70E-04	43 [4]	7.16	14 [3]
2,3,3',4,4',5'-HxCB 69782-90-7 (157)	161-162	58	(3.61E-04)	25	17 [5]	(5.47E-08)	25	18 [4]	5.80E-04	43 [4]	7.19	14 [3]
2,3',4,4',5,5'-HxCB 52663-72-6 (167)	125-127	58	(3.61E-04)	25	17 [5]	(1.95E-07)	25	18 [4]	(1.10E-04)	35 [5]	7.09	14 [3]
3,3',4,4',5,5'-HxCB 32774-16-6 (169)	208-210	58	(3.61E-05)	25	17 [5]	(1.81E-07)	25	56 [5]	(6.52E-05)	35 [5]	7.46	14 [3]
Heptachloro-PCB (MW = 395.33)												
2,3,3',4,4',5,5'-HpCB 39635-31-9 (189)	162-163	58	(6.26E-05)	25	17 [5]	(1.31E-08)	25	18 [4]	(6.65E-05)	35 [5]	(7.71)	15 [5]
2,2',3,3',4,4',5-HpCB 35065-30-6 (170)	136.5-138.5	58	(2.27E-04)	20	41 [2]	(6.46E-09)	25	41 [2]	1.50E-05	41 [4]	(7.27)	15 [5]
2,2',3,4,4',5,5'-HpCB 35069-29-3 (180)	112.5-114	58	(4.40E-04)	20	41 [2]	(2.72E-08)	25	41 [2]	3.20E-05	41 [4]	(7.36)	15 [5]

Footnote References

a Values are presented as they appeared in the referenced article. Values in ( ) are either estimated or are calculated/extrapolated from experimental values.

b [R] is the ranking of the value from the cited reference.

c For several PCB congeners, subcooled liquid values were converted to solid values using the melting points presented in this table and the conversion methodology presented in Eitzer and Hites (1988) and Mackay et al. (1992).

$\ln (P_{sc}/P_s) = 6.79 (T_m\text{-}T)/T$

where: P_{sc} = subcooled value
P_s = solid value
T_m = melting point (°K)
T = ambient temperature (°K)

d The melting point value for this congener obtained from Ref. 21; however, it was attributed through a probably typographical error to 1,2,3,6,8,9-HxCDF.

1. Marple et al. (1986a)
2. USEPA (1990)
3. Podoll et al. (1986)
4. Marple et al. (1986b)
5. Shiu et al. (1988)
6. Friesen et al. (1985)
8. Burkhard and Kuehl (1986)
9. Rordorf (1987)
10 Sijm et al. (1989)
11. Friesen et al. (1990b)
13. Dunnivant and Elzerman (1988)
14. Risby et al. (1990)
15. Hawker and Connell (1988)
16. Sabljic and Gusten (1989)
17. Abramowitz and Yalkowsky (1990)
18. Foreman and Bidleman (1985)
19. Calculated by the VP/WS ratio technique
20. Average of all literature values (measured and calculated)
21. Rordorf (1989)
22. Dulin et al. (1986)
23. Choudhry and Webster (1987)
25. Choudhry et al. (1990)
30. Orth et al. (1989)
31. Rapaport and Eisenreich (1984)
33. Eitzer and Hites (1988)
35. Dunnivant et al. (1992)
41. Murphy et al. (1987)
43. Murphy et al. (1983)
45. Webster et al. (1986)
50. Marple et al. (1987)
51. Santl et al. (1994)
52. Rordorf et al. (1990)
53. Mackay et al. (1992a)
54. Eitzer and Hites (1989)
55. Sacan and Inel (1995)
56. Mackay et al. (1992b)

Table 2-3. P-Chem Properties for the Dioxin-Like Congeners (continued)

within a homologue group 42. EPRI (1990) 58. Bolgar et al. (1995)

Table 2-4. Summary of Selected Deposition Measurements Reported in the Literature

Author	Year[a]	Sampling Method	Analytes	Sampling Locations	Range of Results
Horstmann and McLachlan	1996	Bergerhoff	CDD/CDF	Germany Rural	0.2-2.3 ng I- TEQ_{DF}/m^2-yr
Smith et al.	1995	Wet deposition; Ambient air samples	CDD/CDF	New York, USA	Total CDD/CDF flux wet: 94 ng/m^2-yr dry: 100 ng/m^2-yr total: 194 ng/m^2-yr
Wallenhorst et al.	1995	Bergerhoff	CDD/CDF	Germany Urban Rural	 11 ng I-TEQ_{DF}/m^2-yr 2-3 ng I-TEQ_{DF}/m^2-yr
DeFré et al.	1994	Bergerhoff	CDD/CDF	Flanders, Belgium Background $<$1 km from MSWI Urban	 0.7-5.1 ng I-TEQ_{DF}/m^2-yr 39-374 ng I-TEQ_{DF}/m^2-yr 13-77 ng I-TEQ_{DF}/m^2-yr
Hiester et al.	1993	Bergerhoff	CDD/CDF/PCB	Germany Urban Rural	 3.6-30.3 ng I-TEQ_{DF}/m^2-yr 4.4 ng I-TEQ_{DF}/m^2-yr
Liebl et al.	1993	Bergerhoff	CDD/CDF	Germany Urban Rural/Industrial Rural	 7.6 ng I-TEQ_{DF}/m^2-yr 1.5 ng I-TEQ_{DF}/m^2-yr 1.1 ng I-TEQ_{DF}/m^2-yr
Andersson et al.	1992	Cotton cloth; snow collector	CDD/CDF	Umea, Sweden	1 ng I-TEQ_{DF}/m^2-yr
Fernandez	1992	Wet and dry frisbee collector	CDD/CDF	United Kingdom Urban-Semiurban	 13-17 ng I-TEQ_{DF}/m^2-yr
Koester and Hites	1992 a	Frisbees; flat glass plates; wet-only collector	CDD/CDF	Indiana, USA	Total CDD/CDF flux wet: 210-220 ng/m^2-yr dry: 160-320 ng/m^2-yr total: 370-540 ng/m^2-yr

a Year represents year of publication, not measurement.

Table 2-5. Percentages of CDD/CDFs in Particulate Phase Measured in Air Monitoring Studies

Reference	Temp. (°C)	Percent of Total Congener Group Mass in Particulate Phase									
		TCDD	PeCDD	HxCDD	HpCDD	OCDD	TCDF	PeCDF	HxCDF	HpCDF	OCDF
A	20	23	37	66	87	96	14	31	64	87	91
B	3	40	87	100	100	100	100	60	88	100	98
B	16 - 20	8	28	45	88	100	ND	28	30	93	100
B	>28	5	13	45	60	100	ND	0	38	78	98
C		21	20	24	70	85	23	26	29	59	94
C		3	5	12	64	90	7	12	15	43	91
D	18	NR	NR	92	100	78	14	42	73	100	100
D	18	NR	NR	100	100	100	5	43	100	100	NR
E (urban)	NR	ND	0	65	82	100	20	71	100	100	100
E (rural)	NR	ND	ND	100	100	100	ND	ND	ND	ND	ND
F	18	10	28	45	77	93	9	22	48	77	89
G	9.5	31	59	82	>96	>97	18	55	79	>93	>94

NR = Not reported.
ND = Not detected.
Source: Volume 3. References are as follows:

Reference A: Eitzer and Hites (1989)
Reference B: Hites and Harless(1991)
Reference C: Harless and Lewis (1992)
Reference D: Hunt and Maisel (1992)
Reference E: Bobet et al. (1990)
Reference F: Welsch-Pausch et al. (1995) (data provided by authors); values presented for HpCDD, OCDD, HpCDF, and OCDF represent lower limits.
Reference G: Hippelein et al. (1996); values represent annual means for six sites in the outskirts of Augsburg, Germany.

Table 2-6. Predicted Fractions of CDD/CDF Congeners in Particulate Phase at 20°C in Four Airsheds

Congener	Fraction in Particulate Phase by Airshed Type			
	Clean Continental	Average Background	Background Plus Local Sources	Urban
2,3,7,8-TCDD	0.10	0.29	0.49	0.75
1,2,3,7,8-PeCDD	0.44	0.74	0.87	0.95
1,2,3,4,7,8-HxCDD	0.78	0.93	0.97	0.99
1,2,3,6,7,8-HxCDD	0.78	0.93	0.97	0.99
1,2,3,7,8,9-HxCDD	0.78	0.93	0.97	0.99
1,2,3,4,6,7,8-HpCDD	0.93	0.98	0.99	>0.99
OCDD	0.98	>0.99	>0.99	>0.99
2,3,7,8-TCDF	0.09	0.27	0.47	0.73
1,2,3,7,8-PeCDF	0.27	0.57	0.75	0.91
2,3,4,7,8-PeCDF	0.38	0.69	0.84	0.94
1,2,3,4,7,8-HxCDF	0.63	0.86	0.93	0.98
1,2,3,6,7,8-HxCDF	0.63	0.86	0.93	0.98
1,2,3,7,8,9-HxCDF	0.74	0.91	0.96	0.99
2,3,4,6,7,8-HxCDF	0.74	0.91	0.96	0.99
1,2,3,4,6,7,8-HpCDF	0.86	0.96	0.98	0.99
1,2,3,4,7,8,9-HpCDF	0.92	0.98	0.99	>0.99
OCDF	0.98	>0.99	>0.99	>0.99

Source: Chapter 3 of Volume 3.

Table 2-7. Factors Influencing the Dry Deposition Removal Rate in the Atmosphere

Micrometeorological Variables	Characteristics of Particles	Characteristics of Gases	Surface Variables
Aerodynamic roughness Mass transfer of Particles Gases Heat transfer Momentum transfer Atmospheric stability Diffusion Friction velocity Inversion layer Pollutant concentration Relative humidity Seasonal variation Solar radiation Surface heating Temperature Terrain effects Turbulence Wind velocity Zero plane displacement effect Mass transfer of Particles Gases Heat transfer Momentum transfer	Agglomeration Diameter Diffusion effects Brownian Eddy Particle Momentum Heat Electrostatic effects Attraction Repulsion Gravity settling Hygroscopicity Impaction Interception Momentum Physical properties Resuspension Solubility Thermophoresis	Chemical Activity Diffusion effects Brownian Eddy Partial pressure in equilibrium with the surface Solubility	Accommodation: Exudates Trichomes Pubescence Wax Biotic surface Canopy growth Dormant Expanding Senescent Canopy structure Areal density Bark Bole Leaves Porosity Soils Stem Type Electrostatic properties Water Pollutant penetration of canopy

Source: Adapted from Sehmel (1980).

Table 2-8. Rain Scavenging Ratios (W) and Percent Washout Due to Particulates (%P) for CDDs and CDFs in Bloomington and Indianapolis Ambient Air

Congener Group	Bloomington, IN		Indianapolis, IN	
	W	%P	W	%P
TCDD	a	a	a	a
PeCDD	10,000	50	30,000	67
HxCDD	10,000	88	26,000	69
HpCDD	62,000	93	91,000	78
OCDD	90,000	80	150,000	60
TCDF	22,000	21	33,000	24
PeCDF	14,000	54	18,000	35
HxCDF	11,000	77	15,000	74
HpCDF	34,000	88	32,000	79
OCDF	21,000	52	41,000	87
Total CDD/CDF	---	68	---	64

[a] Rarely detected; no calculations performed.

Sources: Hites and Harless (1991); Koester and Hites (1992a).

Table 2-9. Log BCF Values for CDD/CDFs in Fish

Congener	Measured Log BCFs Various Species (Reference A)	Measured Log BCFs Guppy (Reference B)	Calculated Log BCFs Guppy (Reference C)
2,3,7,8-TCDD	3.73-5.90	5.24	5.48
1,2,3,7,8-PeCDD		5.27	5.34
1,2,3,4,7,8-HxCDD	3.23-4.00	5.01	5.07
1,2,3,6,7,8-HxCDD		4.94	5.08
1,2,3,7,8,9-HxCDD		4.93	5.18
1,2,3,4,6,7,8-HpCDD	2.71-3.32	4.68	4.79
OCDD	1.90-3.97	4.13	4.39
2,3,7,8-TCDF	3.39-4.82		4.93
1,2,3,7,8-PeCDF			4.84
2,3,4,7,8-PeCDF	3.70	5.14	4.79
1,2,3,4,7,8-HxCDF			4.57
1,2,3,6,7,8-HxCDF		4.95	4.58
1,2,3,7,8,9-HxCDF			4.71
2,3,4,6,7,8-HxCDF			4.59
1,2,3,4,6,7,8-HpCDF		4.46	4.26
1,2,3,4,7,8,9-HpCDF			4.32
OCDF	2.77	3.90	3.88

Reference A: Mackay et al. (1992a); wet weight BCFs.
Reference B: Govers and Krop (1996); lipid-adjusted BCFs.
Reference C: Govers and Krop (1996); values calculated with the Solubility Parameters for Fate Analysis model.

Table 2-10. CDD/CDF BSAFs and BEFs for Lake Ontario Lake Trout

Congener	Estimated Log K_{ow}[a]	BSAF	BEF
2,3,7,8-TCDD	7.02	0.059	1.0
1,2,3,7,8-PeCDD	7.50	0.054	0.92
1,2,3,4,7,8-HxCDD	7.80	0.018	0.31
1,2,3,6,7,8-HxCDD	7.80	0.0073	0.12
1,2,3,7,8,9-HxCDD	7.80	0.0081	0.14
1,2,3,4,6,7,8-HpCDD	8.20	0.0031	0.051
OCDD	8.60	0.00074	0.012
2,3,7,8-TCDF	6.5[b]	0.047	0.80
1,2,3,7,8-PeCDF	7.0[b]	0.013	0.22
2,3,4,7,8-PeCDF	7.0[b]	0.095	1.6
1,2,3,4,7,8-HxCDF	7.5[b]	0.0045	0.076
1,2,3,6,7,8-HxCDF	7.5[b]	0.011	0.19
2,3,4,6,7,8-HxCDF	7.5[b]	0.040	0.67
1,2,3,7,8,9-HxCDF	7.5[b]	0.037	0.63
1,2,3,4,6,7,8-HpCDF	8.0[b]	0.00065	0.011
1,2,3,4,7,8,9-HpCDF	8.0[b]	0.023	0.39
OCDF	8.80	0.001	0.016

Source: U.S. EPA (1995).

[a] Burkhard and Kuehl (1986).
[b] Estimated based on degree of chlorination and Burkhard and Kuehl (1986).

Table 2-11. Photolysis Rates of CDDs/CDFs in Water and Water:Acetonitrile Mixtures

CONGENER	LIGHT SOURCE	REACTION MEDIUM	PHOTOLYSIS RATE CONSTANT (1/day)	HALF-LIFE (days) DURING SUMMER	REFERENCE
CDDs					
1,2,7,8-TCCDD	sunlight	water from 7 ponds/lakes	4.06	0.17	Kim and O'Keefe (1998)
1,3,6,8-TCDD	Hg lamp	pond water	0.198	3.5	Choudry and Webster (1989)
2,3,7,8-TCDD	sunlight	water:acetonitrile (1:1 v/v)	0.255	2.7	Podoll et al. (1986)
2,3,7,8-TCDD	Hg lamp	water:acetonitrile (1:1 v/v)	0.78	0.9	Podoll et al. (1986)
1,2,3,4,7,8-HxCDD	Hg lamp	water:acetonitrile (2:3 v/v)	0.111	6.3	Choudry and Webster (1989)
1,2,3,4,6,7,8-HpCDD	Hg lamp	water:acetonitrile (2:3 v/v)	0.0148	47	Choudry and Webster (1989)
OCDD	Hg lamp	water:acetonitrile (2:3 v/v)	0.0397	18	Choudry and Webster (1989)
OCDD	sunlight	water from 7 ponds/lakes	1.04	0.67	Kim and O'Keefe (1998)
CDFs					
2,3,7,8-TCDF	sunlight	water from 7 ponds/lakes	3.87	0.18	Kim and O'Keefe (1998)
1,2,7,8-TCDF	sunlight	HPLC water	1.96	0.35	Dung and O'Keefe (1992)
1,2,7,8-TCDF	sunlight	distilled water	2.18	0.32	Dung and O'Keefe (1992)
1,2,7,8-TCDF	sunlight	Saratoga Lake	3.53	0.20	Dung and O'Keefe (1992)
1,2,7,8-TCDF	sunlight	Hudson River	3.96	0.18	Dung and O'Keefe (1992)
1,2,7,8-TCDF	Hg lamp	HPLC water	24.5	0.03	Dung and O'Keefe (1992)
2,3,7,8-TCDF	sunlight	water:acetonitrile (1:2.5 v/v)	0.106	6.5	Friesen et al. (1993)
2,3,7,8-TCDF	sunlight	lake water	0.58	1.2	Friesen et al. (1993)
2,3,7,8-TCDF	sunlight	distilled water	1.49	0.47	Dung and O'Keefe (1992)
2,3,7,8-TCDF	sunlight	HPLC water	1.56	0.44	Dung and O'Keefe (1992)
2,3,7,8-TCDF	sunlight	Saratoga Lake	2.64	0.26	Dung and O'Keefe (1992)
2,3,7,8-TCDF	sunlight	Hudson River	2.83	0.25	Dung and O'Keefe (1992)
2,3,7,8-TCDF	Hg lamp	HPLC water	16.8	0.04	Dung and O'Keefe (1992)
2,3,4,7,8-PeCDF	sunlight	water:acetonitrile (1:2.5 v/v)	0.015	46.2	Friesen et al. (1993)
2,3,4,7,8-PeCDF	sunlight	lake water	3.59	0.19	Friesen et al. (1993)
OCDF	sunlight	water from 7 ponds/lakes	1.19	0.58	Kim and O'Keefe (1998)

Table 2-12. Estimated Tropospheric Half-Lives of CDDs/CDFs with Respect to Gas-Phase Reaction with the OH Radical

Congener Group	2,3,7,8-Substituted Congener	Estimated OH Reaction Rate Constant (cm^3/molecule-sec)	Estimated Tropospheric Lifetime[a,b] (days)	Estimated Tropospheric Half-Life[a,c] (days)
TCDD	2,3,7,8-TCDD	7.08E-13	17	12
PeCDD	1,2,3,7,8-PeCDD	4.59E-13	26	18
HxCDD	1,2,3,4,7,8-HxCDD 1,2,3,6,7,8-HxCDD 1,2,3,7,8,9-HxCDD	1.97E-13 2.95E-13 2.95E-13	61 40 40	42 28 28
HpCDD	1,2,3,4,6,7,8-HpCDD	1.30E-13	92	64
OCDD	OCDD	5.09E-14	234	162
TCDF	2,3,7,8-TCDF	4.26E-13	28	19
PeCDF	1,2,3,7,8-PeCDF 2,3,4,7,8-PeCDF	2.65E-13 2.49E-13	45 48	31 33
HxCDF	1,2,3,4,7,8-HxCDF 1,2,3,6,7,8-HxCDF 1,2,3,7,8,9-HxCDF 2,3,4,6,7,8-HxCDF	1.06E-13 1.51E-13 1.62E-13 1.40E-13	113 79 74 85	78 55 51 59
HpCDF	1,2,3,4,6,7,8-HpCDF 1,2,3,4,7,8,9-HpCDF	6.04E-14 6.78E-14	198 176	137 122
OCDF	OCDF	2.58E-14	462	321

a Calculated using a 24-hour, seasonal, and global tropospheric average OH radical concentration of 9.7 X 10^5molecule/cm^3 (Prinn et al., 1995).
b Lifetime = $[(\text{reaction rate constant})(\text{OH concentration})]^{-1}$.
c Half-life = 0.693/[(reaction rate constant)(OH concentration)].

Source: Based on Atkinson (1996).

Table 2-13. BAFs, BCFs, and BSAFs for Dioxin-Like PCBs

PCB Congener/ Congener Group	Log BAFs[a]				Log BCFs[b] Various Species	BSAFs[c] Lake Trout
	Zooplankton	Sculpin	Alewive	Salmonids		
77					3.24-4.15	0.29
81[d]	7.47	7.48	7.79	7.96		0.67
105	7.36	7.82	7.72	8.13		2.70-4.49
118	7.37	7.86	7.71	8.15		1.72-4.09
126						3.21
156						3.97
167						0.69
170[e]	8.20	9.15	8.84	9.20		2.06-4.17
180	7.66	8.45	8.15	8.58		3.26-3.78
189						0.71
TeCB					3.95-4.79	
PeCB					5.0-5.30	
HxCB					5.39	
HpCB					5.80	

[a] U.S. EPA (1995); citing data from Oliver and Niimi (1988).
[b] Mackay et al. (1992b)
[c] U.S. EPA (1995).
[d] Includes congeners 81, 56, and 60.
[e] Includes congeners 170 and 190.

Table 2-14. Estimated Tropospheric Half-Lives of Dioxin-Like PCBs with Respect to Gas-Phase Reaction with the OH Radical

Congener Group	Dioxin-Like Congener	Estimated OH Reaction Rate Constant (10^{-12} cm^3/molecule-sec)	Estimated Tropospheric Lifetime (days)[a]	Estimated Tropospheric Half-Life (days)[a]
TCB	3,3',4,4'-TCB	0.583	20	14
	3,4,4',5-TCB	0.710	17	12
PeCB	2,3,3',4,4'-PeCB	0.299	40	28
	2,3,4,4',5-PeCB	0.383	31	22
	2,3',4,4',5-PeCB	0.299	40	28
	2',3,4,4',5-PeCB	0.482	25	17
	3,3',4,4',5-PeCB	0.395	30	21
HxCB	2,3,3',4,4',5-HxCB	0.183	65	45
	2,3,3',4,4',5'-HxCB	0.214	56	39
	2,3',4,4',5,5'-HxCB	0.214	56	39
	3,3',4,4',5,5'-HxCB	0.266	45	31
HpCB	2,2',3,3',4,4',5-HpCB	0.099	121	84
	2,2',3,4,4',5,5'-HpCB	0.099	121	84
	2,3,3',4,4',5,5'-HpCB	0.125	95	66

cm^3 = cubic centimeters.

[a] Calculated using a 24-hour, seasonal, annual, and global tropospheric average OH radical concentration of 9.7×10^5 molecule/cm^3 (Prinn et al., 1995).

Source: Atkinson (1995) [Based on Atkinson (1991) and Kwok et al. (1995)].

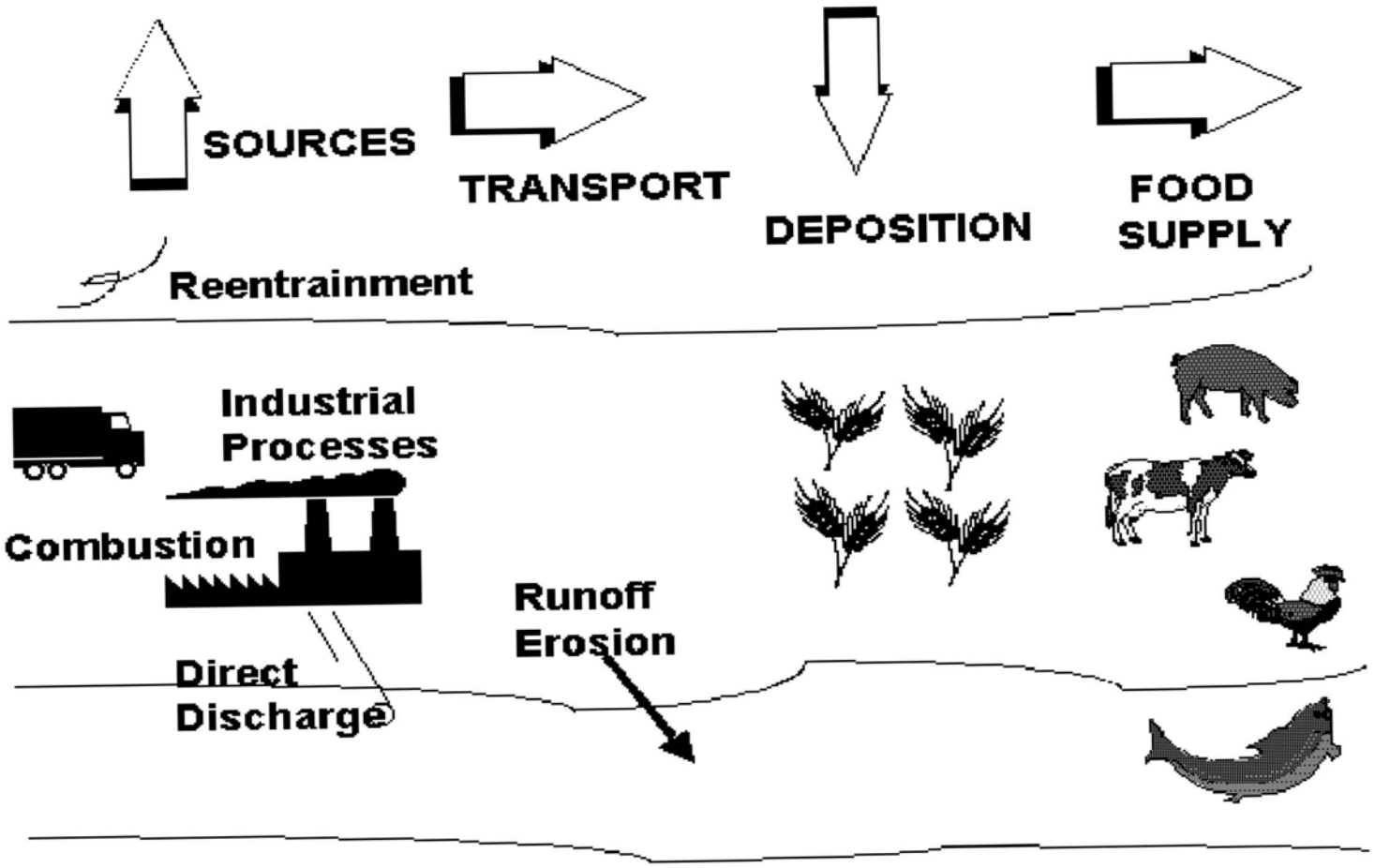

Figure 2-1. Pathways for Entry of Dioxin-like Compounds into the Terrestrial and Aquatic Food Chains

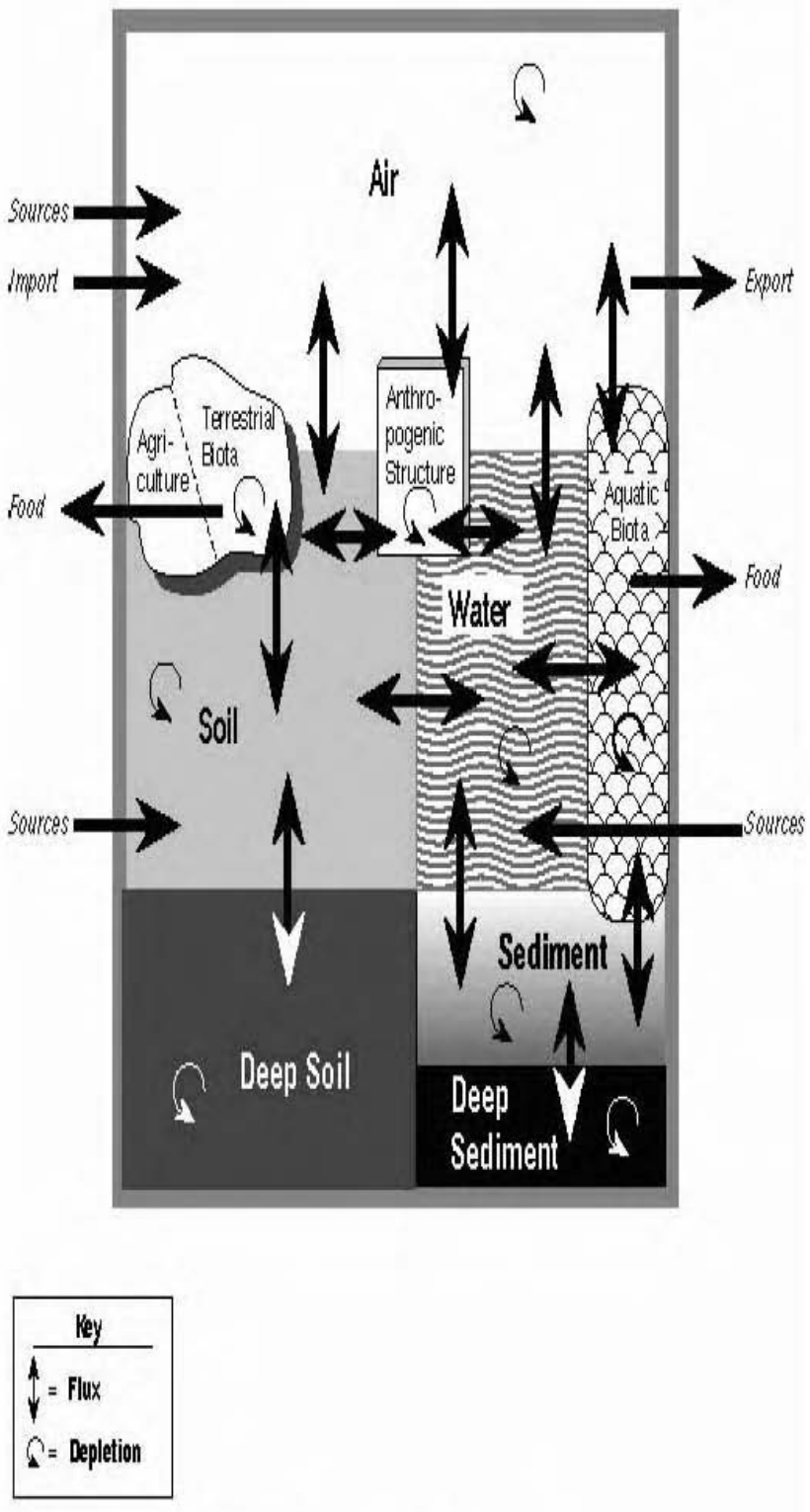

Figure 2-2. Intermedia Movement of CDD/CDFs and PCBs Among Major Environmental Media

3. LEVELS OF CDD, CDF, AND PCB CONGENERS IN ENVIRONMENTAL MEDIA AND FOOD

3.1. INTRODUCTION

Polychlorinated dibenzo-*p*-dioxins (CDDs), polychlorinated dibenzofurans (CDFs), and polychlorinated biphenyls (PCBs) have been found throughout the world in practically all media including air, soil, water, sediment, fish and shellfish, and other food products such as meat and dairy products. Also, not unexpectedly, considering the recalcitrant nature of these compounds and their physical/chemical properties (i.e., low water solubilities, low vapor pressures, and high K_{ow}s and K_{oc}s), the highest levels of these compounds are found in soils, sediments, and biota (parts-per-trillion (ppt) and higher); very low levels are found in water (parts-per-quadrillion (ppq) and lower) and air (pg/m^3). The widespread occurrence observed is not unexpected considering the numerous sources that emit these compounds into the atmosphere (See Volume 1), and the overall resistance of these compounds to biotic and abiotic transformation. (See Chapter 2 of this volume.) Part-per-trillion levels of CDDs/CDFs have been found in everyday materials that are contaminated with dust--clothes dryer lint (2.4 to 6.0 ng I-TEQ_{DF}/kg); vacuum cleaner dust (8.3 to 12 ng I-TEQ_{DF}/kg); room air filters (27 to 29 ng I-TEQ_{DF}/kg); and house furnace filter dust (170 ng I-TEQ_{DF}/kg) (Berry et al., 1993). Although Berry et al. (1993) only analyzed one or two samples of these materials, the findings suggest that these compounds may be ubiquitous.

This chapter provides an overview of the concentrations at which dioxin-like compounds have been found in the U.S. environment and food based on data presented in the published literature. This literature summary is not all inclusive, but is meant to present the reader with a general overview of values reported in the recent literature. Only data from Government-sponsored monitoring studies and studies reported in the peer-reviewed literature are discussed in this chapter. Data are presented as presented in the original studies/reports. No attempt was made to verify or assess the adequacy of the quality assurance/quality control (QA/QC) measures employed in these studies beyond those described in the published reports. In order to represent current exposure concentrations, data used for the calculation of background media levels were based on studies published in the late 1980s and 1990s, but primarily in the 1990s. The studies

used for the estimation of background concentrations were also chosen on the basis of credibility and representativeness.

CDD/CDF profiles for environmental media are also presented in this chapter. CDD/CDF homologue group and 2,3,7,8-substituted congener profiles were calculated for each medium by dividing the mean concentration of individual homologue groups or congeners by the mean total CDD/CDF concentrations for a group of studies or samples. Total CDD/CDF concentration was calculated as the sum of homologue group concentrations. In some cases, however, homologue group concentrations were not available. When this occurred (i.e., for foods), total concentration was redefined as the sum of the concentrations of the 2,3,7,8-substituted congeners rather than the sum of the homologue group concentrations. The fractions of the total for each congener add up to 1.00 in this case rather than some fraction of 1.00, as they would if the total concentration were, more appropriately, the sum of the homologue group concentrations. The text carefully identifies where this occurred. Nondetects were assumed to be zero in the calculation of CDD/CDF profiles. This was done as a matter of consistency - some studies used did not report on the detection limits for some congeners; some had high detection limits such that an assumption of one-half the detection limit would have led to unreasonably high contributions of some congeners to total CDD/CDFs. When available, data on media levels in European countries and in other parts of the world are also presented for comparison to U.S. values. These data are not intended to provide estimates that are representative of CDD/CDF levels in all parts of Europe or the world, but are used to depict similarities or differences between U.S. levels and those observed by researchers in other parts of the world.

Media levels discussed in this chapter that represent background conditions in the United States are used in Chapter 4 to estimate background exposures to dioxin-like compounds. For the purposes of this document, background is defined as the level of dioxin-like compounds in samples of environmental media originating from sites not known to be impacted by point source releases. For soil and air, background concentrations of CDD/CDFs were calculated for both rural and urban background locations. However, urban background concentrations were used in calculating human exposures to CDD/CDFs because a large percentage of the population resides in urban environments. Also, it should be noted that background levels in environmental media are represented by mean

concentrations of multiple background samples. Because mean values are used, it is likely that some background sites may have concentrations that are less than the mean concentration, while others may have higher levels. It should be noted that background concentrations were calculated based on the best available, current (i.e., late 1980s in a few cases, but primarily from the 1990s) studies. For most media, background concentrations used to assess exposure in Chapter 4 were calculated by setting nondetectable concentrations to one-half the detection limit. For some media (i.e., soil, vegetable oil), however, nondetects were set to zero because detection limits were unavailable for some studies or the detection limits were too high. These instances are noted in the text. In general, mean background concentrations were calculated as the average value over all sample locations rather than the average concentration over all samples. For example, if the available background data for a particular medium (e.g., soil, air, fish) were derived from multiple samples collected at multiple locations, the overall mean background concentration was calculated by first averaging the data for each site and then calculating the mean of the site averages. This method ensures that each site is weighted equally; heavily sampled sites do not have any greater impact on the mean than sites with fewer samples.

Studies used for development of background concentrations were also chosen to be representative of nationwide exposures. In general, data were selected that represent typical exposure conditions, so that these levels could be combined with typical ingestion/contact values to estimate background exposures (see Chapter 4). However, the data and strategy used for estimating background media levels varied somewhat, depending on the media:

- **Air and Soil** - Urban data were used to derive background estimates because most people are exposed to these levels. No data were included that were collected near known uncommon point sources (i.e., large incinerators, cement kilns, smelters, etc.). Vehicles, fireplaces, home heating furnaces, etc., are all recognized potential point sources, but are so ubiquitous as to be considered a normal part of the urban background. Estimates are also presented for rural areas, and these are more relevant for evaluating impacts in rural areas. Also a degree of uncertainty is expected from the air and soil concentration estimates due to a lack of geographic coverage and non-uniform study design.

- **Water and Sediment** - No data were included that were collected near known uncommon point sources (pulp and paper mills, POTWs, etc.). No distinction was made between urban and rural sites. For water, the data for treated drinking water were very limited (i.e., based on octa-chlorinated compounds only). Sediment data were collected from non-impacted lakes.

- **Fish** - No data were included that were collected near known uncommon point sources (pulp and paper mills, POTWs, etc.). Background data for freshwater and marine fish and shellfish were based on species-specific data from various studies, including a national survey conducted by EPA, market basket surveys conducted by FDA, and individual site-specific studies were used.

- **Food** - Only samples from national EPA/USDA surveys and grocery stores (e.g., eggs) were used. National EPA/USDA surveys used statistically-based sampling methods to collect samples representative of the national food supply. Grocery store samples represent the most common source of foods.

3.2. CONCENTRATIONS IN AIR

Tables B-1 through B-3 (Appendix B) contain summaries of data from studies of ambient air measurements of CDDs, CDFs, and PCBs in the United States and Europe. Environmental levels of PCBs in North American air are based on a single source of information (Hoff et al., 1992). Relatively few studies have been conducted to measure ambient air levels of CDDs/CDFs. This may be, in part, because of the low analytical detection limits required to detect the expected low concentrations of specific CDD/CDF congeners and the relatively large volumes of air (e.g., 350 to 450 cubic meters of ambient air over a 24-hour period) required to obtain subparts-per-trillion levels of analytical detection. These low detection limits in ambient air samples were not achieved until the mid 1980s. The results of several of these more recent ambient air studies are summarized in the following paragraphs. It should be noted, however, that these studies lack geographic coverage and may not be representative of the nation as a whole. Currently, EPA is establishing a network of stations equipped with high-volume air samplers capable of detecting concentrations of dioxin and dioxin-like compounds as low as 0.1 parts per trillion. The network, known as the National Dioxin Air Monitoring Network (NDAMN), will provide information on background concentrations of dioxin-like compounds, as well as data for use in tracking long-range transport of dioxin and calibrating atmospheric models. The sampling sites included in the network were selected with the intent of covering a wide geographic region, with special attention to rural,

agricultural areas. Many of the sites are shared with the National Atmospheric Deposition Program (NADP), which is a collaborative effort involving dozens of public and private research and educational institutions. The NDAMN project calls for a total of 29 sites in 24 states. Currently, results are available for 9 monitoring locations. These data are reported in this chapter. Additional data from the other sites will eventually be used to update the background air concentration data presented in this chapter.

It should also be noted that this chapter focuses on the concentrations of CDD/CDF/PCBs in outdoor air. Data on indoor air concentrations are extremely limited. PCB data for one recent indoor air study in the United Kingdom are presented. No background CDD/CDF data for indoor environments were available.

3.2.1. U.S. Data

An extensive ambient air monitoring study of CDD/CDFs was conducted as part of a multiyear monitoring effort at eight sampling locations in the Southern California area by the Research Division of the California Air Resources Board from December 1987 through March 1989 (Hunt et al., 1990). The monitoring network "included a number of sites situated in primarily residential areas (San Bernadino, El Toro, and Reseda), as well as several sites in the vicinity of suspected sources of CDD/CDFs (Cal. Trans, Commerce, North Long Beach, and West Long Beach) (Hunt et al., 1990)." The seven sites mentioned above were classified as urban locations by the definitions used in this document, while the eighth site was classified as an industrial site (i.e., Carson--onsite at manufacturer of gas cooking equipment). Additionally, four of the eight sites were part of the South Coast Air Quality Management District (SCAQMD) monitoring network. All totaled, there were nine sample collection intervals throughout this study. "Typically, five to seven stations were in contemporaneous operation during a particular session" (i.e., samples were not collected from each location at each interval). Total tetra- through octa-chlorinated CDDs and CDFs were screened for in the study as well as various 2,3,7,8-substituted CDD and CDF congeners. A total of 34 analyses were performed throughout the study for all congeners except for OCDD and OCDF, respectively, for which only 31 analyses were performed. Samples were collected over a maximum of seven intervals at each site throughout the study (i.e., Reseda and El Toro--six dates, duplicate samples on one date), while a sample was collected from the Commerce site during only a single

collection interval. Sample collection intervals generally averaged 24 hours (Hunt et al., 1990).

Generally, higher substituted CDD and CDF congeners accounted for the majority of positive samples containing quantifiable CDD/CDF residues in this study (i.e., total HxCDD/HxCDF and above). In fact, over 90 percent of the samples collected contained quantifiable levels of 1,2,3,4,6,7,8-HpCDD, total HpCDD, and OCDD. Additionally, approximately 50 to 70 percent of the samples collected contained quantifiable levels of total HxCDD; 2,3,7,8-TCDF; total TCDF; total PeCDF; total HxCDF; 1,2,3,4,6,7,8-HpCDF; total HpCDF; and OCDF. For all other congeners, quantifiable residues were detected in less than 25 percent of the samples collected. All CDD congener concentrations ranged from nonquantifiable levels (low limit of 0.0026 pg/m^3) to an upper limit of 18.0 pg/m^3. Additionally, CDF congener levels ranged from nonquantifiable levels (low limit of 0.0040 pg/m^3) to an upper limit of 2.70 pg/m^3.

According to Hunt et al. (1990), "The highest concentration of CDDs/CDFs congener class sums (Cl_4-Cl_8) and 2,3,7,8-substituted species were noted during a period predominated by off-shore air flows in December 1987, suggesting a regional air mass and transport phenomena. Concentrations of the CDDs/CDFs were diminished markedly in subsequent sessions where air flow patterns were primarily off-shore or of coastal origin." Hunt et al. (1990) indicated that the "CDD/CDF congener profiles (Cl_4-Cl_8) and 2,3,7,8-substituted isomeric patterns strongly suggest combustion source influences in the majority" of the samples collected.

Smith et al. (1989) quantified CDD/CDFs in air samples collected from two locations in Niagara Falls, New York, over a 6-month period in 1986/87. One site was located upwind of a large industrial complex (i.e., background), and the other site was located downwind of the complex (i.e., industrial). OCDD concentrations at the downwind location were more variable, but consistently higher, than at the upwind location. The maximum OCDD concentration observed at the downwind site was 8.8 pg/m^3. Total I-TEQ_{DF}s for the two locations were estimated to be 0.038 pg/m^3 (TEQ_{DF}-WHO_{98} = 0.041 pg/m^3) (n = 3) for the upwind (i.e., background) site and 0.84 pg/m^3 (TEQ_{DF}-WHO_{98} = 0.92 pg/m^3) (n = 3) for the downwind site, using one-half the detection limit to represent nondetects (Table 3-1). In another study, Smith et al. (1990a) analyzed ambient air samples from several other New York cities for CDD/CDFs. Samples were

collected in Albany (n = 3), Binghamton (n = 1), and Utica (n = 2). Total CDD/CDF concentrations ranged from 3.02 pg/m^3 to 13.1 pg/m^3. None of the samples had detectable levels of 2,3,7,8-TCDD, but 2,3,7,8-TCDF was detected at concentrations ranging from 0.18 pg/m^3 to 1.24 pg/m^3.

Maisel and Hunt (1990) reported on ambient air concentrations of CDD/CDFs in Los Angeles, California, during the winter of 1987. Concentrations were highest for OCDD, and the estimated I-TEQ_{DF} concentration was 0.12 pg/m^3 (TEQ_{DF}-WHO_{98} = 0.13 pg/m^3, assuming that nondetects equal one-half the detection limits. Edgerton et al. (1989) measured CDD/CDFs in air samples from Ohio during 1987 to evaluate the impact of potential CDD/CDF sources on ambient levels in air. Samples were collected from various locations, including those at an industrial site, near a municipal refuse-derived fuel power plant, near a sewage sludge incinerator, downwind of a municipal incinerator, at a high traffic density site, and at a rural background site in Waldo, Ohio. Total CDD/CDF concentrations were found to be higher in samples collected near incinerators than at the background site. None of the samples had detectable levels of 2,3,7,8-TCDD, and the hepta- and octachlorinated CDD/CDFs were the most abundant. Using congener profiles developed for several source categories, Edgerton et al. (1989) compared the CDD/CDF patterns in ambient air from this study to the profiles for each source and found that the profile for the background sample was "almost identical to the profile constructed for municipal incinerators."

The Ohio Environmental Protection Agency, Division of Air Pollution Control, conducted an ambient air monitoring study in 1994/1995 for CDD and CDF compounds in the vicinity of the Columbus Waste to Energy (WTE) facility. The purpose of the study was to evaluate the impact of the facility on air quality. The Columbus WTE was a major source of dioxins to the Columbus environment. Based on a 1992 stack emission test, the Ohio EPA estimated that annual emissions from the facility exceeded 900 g I-TEQ_{DF}/yr (OEPA, 1994a). The sampling in 1994 occurred while the facility was operating. The facility ceased operation in December 1994; therefore, the 1995 sampling did not include impacts from the facility. A total of seven sites were sampled; six were located in the urban area of Columbus, within 1-2 miles of the facility, and mostly in the historically predominant downwind direction, and the seventh was located 28 miles away in the upwind direction in a rural background setting. Five urban samples were taken in both

March and April 1994 (one of the six samplers was not operating on each of these sampling dates), and six urban samples were taken in June 1995, for a total of 16 urban samples. One rural sample was taken on each sampling date for a total of three background samples. All samples were collected over a 48-hour sampling period using modified high-volume air samplers. Further details on these studies can be found in OEPA (1994b, 1995).

Table 3-2 presents the mean concentrations of congeners and homologue groups from four groups of air samples:

1. The "impacted air" samples include one sample taken in each of the March and April 1994 sampling periods. Wind rose data in OEPA (1994b) show that the samplers from which these samples came from were downwind of the Columbus WTE during the 48-hour sample.
2. The 1994 urban samples include the eight other samples taken in 1994 while the Columbus WTE was still operating.
3. The 1995 urban samples include the six samples taken in the urban setting once the incinerator was no longer operating.
4. The three rural samples include those taken at a site 28 miles away in the historical upwind direction from the Columbus WTE.

OEPA (1994b) also notes that the highest air concentrations were found in the downwind samples.

Generally, total CDD/CDF concentrations were higher for the urban sites than for the background sites. Overall, the average total urban background air CDD/CDF concentration was 3.5 pg/m^3, and the I-TEQ_{DF} and TEQ_{DF}-WHO_{98} concentrations were 0.050 pg/m^3 and 0.055 pg/m^3, respectively. These values were the average of the 1994 and 1995 urban samples. The rural background total CDD/CDF concentration was 2.2 pg/m^3, and the I-TEQ_{DF} and TEQ_{DF}-WHO_{98} concentrations were 0.022 pg/m^3 and 0.024 pg/m^3, respectively. The impact of the Columbus facility can be seen by examining the impacted air samples. As noted above, one sample in each of the two 1994 sampling dates was downwind of the Columbus facility. In fact, the air sampler was the same in both cases and was located about 1.5 miles in the easterly direction. The air

concentration in this sampler was the highest in both these sampling dates, equaling 9.2 pg/m^3 total and 0.17 pg I-TEQ_{DF}/m^3 in March and 19.0 pg/m^3 total and 0.35 pg I-TEQ_{DF}/m^3 in April. The average total CDD/CDF concentration for these impacted samples was 14 pg/m^3, and the I-TEQ_{DF} and TEQ_{DF}-WHO_{98} concentrations were 0.26 pg/m^3 and 0.29 pg/m^3, respectively. Further analysis of these Columbus air data can be found in Lorber et al. (1998a).

In accordance to the Connecticut Ambient Air Quality standards, the State of Connecticut's Department of Environmental Protection (CDEP) implemented a monitoring program which measured CDD/CDFs in ambient air at six sites in Connecticut (CDEP, 1995). The air monitoring program was conducted from fall 1993 through summer 1994 in the vicinity of five Resource Recovery Facilities (RRFs), located in Bridgeport, Hartford (mid-Connecticut), Bristol, Preston, and Wallingford, Connecticut, as well as one background rural site located at Mohawk Mountain. The monitoring activity involved four quarterly 1-month sampling periods (CDEP, 1995). Ambient concentrations measured for the four quarterly monitoring sessions at the rural background site (Mohawk Mountain) are presented in Table 3-3. Based on the CDD congeners, OCDD had the highest background concentration (0.451, 0.196, 0.155, and 0.056 pg/m^3) for all four sampling periods. The total I-TEQ_{DF}s for these rural background samples were 0.015 pg/m^3, 0.009 pg/m^3, 0.006 pg/m^3, and 0.005 pg/m^3 for the November 1993, February 1994, May 1994, and August 1994 sampling periods, respectively. The average I-TEQ_{DF} for these sampling periods was 0.0087 pg/m^3 (TEQ_{DF}-WHO_{98} = 0.010). The average I-TEQ_{DF} and TEQ_{DF}-WHO_{98} values for the five urban locations, over the four sampling periods, were 0.026 pg/m^3 and 0.029 pg/m^3, respectively. Data for all samples collected during the monitoring program show that the I-TEQ_{DF} concentrations were below the 1.0 annualized pg/m^3 ambient standard adopted by the State of Connecticut for CDD/CDFs (CDEP, 1995).

In an earlier study of ambient air monitoring in the vicinity of Wallingford, Connecticut, CDEP (1988) reported on CDD/CDF levels in 28 ambient air samples collected in 1988. The mean total I-TEQ_{DF} for these samples was 0.05 pg/m^3, when nondetects were set to one-half the detection limit. Hunt and Maisel (1990) conducted pre-operational air monitoring in the vicinity of the site of a municipal solid waste incinerator. I-TEQ_{DF} concentrations, averaged over seven sites and all seasons, were 0.1 pg/m^3, when nondetects set to one-half the detection limit. Mean concentrations were

highest for the higher-chlorinated dioxin homologue groups and lower furan homologue groups.

In a long-term study of CDD/CDFs in the ambient air around Bloomington, Indiana, methods were developed for measuring individual CDD/CDFs at concentrations as low as 0.001 pg/m^3 (Eitzer and Hites, 1989). Total CDD/CDF concentrations were 0.480 pg/m^3 and 1.360 pg/m^3 for the vapor phase and the particle-bound phase, respectively. For individual congeners, CDFs were found to decrease in concentration with increasing levels of chlorination, and CDD concentrations were found to increase with increasing levels of chlorination (Eitzer and Hites, 1989).

Fiedler et al. (1995a) conducted a sampling and monitoring program in rural Mississippi using pine needles as indicators of the presence of CDDs and CDFs in the atmosphere. Pine needles have been shown to be passive samplers for lipophilic substances present in the air, because their outer waxy surface absorbs these atmospheric pollutants. Pine needle samples were collected from eight locations in southern Mississippi. CDD and CDF I-TEQ_{DF} concentrations ranged from 0.11 to 0.23 pg/kg dry mass for 1994 shoots and 0.07 to 0.51 pg/kg dry mass for 1993 shoots. The authors concluded that the data suggest that the atmospheric concentrations of CDDs and CDFs in rural Mississippi are relatively low, but higher concentrations were observed at more populated sites.

In a subsequent study, Fiedler et al. (1997a) analyzed CDD/CDF levels in ambient air in a rural area in southern Mississippi using three sampling methodologies: high-volume ambient air sampling to measure direct atmospheric levels of CDD/CDFs; Bergerhoff samplers to collect atmospheric deposition samples; and pine needles as passive samplers. The study was conducted from December 1995 to January 1996 and from June to July 1996 to assess the concentrations of CDD/CDFs during these time periods. The sampling location had no known local sources of CDD/CDFs. In general, winter CDD/CDF concentrations were higher than summer concentrations. CDD/CDF concentrations measured using high-volume air samples averaged 1.126 pg/m^3 in the winter and 0.36 pg/m^3 in the summer (i.e., three times higher in winter than in summer). The mean I-TEQ_{DF} concentrations were 0.0109 pg I-TEQ_{DF}/m^3 in the winter and 0.0037 pg I-TEQ_{DF}/m^3 in the summer, when using one half the limit of quantification for nonquantifiable congeners. The results of the deposition study suggested that deposition is also higher in

winter than in summer. The mean CDD/CDF deposition rate was 152 pg/m^3-day in winter and 108 pg/m^3-day in summer, when nonquantifiable congeners were set to one-half the limit of quantification. Normalized to pg I-TEQ_{DF}/m^3-day, the deposition rate was 2.6 pg I-TEQ_{DF}/m^3-day in winter and 0.58 pg I-TEQ_{DF}/m^3-day in summer. Analysis of the pine needles showed that CDD/CDF concentrations increase with increasing exposure times. Concentrations in pine needles ranged from 10 to 54 pg/g d.m. (0.16 to 0.79 pg I-TEQ_{DF}/g d.m.), when nonquantifiable congeners were set to one-half the limit of quantification. The authors concluded that the CDD/CDF concentrations observed in ambient air in this study (0.0023 to 0.017 pg I-TEQ_{DF}/m^3) were lower than similar remote locations in Germany (0.015 to 0.020 pg I-TEQ_{DF}/m^3). Deposition rates were also lower in southern Mississippi (0.42 to 3.1 pg I-TEQ_{DF}/(m^2-day)) than in rural areas of Germany (5 to 7 pg I-TEQ_{DF}/(m^2-day).

Hunt et al. (1997) conducted a study in Phoenix, Arizona, aimed at assessing the influence of motor vehicle emissions on ambient air concentrations of CDD/CDFs. Four sets of 24-hour integrated samples were collected between December 15 and 20, 1994. The sampling site was located near a heavily traveled roadway in metropolitan Phoenix. The month of December was chosen for sampling, because inversion conditions are expected during the winter months. CDD/CDFs were detected in all four sample sets. Average total I-TEQ_{DF} values varied from 0.092 pg/m^3 (December 15) and 0.094 pg/m^3 (December 19) to 0.37 pg/m^3 (December 16) and a high of 0.45 pg/m^3 (December 20). Average congener-specific I-TEQ_{DF} (and TEQ_{DF}-WHO_{98}) values are shown in Table 3-4. The average total I-TEQ_{DF} value of 0.25 pg/m^3 and TEQ_{DF}-WHO_{98} values of 0.27 pg/m^3 are higher than the TEQ data reported for other U.S. urban locations, such as Los Angeles and Connecticut (Maisel and Hunt, 1990). The first 2 sampling days of this study demonstrated congener class profiles typical of those reported in the literature for urban U.S. settings, showing a predominance of CDDs over CDFs. Hunt et al. (1997) also noted that the "predominance of 1,2,3,4,6,7,8-HpCDD as the most persistent 2,3,7,8-substituted CDD congener is consistent with the observations of others in the open literature, and is prevalent at sites known to be influenced by stationary or mobile combustion source emissions." Data from the last 2 sampling days of this study produced distinctly different congener profiles from the first 2 days. The last 2 sample dates' results showed a predominance of CDFs over CDDs. On December 20, for example,

1,2,3,4,6,7,8-HpCDF was present at a level of 2.16 pg/m^3, while the typically most predominant isomer 1,2,3,7,8-HpCDD had a value of 1.30 pg/m^3. Hunt et al. (1997) stated that further study "beyond examination of CDDs/CDFs data alone is warranted to provide a more conclusive source determination." Data from this study are not included in the ambient background level determinations in this chapter due to recommendations of the authors that "due to site-specific bias likely introduced by vehicular traffic at the Indian School Road site, the ambient CDDs/CDFs measured should not be construed to be representative of ambient CDDs/CDFs burdens in metropolitan Phoenix, as a whole."

Beginning in September 1996, a Canadian survey of CDD/CDFs in air was conducted at locations across Canada (Belzer et al., 1998). Some of the samples were collected near a coastal pulp mill operation at a location 1 kilometer southeast of a mill area. Data analysis indicated that CDD/CDFs concentrations from the mill area ranged from 0.006 to 0.067 pg I-TEQ_{DF}/m^3. These values were similar to those observed in other Canadian urban sites (0.01 to 0.08 pg I-TEQ_{DF}/m^3), but were lower than those measured near industrial point sources (0.01 - 0.4 pg I-TEQ_{DF}/m^3). The total CDD and CDF congener values for the mill area ranged from 0.17-3.94 pg/m^3, and the values of total homologue groups ranged from 0.77-5.53 pg/m^3. The results of this study suggest that production of CDD/CDFs from combustion sources is highly dependent on combustion material, temperature and moisture values (Belzer at al., 1998).

In 1997, EPA established the National Dioxin Air Monitoring Network (NDAMN) to determine the temporal and geographical variability of atmospheric CDDs, CDFs, and dioxin-like PCBs at rural locations through out the United States. NDAMN consists of 29 sampling stations whose three primary purposes are: (1) to determine the atmospheric levels and occurrences of dioxin-like compounds in rural and agricultural areas where livestock, poultry, and animal feed crops are grown; (2) to provide measurements of atmospheric levels of dioxin-like compounds in different geographic regions of the U.S.; and (3) to provide information regarding the long-range transport of dioxin-like compounds in air over the U.S. The first phase of NDAMN, which operated from June 1998 to June 1999, consisted of an array of 10 monitors at 9 sites spread out across the mid- to eastern-U.S. in the States of Pennsylvania (2), North Carolina, Florida, Wisconsin, Illinois, Iowa, Arkansas, Kansas, and Oklahoma. The sampling regime consisted of sampling 24 days (i.e., 6 days per week for 4 weeks), every other month, starting in the month of

June. This produced six sampling moments over a period of 1 year, with four composite samples (i.e., 4 weeks) per sampling moment. The analytes of interest in this monitoring program are the 17 CDD/CDFs and the coplanar PCBs (77, 105, 118, 126, 156, 157, and 169). The interim results from the nine monitoring stations are shown in Table 3-5, and are summarized as follows:

1. The overall annual average TEQ_{DF}-WHO_{98} air concentration was 12 fg/m^3.

2. All congeners were detected at a frequency >95%.

3. There was a 6-fold range in TEQ_{DF}-WHO_{98} annual average air concentrations from the lowest to the highest: 4.2 fg/m^3 at Lake Scott, Kansas, to 25.4 fg/m^3 at Monmouth, Illinois.

4. The variability of TEQ_{DF}-WHO_{98} over 6 monitoring moments at the 9 sites indicate a significant increase in TEQ_{DF}-WHO_{98} across all sites during the November/ December monitoring period. During this month, the TEQ_{DF}-WHO_{98} increased by up to 9-fold over any other moment during the year. The increase in TEQ was characterized by a large increase in actual measured concentrations of 1,2,3,7,8-PeCDD and 2,3,7,8-TCDD. This is consistent with the seasonal patterns reported in previous studies.

5. The TEQ_P-WHO_{98} was small compared to TEQ_{DF}-WHO_{98} (range: 0.2 to 1.3 fg/m^3; mean: 0.7 fg/m^3).

PCBs in ambient Canadian air were evaluated by Hoff et al. (1992). A total of 143 air samples from Egbert, Ontario, Canada, taken in 1988 and 1989 were analyzed for various vapor-phase PCB congeners. The annual mean concentrations for these samples are presented in Table 3-6. These means were calculated by assuming that nondetectable concentrations were zero. Based on the mean concentrations for the limited set of toxic PCB congeners in Hoff et al. (1992) (i.e., PCBs 105, 114, 118, 156, 170, 180, and 189),

the total TEQ_P-WHO_{94} concentration is estimated to be 0.00094 pg/m^3 (TEQ_P-WHO_{98} = 0.00088 pg/m^3).

3.2.2. European Data

Clayton et al. (1993) conducted a study of CDDs and CDFs in the ambient air of three major cities (London, Manchester, and Cardiff) and an industrial town (Stevenage) in the United Kingdom. Annual median I-TEQ_{DF} concentrations of CDDs and CDFs ranged from 0.04 to 0.10 pg/m^3. Hepta- and octachlorinated dioxin congeners contributed the most to the total concentration of 2,3,7,8-substituted CDD/CDFs, and a large number of nondetect values were reported for the tetra-, penta-, and hexachlorinated dioxins. Congeners that contributed most to the total I-TEQ_{DF} concentrations were 2,3,7,8-TCDF; 1,2,3,4,7,8-; 1,2,3,6,7,8-; and 2,3,4,6,7,8-HxCDF. The United Kingdom's Department of the Environment, Transport and the Regions has posted air monitoring data from 1991 through 1993 on the Internet (Department of the Environment, Transport and the Regions, 1998). Sampling locations include the same UK cities monitored by Clayton et al. (1993), as well as an urban site in Middlesbrough and a rural site at Hazelrigg. Mean CDD/CDF I-TEQ_{DF} concentrations from the quarterly sampling periods ranged from 0.15 to 0.34 pg/m^3 for Cardiff (8 quarters monitored), 0.10 to 0.34 pg/m^3 for Stevenage (5 quarters), 0.012 to 0.33 pg/m^3 for Middlesbrough (7 quarters), 0.044 to 1.4 pg/m^3 for Manchester (12 quarters), 0.016 to 0.28 pg/m^3 for London (12 quarters), and 0.004 to 0.21 pg/m^3 for Hazelrigg (12 quarters), when nondetects were set at the detection limit. When nondetects were set to zero, mean I-TEQ_{DF} concentrations ranged from 0.063 to 0.30 pg/m^3 for Cardiff, 0.034 to 0.30 pg/m^3 for Stevenage, $<$0.001 to 0.21 pg/m^3 for Middlesbrough, 0.036 to 0.69 pg/m^3 for Manchester, 0.008 to 0.24 pg/m^3 for London, and 0.003 to 0.17 pg/m^3 for Hazelrigg. The sum of the quarterly mean PCB concentrations of PCBs 2, 52, 101, 118, 138, 153, and 180, for these same cities, ranged from 164 to 985 pg/m^3 for Cardiff (10 quarters monitored), 189 to 395 pg/m^3 for Stevenage (5 quarters), 78 to 359 pg/m^3 for Middlesbrough (9 quarters), 181 to 704 pg/m^3 for Manchester (14 quarters), 651 to 2,482 pg/m^3 for London (14 quarters), and 77 to 198 pg/m^3 for Hazelrigg (8 quarters). These CDD/CDF values are relatively consistent with the concentrations in ambient German air observed by Liebl et al. (1993) and König et al. (1993a). Liebl et al. (1993) analyzed ambient air samples collected from 10 sites in

Hessen, Germany, from 1990 through 1992. Concentrations ranged from 0.04 to 0.15 pg I-TEQ_{DF}/m^3. The higher concentrations were presumed to result from direct local industrial sources. König et al. (1993a) collected air samples from six sites in Hessen, Germany. CDD/CDF concentrations ranged from 0.048 pg I-TEQ_{DF}/m^3 at a rural reference site to 0.146 pg I-TEQ_{DF}/m^3 at an industrial site. The results of the study also indicated that concentrations of CDDs and CDFs are typically higher in the winter than in the summer. Sugita et al. (1993) also observed higher concentrations of CDDs and CDFs in winter than in summer in an ambient air study in urban Japan. The average concentration of CDDs and CDFs was 0.788 pg I-TEQ_{DF}/m^3 in the summer and 1.464 pg I-TEQ_{DF}/m^3 in winter.

Fiedler et al. (1997b) conducted a 3-year air monitoring study that examined the CDD/CDF levels near two municipal solid waste incinerators (MSWI) located in Bavaria, Germany (Augsburg and Burgkirchen). The authors observed that the I-TEQ_{DF} concentrations at these locations were comparable and concentrations were consistently higher during winter months that in summer months. For example, at Augsburg, the lowest concentration (0.009 pg I-TEQ_{DF}/m^3) was obtained during the summer of 1995, and the highest concentration (0.206 pg I-TEQ_{DF}/m^3) was observed in the winter of 1994/1995. Background concentrations for these time periods ranged from 0.0076 to 01.29 pg I-TEQ_{DF}/m^3. For Burgkirchen, the lowest concentration (0.0044 pg I-TEQ_{DF}/m^3) was observed during the summer of 1994, and the highest concentration (0.078 pg I-TEQ_{DF}/m^3) was observed during the winter of 1995/1996.

In a Swedish study, air samples were collected from a city center, suburb, remote countryside, and open coastal area (Broman et al., 1991). Analyses of the samples for dioxins and furans indicated that the concentrations of these compounds decreased with increasing distance from the city center. Total CDD/CDF concentrations were 1.40 pg/m^3, 1.10 pg/m^3, 0.40 pg/m^3, and 0.22 pg/m^3 for the city center, suburb, countryside, and open coastal areas, respectively. Similar patterns of decreasing concentrations with increasing distances from urban areas were also observed for individual CDD/CDF congeners (Broman et al., 1991). In a study of ambient air concentrations of CDDs and CDFs in Flanders, samples were collected and analyzed at rural, industrial, and urban sites (Wevers et al., 1993). Average ambient air concentrations ranged from 0.0696 pg I-TEQ_{DF}/m^3 at a rural site to 0.254 pg I-TEQ_{DF}/m^3 at a site believed to be influenced by a

chemical industry and a highway. Naf et al. (1990) analyzed urban air samples from a site near a wastewater treatment plant in Sweden. The samples were collected as part of a study to estimate the flux of CDD/CDFs through the treatment plant. All 2,3,7,8-substituted congeners (except 1,2,3,7,8,9-HxCDD and 1,2,3,4,7,8,9-HpCDF) were detected. The mean I-TEQ_{DF} for urban air was estimated to be 0.02 pg/m^3.

Hiester et al. (1995) observed a decrease of CDD/CDF concentrations in Germany's ambient air over a 6-year period. Ambient air samples were collected over 12 sampling intervals from 4 sites in the heavily industrialized Rhine-Ruhr region of Germany during 1987/88 and 1993/94. Total I-TEQ_{DF}s for these sites ranged from 0.13 pg/m^3 to 0.33 pg/m^3 during 1987/88 and from 0.04 pg/m^3 to 0.12 pg/m^3 for the 1993/94 time period. Reductions in I-TEQ_{DF}s ranged from 46 to 69 percent at these sites over the 6-year period (i.e, from 0.22 pg/m^3 to 0.13 pg/m^3 at Dortmund and from 0.13 pg/m^3 to 0.04 pg/m^3 at Köln). These reductions were attributed to abatement actions taken since 1989 (Hiester et al. 1995).

Between November 1992 and October 1993, the Austrian Federal Environmental Agency monitored six air stations for ambient air concentrations of CDD/CDFs (Umweltbundesamt, 1994; 1996). One hundred samples were taken from industrial and population sites; three sites in Vienna, one in Steyregg, one in Linz, and one in Graz. The arithmetic annual average value of ambient levels for all samples ranged from 0.03 to 0.12 pg I-TEQ_{DF}/Nm^3. Average winter levels ranged from 0.05 to 0.24 pg I-TEQ_{DF}/Nm^3; while the summer levels ranged from 0.02 to 0.04 pg I-TEQ_{DF}/Nm^3. Winter levels observed in Graz were two times the winter concentrations found at the other sampling sites. Levels were consistently highest (i.e., two to three times higher) for the measuring period between February 1 and 4 at all the measuring sites. This time period coincided with an extremely stable meteorological condition or inversion. All locations demonstrated a decrease in the proportion of CDFs from the tetra- to octachlorinated congeners, while the opposite was true for CDDs. However, there were differences in the congener profiles for different locations. For example, the Graz location showed a higher proportion of octa- and heptachlorinated dioxins, while tetrachlorofurans predominated at the hospital site in Vienna and also at the Steyregg and Linz sites.

Samples of ambient air were collected from 15 locations throughout Slovakia, including urban, industrial, agricultural and rural sites, between October 1996 and August

1997 (Stenhouse et al., 1998). A total of 113 samples were analyzed for CDD/CDFs. The average ambient I-TEQ_{DF} concentrations for these locations ranged from 0.05 pg/m^3 to 0.13 pg/m^3 at urban/industrial areas (with an average of 0.1 pg/m^3), 0.07 pg/m^3 for agricultural areas and 0.04 pg/m^3 for rural background. The values of any congeners below the detection limit (0.01 pg/m^3) were included in the I-TEQ_{DF} at the detection limit. Higher ambient I-TEQ_{DF} values were observed in the winter than in the summer at the places where the major source was combustion. Stenhouse et al. (1998) suggested that seasonal variation would not be expected if industrial processes and traffic were significant contributors.

PCBs have also been evaluated in European air samples (Halsall and Jones, 1993; König et al., 1993b). Halsall and Jones (1993) monitored urban air at two sites in the United Kingdom. The annual mean total PCB concentrations were 520 and 590 pg/m^3. PCBs existed in ambient air predominantly in the vapor phase. This study also indicated that summer PCB concentrations were higher than winter concentrations. These researchers attributed the differences in seasonal patterns to volatilization from soil during summer months. Ambient air concentrations of PCBs in Hessen, Germany, ranged from 350 to 1630 pg/m^3 during the period of 1990 to 1992 (König et al., 1993b). Urban areas characterized by industry and/or heavy traffic had the highest PCB concentrations in ambient air. Hiester et al. (1995) also evaluated total PCB concentrations in ambient air samples from several sites in Germany during 1993/94. Table 3-7 presents the annual average dioxin-like PCB concentrations in ambient air of several German cities. Annual mean total PCB concentrations ranged from 1,000 pg/m^3 to 2,000 pg/m^3 in urban locations and from 100 pg/m^3 to 300 pg/m^3 in rural locations.

Recently, Currado and Harrad (1997) measured indoor air concentrations of PCBs from nine different indoor environments, including two laboratories, two offices, and five residential homes in the United Kingdom. The results indicated that the total PCB levels found in indoor air (1.4 to 19.1 ng/m^3; mean 7.1 ng/m^3) were between 2 and 19 times higher than the levels in outdoor air (0.77 to 0.87 ng/m^3; mean 0.82 ng/m^3). It should be noted that the study did not focus on dioxin-like PCBs; only concentrations of four dioxin-like PCB congeners were reported in indoor and outdoor areas. Thus, TEQ concentrations in indoor air were not calculated. Studies that examine background CDD/CDF levels in indoor environments were not available.

3.2.3. Air Observations and Trends

Some general observations for CDD/CDF levels in air are possible from the various air studies discussed in this chapter:

- Concentrations in urban settings are higher than those in rural settings.
- Concentrations associated with source impacted areas are the highest.
- As the degree of chlorination increases, so does the congener concentration.
- Based on the limited ambient air measurements made in selected cities in the United States and Europe, there appears to be good agreement with respect to the magnitude of specific congeners of CDDs and CDFs in urbanized areas in the United States and Europe.
- Many of the air measurements tend to be very close to the current analytical detection limit. This increases the probability that congeners indicated as not detected (ND) may actually be present.

3.2.4. Air CDD/CDF Profiles and Background TEQ Concentrations

CDD/CDF profiles were calculated for rural and urban air. Rural air profiles used data from OEPA (1995), CDEP (1988), and Cleverly et al. (2000). Urban air profiles used data from CDEP (1988, 1995), Smith et al. (1989, 1990a), Maisel and Hunt (1990), Hunt et al. (1990), and OEPA (1995). CDD/CDF homologue group and 2,3,7,8-substituted congener profiles for air are presented in Table 3-8 and Figures 3-1 and 3-2. The CDD/CDF homologue profile was calculated by dividing individual homologue group concentrations by the total CDD/CDF concentration. This profile indicates that OCDD is the predominant homologue group in rural and urban background air followed by HpCDD. TCDD accounts for the lowest percentage of total CDD/CDFs. Congener group profiles were calculated as the ratio of individual 2,3,7,8-substituted congener concentrations to total CDD/CDF concentration (i.e., the sum of homologue group concentrations). The concentration of 2,3,7,8-substituted congeners accounts for 57 percent of the total CDD/CDF concentration in urban background air. In rural background air, 2,3,7,8-substituted CDD/CDFs account for 59 percent of the total CDD/CDF concentration. Of the 2,3,7,8-substituted CDD/CDF congeners, OCDD accounts for the highest percentage (i.e., 39 percent rural; 34 percent urban) of total CDD/CDFs, followed by the 1,2,3,4,6,7,8-HpCDD in rural and urban background air.

Table 3-9 presents a summary of the TEQ_{DF}-WHO_{98} concentrations of CDD/CDFs in the United States. Assuming that nondetects are equal to one-half the detection limit, the mean TEQ_{DF}-WHO_{98} concentration was 0.013 pg/m^3 for rural background sites (i.e., sites in Connecticut and Ohio, and NDAMN sites in Pennsylvania (2), North Carolina, Florida, Wisconsin, Illinois, Iowa, Arkansas, Kansas, and Oklahoma) (n = 60; CDEP, 1995 (n = 4); OEPA, 1995 (n = 3); Cleverly et al., 2000 (n = 53)), and 0.12 pg/m^3 for urban background sites (i.e., from 14 sites in Connecticut, California, Ohio, and New York) (n = 106; CDEP, 1988; CDEP, 1995; Hunt and Maisel, 1990; Maisel and Hunt, 1990; OEPA, 1995; Smith et al., 1989; Smith et al., 1990a). These mean concentrations represent the average of the mean concentrations for the various sites and not the mean of all individual samples. (See weighted mean in Table 3-9.) The mean value is used to ensure that each site is weighted equally (i.e., heavily sampled sites do not have any greater impact on the overall mean than sites with fewer samples). Samples collected from urban locations not expected to be impacted by industrial point sources were assumed to represent "background" conditions for the majority of the U.S. population. The "typical" urban background TEQ_{DF}-WHO_{98} level was estimated to be 0.12 pg/m^3 based on the mean of the background samples collected in urban environments. (The I-TEQ_{DF} value for these sites is 0.11 pg/m^3). This value was used in Chapter 4 to characterize background exposures. The mean TEQ_P-WHO_{98} for rural sites was estimated to be 0.00071 pg/m^3 based on data from Cleverly et al. (2000).

Based on the results of European studies, ambient air concentrations of CDDs and CDFs appear to be similar to those found in the United States. Based on the midpoints of the European studies for which I-TEQ_{DF} concentrations were reported (Clayton et al. 1993; Liebl et al. 1993; König et al. 1993a; Wevers et al. 1993), the I-TEQ_{DF} air concentration for Europe is 0.11 pg/m^3. Data for these European studies are not included in Tables B-1 and B-2 of Appendix B because individual congener data were not reported.

It is interesting to compare these background air values with the CDD/CDF concentrations in air measured by Lugar (1993) in and around McMurdo Station, Antarctica, a logistics and staging facility with a population of about 1,100. Four locations were sampled: a site upwind of the station, downwind of the station, in the center of the station, and a remote unpopulated island 30 kilometers distant from the station. CDD/CDFs were not detected in the samples from the upwind site (congener

detection limits ranged from <0.01 to 0.03 pg/m^3), and few CDD/CDF congeners were detected at the remote island sites (congener detection limits ranged from 0.001 to 0.008 pg/m^3). CDD/CDFs were detected only sporadically at the downwind site (some congeners detected in three of five samples) and in all five samples collected from the station center site (mean I-TEQ$_{DF}$ concentration of 0.0153 pg/m^3). Similar results were obtained in a follow-up study during the austral summers 1992/93 and 1993/94. A total of 28 air samples were collected from these four sites (Lugar et al., 1996). CDD/CDFs were not detected at the upwind or remote island sites and trace levels of only a few CDD/CDFs were found in the downwind site. The highest CDD/CDF concentrations were observed at the downtown site, where CDD concentrations ranged from 0.12 to 1.80 pg/m^3, and CDFs ranged from 0.02 to 2.77 pg/m^3. I-TEQ$_{DF}$ values for this central McMurdo location were 0.074 pg/m^3 for 1992/93 and 0.0015 pg/m^3 for 1993/94. The most frequently detected congeners were the octa- and hepta-chlorinated CDDs.

3.3. CONCENTRATIONS IN SOIL

Tables B-4 and B-5 (Appendix B) contain summaries of data from several of the numerous studies in the published peer-reviewed literature regarding concentrations of CDDs and CDFs in soil. Only limited data on dioxin-like PCB congener soil concentrations were found in the literature (e.g., EPA Region 8, 2000); most of the PCB soil concentration data found in the literature were reported as either total PCB concentrations or concentrations of Aroclor PCB mixtures. Descriptions of several of the studies summarized in Appendix B are presented below. It should be noted that, the review of soil data presented here is not based on a comprehensive review of the published studies on CDD/CDFs in soil. Instead, it is intended to provide a brief overview of soil levels of CDD/CDFs from a sampling of representative studies. Because of the lack of geographic coverage and non-uniform study design associated with the soil data presented in this section, there is a degree of uncertainty associated with the estimates of background concentrations of CDD/CDFs in soil.

3.3.1. North American Data

Soil sampled in 1987 from the vicinity of a sewage sludge incinerator was compared with soil from rural and urban sites in Ontario, Canada, by Pearson et al.

(1990). Soil in the vicinity of the incinerator showed a general increase in CDD concentration with increasing degree of chlorination (Table 3-10). Of the CDFs, only OCDF was detected (mean concentration 43 ppt). Rural woodlot soil samples contained only OCDD (mean concentration of 30 ppt). Soil samples from undisturbed urban parkland settings revealed only HpCDDs and OCDD, but all CDF congener groups (Cl_4 to Cl_8) were present. Those samples showed an increase in concentration from the HpCDDs to OCDD and PeCDFs to OCDF. TCDFs had the highest mean value (29 ppt) of all the CDF congener groups. Resampling of one urban site in 1988, however, showed high variability in the concentrations of CDDs and CDFs.

Reed et al. (1990) analyzed background soil samples from a semi-rural location in Elk River, Minnesota, as part of a baseline assessment prior to the operation of a refuse-derived fuel-powered electric generation station. Four soil samples (two from an untilled site and two from a tilled site) were collected and analyzed for CDD/CDFs. Of the CDD/CDF congeners, OCDD concentrations were the highest, ranging from 340 ppt to 3,300 ppt. OCDF concentrations ranged from nondetect to 270 ppt. The 2,3,7,8-tetra and penta chlorinated congeners were not detected in any of the samples analyzed (Table 3-11).

Data were collected on CDD and CDF levels in soil samples from industrial, urban, and rural sites in Ontario and some U.S. Midwestern States (Birmingham, 1990). CDD/CDF levels in rural soils were primarily nondetect (ND), although the HpCDDs and OCDD were found in a few samples. In urban soils, the tetra- through octa-homologue groups were measured for both CDDs and CDFs. The HpCDDs and OCDD dominated and were two orders of magnitude greater than in the rural soils. These soils also contained measurable quantities of the TCDDs and PeCDDs. Industrial soils did not contain any TCDDs or PeCDDs, but they contained the highest levels of the TCDFs, HpCDFs, and OCDF. Total CDD/CDF concentrations averaged 73 $\pm$ 50 ppt in rural soils (n = 30), 2,075 $\pm$ 3,608 ppt in urban soils (n = 47), and 8,314 $\pm$ 9,955 ppt in industrial soils (n = 20) when nondetects were assumed to be zero. I-TEQ_{DF}s were also calculated for these three types of sites by Birmingham (1990) by assuming that the 2,3,7,8-substituted CDD/CDF congeners represent specified proportions of the homologue group concentrations and by applying I-TEF_{DF}s. Birmingham (1990) estimated the I-TEQ_{DF}s to be

0.4 ± 0.6 ppt for rural soil, 11.3 ± 21.8 ppt for urban soils, and 40.8 ± 33.1 for industrial soils.

In another study, soils from industrialized areas of a group of cities from Midwestern and Mid-Atlantic States (Michigan, Illinois, Ohio, Tennessee, Pennsylvania, New York, West Virginia, Virginia) were analyzed for levels of 2,3,7,8-TCDD (Nestrick et al., 1986). Many of the samples were taken within 1 mile of major steel, automotive, or chemical manufacturing facilities, or municipal solid waste incinerators. Concentrations of 2,3,7,8-TCDD measured in this study ranged from ND to 9.4 ppt.

Nine background soil samples were collected from the Yarmouth Pole Yard Site located in Yarmouth, Maine (Tewhey Associates, 1997). One of these samples, collected from soil near the base of a utility pole, yielded an I-TEQ_{DF} concentration of 57,000 pg/g. The I-TEQ_{DF} concentrations for the other eight samples ranged from 0.73 pg/g to 5.9 pg/g when nondetects were assumed to be zero, and 1.46 pg/g to 6.07 pg/g when nondetects were assumed to be one-half the detection limit. These samples are from rural background locations. The mean I-TEQ_{DF} for these eight samples was 3.58 pg/g (TEQ_{DF}-WHO_{98} was 2.89 pg/g) when nondetects were set to zero and 3.93 pg/g when nondetects were set to one-half the detection limit. The sample collected near the utility pole was not included in these mean TEQ values, because its results were not considered to be representative of typical rural background concentrations.

In an effort to determine whether incineration of municipal waste influenced CDD/CDF levels in the immediate area of waste incineration facilities, soil samples were collected from cities with, and without operating incinerators throughout Connecticut. Between the years of 1987 and 1990, 34 soil samples were collected from eight different Connecticut cities where no municipal waste incinerators were operating (MRI, 1992). These pre-operational samples were considered to be representative of rural background concentrations. The total I-TEQ_{DF} reported for these samples was 6.07 pg/g, with nondetects assumed to be one-half the detection limit. When the total TEQ was recalculated in units of TEQ_{DF}-WHO_{98}, the total TEQ for these samples was 5.74 pg TEQ_{DF}-WHO_{98}/g. The proportion of nondetects ranged from 3 to 11 percent of samples for each analyte, with the exception of 2,3,7,8-TCDD and 1,2,3,7,8,9-HxCDF, which had 56 and 49 percent nondetects, respectively (MRI, 1992).

The Ministry of Environment in British Columbia conducted a 2-year monitoring study during 1990/91 and 1991/92 to evaluate the levels of CDD/CDF contamination in various types of environmental media (BC Environment, 1995). Soil samples were collected from sites close to a source (primary sites), in the receiving environment adjacent to a suspected source (secondary sites), and in areas not expected to be contaminated (background). Primary and secondary sources were identified as chemical or combustion sources. Chemical sources included sites associated with chlorophenol, herbicide, or PCB contamination; oil refineries; pulpmill landfills; or sewage facilities. Combustion sources included biomedical, industrial, municipal, or sewage sludge incineration; PCB or forest fires; pulp mill boilers; salt-laden wood burning, woodwaste burners, or slash burning; and scrap iron yards or smelters. The highest mean concentrations of 2,3,7,8-TCDD and 2,3,7,8-TCDF were observed in primary and secondary soils associated with chemical sources (Table 3-12). For the 53 background samples, 2,3,7,8-TCDD was not detected, and 2,3,7,8-TCDF concentrations ranged from nondetected to 3.2 ppt. For the purposes of calculating I-TEQ_{DF} values for this study, nondetects were set to zero. I-TEQ_{DF}s were highest among samples associated with primary and secondary chemical sources (Table 3-12). The mean I-TEQ_{DF} for the background soil samples was 5.0 ppt (BC Environment, 1995). When the mean TEQ was recalculated in units of TEQ_{DF}-WHO_{98}, the total TEQ for these samples was 4.4 pg TEQ_{DF}-WHO_{98}/g.

Grundy et al. (1995) and Bright et al. (1995) collected soil samples from remote locations in the Canadian Arctic as part of an environmental assessment of abandoned military installations in the Canadian North. Four soil samples from remote pristine areas (i.e., at least 20 km away from any human activity) were analyzed for CDD/CDFs. The total I-TEQ concentrations for these samples ranged from 0.2 to 0.9 ppt (Grundy et al., 1995). Of the CDD/CDF homologue groups, OCDD and TCDF levels were the highest among these remote soil samples, and the HxCDFs made up the smallest portion of the total CDD/CDF concentrations (Bright et al., 1995).

EPA conducted a 2-year nationwide study to investigate the national extent of 2,3,7,8-TCDD contamination (U.S. EPA, 1987). Results of this large study were summarized broadly in the primary reference (i.e., the number and types of samples per site and range of detection). The method used to analyze samples for five of the seven

study "tiers" had a detection limit in soil, sediment, and water of 1 part per billion (ppb). [Each "tier" of sites is a grouping of sites with a common past or present use (e.g., industrialized, pristine, etc.)]. Only Tier 5 (sites where pesticides derived from 2,4,5-trichlorophenol (TCP) had been or were being used for commercial purposes) and Tier 7 (ambient sampling for fish and soil) had detection limits of 1 ppt. Consequently, the data from this study are not included in the Appendix B tables; however, some observations from this study with regard to soil contamination are discussed below.

Soil concentrations found in most of the 100 Tier 1 and 2 sites (i.e., sites already on or expected to be on the NPL list) were in the ppb range; although in a few sites where concentrated 2,4,5-TCP production wastes were stored or disposed, concentrations were as high as 2,000 parts per million (ppm). Off-site soil contamination of concern was confirmed in 7 of the 100 Tier 1 and 2 sites, with soil concentrations in the ppb range. Eleven of the 64 Tier 3 sites (facilities and associated disposal sites where 2,4,5-TCP and its derivatives were formulated into pesticide products) were found to have soil concentrations exceeding 1 ppb, and in 7 of 11 sites where contamination was found, only one or two soil samples were above 1 ppb. Fifteen of the 26 Tier 5 sites (areas where 2,4,5-TCP and pesticide derivatives had been or were being used) had concentrations above 1 ppt, and one of those had a single detection of 6 ppb. Two-thirds of all detections at the Tier 5 sites were below 5 ppt. Three of the 18 Tier 6 sites (organic chemical and pesticide manufacturing facilities where improper quality control on production processes could have resulted in 2,3,7,8-TCDD being introduced into the wastestreams) had soil concentrations that exceeded the detection limit of 1 ppb, although these levels were limited to one or two samples per site. Seventeen of the 221 urban soil sites and 1 of the 138 rural sites from Tier 7 (background sites not expected to have contamination) had soil concentrations exceeding 1 ppt. The highest concentration detected (11.2 ppt) was found in an urban sample. Results from Tier 7 are consistent with the other studies discussed in this chapter regarding soil concentrations of 2,3,7,8-TCDD in nonindustrial settings.

Rappe et al. (1995a) and Fiedler et al. (1995a) analyzed soil samples collected from rural sites in southern Mississippi for CDDs and CDFs. Sites not directly impacted by human activities such as heavy traffic or dust were selected. A total of 36 composite soil samples from 8 Mississippi counties were analyzed. The I-TEQ_{DF} concentration of

CDD/CDFs in soil ranged from 0.16 to 22.9 ppt dry mass (Fiedler et al., 1995a). The mean I-TEQ_{DF} concentration was 3.1 ppt dry mass, and the median I-TEQ_{DF} concentration was 0.8 ppt dry mass (Fiedler et al., 1995a). CDDs were found at higher concentrations than CDFs, and OCDD was the most dominant congener.

Soil samples were collected from the National Institutes of Health (NIH) campus in Bethesda, Maryland, during 1995 in an effort to determine the effect of 30 years of pathological waste incineration on the campus and its surroundings (NIH, 1995). Thirty-seven samples were collected from the soil at a depth of 6 inches. The total I-TEQ_{DF} for these samples was 7.83 pg/g, when nondetects were assumed to be zero, and 8.49 pg/g, when nondetects were assumed to be one-half the detection limit. OCDD, at a I-TEQ_{DF} concentration of 6.29 pg/g, was the principal contributor to the total I-TEQ_{DF} for these samples, regardless of whether nondetects were assumed to be zero or one-half the detection limit. It should be noted that using the new TEF_{DF}-WHO_{98}s, the TEQ for OCDD would be 10 times lower (i.e., 0.63 pg/g). This reduction would also result in a significant decrease in the total TEQ. The total TEQ_{DF}-WHO_{98} would be 2.21 pg/g, when nondetects were set to zero. Samples were also collected at depths of 12 and 24 inches for comparison to levels found in the shallow (6-inch) samples. While CDD/CDF concentrations found at the surface indicate deposition, strong correlation with I-TEQ_{DF} concentrations at the deeper depths were observed. This seemed to indicate either long-term presence of the source (i.e., greater than 40 years), or soil mixing that has occurred either during or after deposition. An expert panel (comprised of toxicologists, chemists, soil scientists, engineers, risk assessors, and public health professionals) concluded that the levels of I-TEQ_{DF} in the samples are low and not significantly different from background. Thus, these samples are assumed to be representative of urban background concentrations. The spatial pattern of I-TEQ_{DF} concentrations showed no particular trends that could be related to the incinerator. Other anthropogenic activities, such as vehicular traffic, other medical waste incinerators not related to NIH, and fireplaces burning in the vicinity, may have contributed to the deposition (NIH, 1995).

U.S. EPA (1996) collected soil samples in the vicinity of a municipal waste-to-energy (WTE) facility in Columbus, Ohio, to determine whether surface soils around the incinerator contained higher CDD/CDF levels than soils collected from background sites. The facility is not currently in operation, but CDD/CDF residues may be present in the soil

near the facility as a result of past emissions. Samples were collected from (1) on-site, (2) urban background locations near the incinerator, and (3) areas remote from the facility (i.e., rural background sites). The results of the analyses indicate that soil from the rural background sites had the lowest I-TEQ_{DF} concentrations and on-site samples had the highest I-TEQ_{DF} concentrations (Table 3-13). For rural background soil samples, total I-TEQ_{DF}s ranged from 0.9 to 1.3 ppt (n = 3) with a mean of 1.1 ppt (TEQ_{DF}-WHO_{98} = 0.9 ppt), when nondetects were assumed to be zero, and 1.0 to 2.0 ppt with a mean of 1.4 ppt (TEQ_{DF}-WHO_{98} = 1.3 ppt), when nondetects were set to one-half the detection limit. Total I-TEQ_{DF}s for urban background soils ranged from approximately 3 to 60 ppt (n = 18) with a mean of 19 ppt (TEQ_{DF}-WHO_{98} = 21 ppt), when nondetects were set to either zero or one-half the detection limit. For on-site samples, all 2,3,7,8-CDD/CDF congeners were detected in all samples (n = 4). Total I-TEQ_{DF} concentrations ranged from 50 to 760 ppt with a mean of 356 ppt (TEQ_{DF}-WHO_{98} = 444 ppt). Additional detail and analyses of these data are presented in Lorber et al. (1998a).

Brzuzy and Hites (1995) examined soil cores from four U.S. locations to evaluate the accuracy of using measurements of CDD/CDF homologue groups in estimating the atmospheric flux of these compounds into the environment. Soil cores were collected from undisturbed areas near Shingleton, Grayling, and Verona, Michigan, and near Mitchell, Indiana. CDD/CDF concentrations varied according to depth of the soil samples, with deeper samples having lower CDD/CDF concentrations. Approximately 80 percent of the CDD/CDF load were contained in the top 15 cm of the cores, and CDD/CDF concentrations were close to the detection limit in samples collected at a depth of 20-25 cm. Based on the graphs presented in Brzuzy and Hites (1995), total CDD/CDF concentrations in the uppermost 5 cm of the core ranged from approximately 60 pg/g to 200 pg/g for the three Michigan sites. CDD/CDFs in these soil cores were also found to be highly correlated with the organic carbon content of the soil, indicating that organic carbon is an important factor in the sorption of CDD/CDFs to soil (Brzuzy and Hites, 1995). Higher concentrations of CDD/CDFs were observed in two cores taken from the Indiana site. Concentrations in the uppermost layer (i.e., 9 cm) of these cores ranged from approximately 700 pg/g to nearly 10,000 pg/g. CDD/CDF concentrations in these cores peaked at a depth of approximately 40 to 50 cm with concentrations ranging from approximately 1,000 pg/g to over 20,000 pg/g. Brzuzy and Hites (1995) used the

Michigan data to estimate soil-derived CDD/CDF flux rates ranging from 264 ng/m^2/yr for upper Michigan to 663 ng/m^2/yr for lower Michigan. These soil-derived flux estimates were compared to sediment-derived fluxes from previous studies to determine if soil samples can also be used to accurately predict atmospheric flux. Good agreement for the fluxes to these two media was observed. In addition, the CDD/CDF homologue profiles for soil and sediment were similar.

Recently, Washington State Department of Ecology (Rogowski et al., 1999) collected soil samples as part of a study of metals and dioxin-like compounds in agricultural fertilizers and soil amendments. Soils were analyzed to evaluate whether these compounds had accumulated as a result of fertilizer use and to assess typical concentrations of dioxin-like compounds in Washington State soils. A total of 30 soil samples were collected from urban (N = 14), rangeland (N = 8), and forested (N = 8) locations. Each sample was a composite of 10 sub-samples collected within a 1-acre sampling unit. The sampling units were selected to represent typical or background locations for each land use. Mean TEQ_{DF}-WHO_{98} concentrations were higher in urban locations (4.1 ppt) than in open rangeland/forest locations (1.8 ppt). During a later sampling event (Rogowski and Yake, 1999), agricultural soils were collected to characterize typical or background concentrations of dioxin-like concentrations in soil. Fifty-four samples were collected. Each sample was a composite of 10 sub-samples collected from each sampling location to a depth of 5 cm. The mean TEQ_{DF}-WHO_{98} concentration for the agricultural samples was 0.12 ppt.

U.S. EPA Region 8 (2000a) is conducting a set of four related studies on dioxin-like compounds in surficial soils along Denver, Colorado's, Front Range. One of these studies (U.S. EPA Region 8, 2000b) evaluated regional background soil; other sampling efforts include characterization of the Rocky Mountain arsenal using random samples at the site or from historic use sites. A large number of reference soils were collected and analyzed for CDD/CDFs and dioxin-like PCBs. These data will be used to assess whether the soil concentrations observed in the Western Tier Parcel of the Rocky Mountain Arsenal, an EPA National Priority List site, are higher than regional background levels. U.S. EPA Region 8 (2000b) collected and analyzed 162 surface soil samples for investigation into background concentrations of dioxin-like compounds at multiple locations within 1,000 square miles of Denver, Colorado's, front range. The multi-land use areas that were

sampled were situated on public lands and were categorized as agricultural (n = 27), commercial (n = 31), industrial (n = 29), open space (n = 36), and residential (i.e., within 200 feet of private land) (n = 39). The fine-soil fractions of samples obtained in the upper two inches of the soil were analyzed for the 17 dioxins and furans and 12 PCBs (77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, and 189). The mean TEQ_{DFP}-WHO_{98} ranged from less than 1 ppt TEQ to approximately 100 ppt TEQ (with two outliers of 142 and 155 ppt removed; one from a residential site and one from a commercial site). The mean TEQ_{DFP}-WHO_{98} values were: 1.9 ppt for agricultural sites, 8.5 ppt for commercial sites, 15.4 ppt for industrial sites, 2.8 ppt for open space, and 8.6 ppt for residential locations, with a total mean of 7.5 ppt when non-detects were set to one-half the detection limit (U.S. EPA Region 8, 2000b, with revised data provided by Gerry Henningsen, Region 8 to Jim Buchert, Versar, Inc., March 2001). PCBs comprised approximately 20 percent of the TEQ_{DFP}-WHO_{98}. The analytical values indicate that open space and agricultural lands have the lowest TEQ_{DFP}-WHO_{98} concentrations, while industrial, commercial, and residential locations have slightly higher concentrations. It should be noted that because sieved samples were analyzed, these results may be higher than if bulk samples had been analyzed. Further testing is being conducted to identify if the increased total organic carbon content of agricultural and open space soils have a higher affinity for dioxin-like compounds than other soil types, thereby skewing the analytical results to produce lower than actual values.

3.3.2. European Data

Soil samples from rural and semi-urban sites in England, Wales, and lowland Scotland showed a general increase in concentration from the TCDDs to OCDD, whereas CDF levels showed very little variation between the congener groups (Creaser et al., 1989). Concentrations of 2,3,7,8-TCDD at those sites ranged from <0.5 to 2.1 ppt. The median values for the TCDDs to OCDD were 6.0, 4.6, 31, 55, and 143 ppt, respectively. The median values for the TCDFs to OCDF were 16, 17, 32, 15, and 15 ppt. Evaluation of soil data from urban sites in the same geographical area showed that the mean levels for the CDD and CDF congeners were significantly greater ($p<0.01$) than those for rural and semi-urban background soils (Creaser et al., 1990). Concentrations of 2,3,7,8-TCDD at the urban sites ranged from <0.5 to 4.2 ppt. The median values for the

TCDDs to OCDD were 40, 63, 141, 256, and 469 ppt, respectively. The median values for the TCDFs to OCDF were 140, 103, 103, 81, and 40 ppt. Significantly elevated levels of the lower congeners, together with higher overall CDD/CDF concentrations, are indicative that local sources and short-range transport mechanisms are major contributors of CDDs and CDFs to urban soils. Cox and Creaser (1995) evaluated soils from urban and rural locations in the United Kingdom before the introduction of Integrated Pollution Control in 1991. I-TEQ_{DF}s for 11 rural locations ranged from 0.78 ppt to 17.48 ppt, with a mean of 5.17 ppt, and the I-TEQ_{DF}s for 5 urban samples ranged from 4.88 pt to 87.34 ppt with a mean of 28.37 ppt.

Analysis of four sites in Hamburg, Germany, contaminated by an organochlorine pesticide manufacturing company showed patterns of CDD and CDF distribution similar to the urban and industrial sites examined in England, Wales, and Scotland (Sievers and Friesel, 1989). The study indicated that CDDs and CDFs showed a regular increase in concentration with increasing degree of chlorination (although individual data points were not presented). Maximum concentrations of 2,3,7,8-TCDD ranged from 900 ppt to 874,000 ppt. Very high concentrations of 2,3,7,8-TCDD at the sites were attributed to an admixture of wastes from 2,4,5-T production.

A soil sampling survey in Salzburg, Austria, also showed that the concentrations of CDD/CDFs were higher in urban and industrial sites than in rural sites (Boos et al., 1992). The total CDD content of the soils ranged from 33.7 to 1236.7 ppt for urban sites, 92.2 to 455 ppt for industrial sites, and 7.1 to 183.6 ppt for rural sites. The total CDF content of the soils ranged from 45.6 to 260.8 ppt for urban sites, 53.0 to 355.3 ppt for industrial sites, and 12.0 to 77.7 ppt for rural sites. I-TEQ_{DF}s ranged from 0.1 ppt to 3.1 ppt for rural sites, 1.0 ppt to 8.3 ppt for urban sites, and 3.5 ppt to 11.5 ppt for industrial sites, when nondetects were assumed to be zero. When nondetects were set to one-half the limit of detection, I-TEQ_{DF}s ranged from 1.3 ppt to 3.8 ppt for rural sites, 2.0 ppt to 8.6 ppt for urban sites, and 4.1 ppt to 12.5 ppt for industrial sites.

Rappe and Kjeller (1987) presented data on CDD/CDFs in soil collected from rural ($n = 3$) and industrial ($n = 2$) sites in various parts of Europe. Concentrations were higher among industrial soils than rural soils for all of the CDD/CDF homologue groups, and the hepta-chlorinated compounds made up the largest portion of the total CDD/CDF concentrations in both rural and industrial samples. HpCDDs ranged from nondetected to

17 ppt in rural samples and 370 to 1,600 ppt in industrial samples. HpCDFs ranged from 14 to 22 ppt in rural soils and 260 to 4,500 ppt in industrial soils.

Rotard et al. (1994) measured CDD/CDFs in soil samples collected from forest, grassland, and plowland sites in western Germany. The highest mean concentration of CDD/CDFs were found in the subsoil and topsoil layers of deciduous (38.0 ng I-TEQ_{DF}/kg dry matter; n = 9) and coniferous forests (36.9 ng I-TEQ_{DF}/kg dry matter; n = 11). Grassland and plowland sites had mean concentrations of 2.3 ng I-TEQ_{DF}/kg dry matter (n = 7) and 1.7 ng I-TEQ_{DF}/kg dry matter (n = 14), respectively.

Stenhouse and Badsha (1990) collected baseline data for soils around a site proposed for a chemical waste incinerator in Great Britain. All of the 2,3,7,8-substituted CDD/CDF congeners, except PeCDD, were detected in all samples. Concentrations were highest for the octa-chlorinated CDD/CDFs. Background I-TEQ_{DF} concentrations ranged from 3 to 20 ppt. The mean I-TEQ_{DF} concentration was 8 ppt (n=12), with a standard deviation of 4 ppt.

Buckland et al. (1998) evaluated soils collected in New Zealand. Dry weight CDD/CDF concentrations ranged from 0.17 to 1.99 pg I-TEQ_{DF}/g for pristine soils, 0.17 to 0.90 pg I-TEQ_{DF}/g for agricultural soils, and 0.52 to 6.67 pg I-TEQ_{DF}/g for urban soils. The PCB concentrations ranged from 0.067 to 2.3 pg TEQ_P/g (the TEFs used for PCBs were not identified) for provincial centers and 0.087 to 1.33 pg TEQ_P/g for metropolitan centers. The congeners below the detection limit were included in the total TEQ using half their limits of detection.

Masahide et al. (1998a) examined soil samples collected at the depth of 0-10 cm from various sites located in Poland between 1990 and 1994. The mean dry weight total PCB concentration was 8.6 ng/g for agricultural and forest soils, 170 ng/g (n=31) for urban soils, and 900 ng/g for the soils sampled at the military area. Dry weight PCB concentrations increased from 21 ng/g in Northern Poland to 48-380 ng/g in highly populated and industrialized regions in Southern Poland.

3.3.3. Soil Observations and Trends

Some general observations for CDD and CDF levels in soils are possible from the data presented in the various soil studies discussed above:

- As the degree of chlorination increases, the concentrations increase. Concentrations of the hepta- and octa-chlorinated congeners are generally higher than the tetra-, penta-, and hexa-chlorinated congeners.
- Concentrations in settings identified as urban are higher than those in areas identified as rural.
- Concentrations associated with industrial sites clearly are the highest, with concentrations in the hundreds to thousands of parts per trillion.

3.3.4. Soil CDD/CDF Profiles and Background TEQ Concentrations

CDD/CDF homologue group profiles for soil were calculated as the mean homologue group concentrations divided by the mean total CDD/CDF concentration. Nondetects were assumed to be zero in these calculations. For rural background soil, homologue group profiles were calculated based on data from Reed et al. (1990), Birmingham (1990), Pearson et al. (1990), BC Environment (1995), U.S. EPA (1985, 1996), Tewhey Associates (1997), MRI (1992), Rogowski et al. (1999), and Rogowski and Yake (1999). They indicate that of the homologue groups, the higher chlorinated compounds dominate. OCDD and HpCDD account for the highest percentages of total CDD/CDFs (Figure 3-3; Table 3-14). CDD/CDF homologue group profiles for urban background samples, based on Birmingham (1990), Pearson et al. (1990), NIH (1995), U.S. EPA (1996), and Rogowski et al. (1999), are similar (Figure 3-4; Table 3-14). The sum of 2,3,7,8-substituted congener concentrations account for 83 percent of the total CDD/CDF concentrations in rural background soil and 91 percent in urban background soil. Profiles based on the ratio of 2,3,7,8-substituted congeners to total CDD/CDFs in rural background soil indicate that OCDD and 1,2,3,4,6,7,8-HpCDD account for the highest percentages of total CDD/CDFs, followed by OCDF and 1,2,3,4,6,7,8-HpCDF (Reed et al., 1990; BC Environment, 1995; U.S. EPA, 1996; Tewhey Assoc., 1997; MRI, 1992; Rogowski et al., 1999; and Rogowski and Yake, 1999) (Figure 3-3). For urban background soils, profiles were similar to those observed in rural background soils, based on data from NIH (1995), U.S. EPA (1996), and Rogowski et al. (1999) (Figure 3-4).

Based on several of the studies described in this chapter, mean TEQ_{DF}-WHO_{98} levels were calculated (Table 3-15), based on the available data, to represent "typical" background conditions in the North America. The mean rural background TEQ_{DF}-WHO_{98}

level was estimated to be 2.6 ppt, and the "typical" urban background TEQ_{DF}-WHO_{98} level was estimated to be 8.8 ppt, assuming that nondetects equal zero. The mean rural background concentration is based on data from eleven studies in seven U.S. States (i.e., Ohio, Minnesota, Illinois, Maine, Connecticut, Colorado, and Washington) and two areas in Canada (i.e., British Columbia and Ontario) (n = 319; BC Environment, 1995; Birmingham, 1990; MRI, 1992; Pearson et al., 1990; Reed et al., 1990; Tewhey Associates, 1997; U.S. EPA, 1985; U.S. EPA, 1996; Rogowski et al., 1999; Rogowski and Yake, 1999; U.S. EPA Region 8, 2000b). The mean urban background concentration is based on data from five U.S. States (i.e., Michigan, Maryland, Ohio, Colorado, and Washington) and Ontario, Canada (n = 305; Birmingham, 1990; Nestrick et al., 1986; NIH, 1995; Pearson et al., 1990; U.S. EPA, 1985; U.S. EPA, 1996; Rogowski et al., 1999; U.S. EPA Region 8, 2000b). The TEQ_{P}-WHO_{98} was 0.31 ppt (n = 27) for rural soil and 2.0 ppt (n = 134) for urban soil, based on soil data from U.S. EPA Region 8 (2000b) which were collected in and around Denver, Colorado. In calculating the mean concentrations, each site was weighted equally (i.e., the means are based on the average of the mean concentrations from each location). In contrast, the weighted means in Table 3-15 represent average concentrations for rural and urban sites that have been weighted according to the number of samples at each site; all soil samples are treated individually regardless of location. Thus, more heavily sampled locations have a greater impact on the weighted mean than those sampled less frequently. Therefore, means, not weighted means, were used to depict typical rural and urban background concentrations in North America. It should be noted, however, that the means and weighted means in Table 3-15 are quite similar.

Background TEQ_{DF}-WHO_{98} levels for soils were estimated by setting nondetects to zero instead of one-half the detection limit, because congener-specific detection limits were not available for some of the early studies. If one-half the detection limits had been used to represent nondetected congeners, the estimated background TEQ_{DF}-WHO_{98} levels may have been slightly higher. Based on the results of European studies, it appears that background TEQ_{DF}-WHO_{98} concentrations in European soil are similar to those of the United States. The TEQ_{DF}-WHO_{98} concentration in urban background soil is used in Chapter 4 to calculate background exposures. Urban soils are used because the majority of the population lives in urban areas. Thus, using these concentrations would represent typical exposure levels.

3.4. CONCENTRATIONS IN WATER

Tables B-6 and B-7 (Appendix B) contain summaries of data from the limited number of published studies regarding concentrations of CDDs and CDFs in water. Data on dioxin-like PCB congener concentrations in water were not found in the literature. Several of the CDD/CDF studies are discussed below.

3.4.1. North American Data

A survey of 49 drinking water supplies in Ontario, including supplies in the vicinity of chemical industries and pulp and paper mills, was initiated in 1983 (Jobb et al., 1990). As of February 1989, 4,347 congener analyses had been performed on 399 raw and treated water samples. OCDD was detected in 36 of 37 positive results and ranged from 9 to 175 ppq in raw samples (33 positive samples) and 19 to 46 ppq in treated samples (4 positive samples). These low concentrations were found primarily in water obtained downstream of industrialized areas in the St. Clair/Detroit River system. No samples contained detectable levels of 2,3,7,8-TCDD. Because CDDs and CDFs are hydrophobic compounds, and consequently, have a tendency to sorb onto particulate matter in water, conventional water treatment processes are expected to be effective in removing the contaminants along with the particulates. This is substantiated by the fact that 33 of the 37 positive results were raw water samples. Because of the relatively low levels of CDDs detected in the samples, it is difficult to ascertain whether the CDDs were particulate-associated or dissolved.

A survey of 20 community water systems throughout New York State was conducted in 1986 (Meyer et al., 1989). The sampling sites were representative of the major surface source waters in New York. They included sources receiving industrial discharges or known to contain dioxin-contaminated fish, as well as waters in more remote areas. TCDFs were detected in the finished water at the Lockport facility (duplicate samples had concentrations of 2.1 and 2.6 ppq). Except for a trace of OCDF detected at one location, no other CDDs/CDFs were detected in finished water at any of the other 19 community water systems surveyed. Raw water sampled at the Lockport facility contained concentrations of TCDDs (1.7 ppq), as well as TCDFs to OCDF (18, 27, 85, 210, and 230 ppq, respectively). As can be seen from the data, the CDF congener group concentrations increased with increasing chlorine number.

3.4.2. European and Japanese Data

CDDs in surface water samples collected from the Eman River in southern Sweden generally increased in concentration from the TCDDs to OCDD; whereas, the CDF levels showed very little variation between the congener groups (Rappe et al., 1989a). In general, however, the levels of CDFs were higher than the levels of CDDs. Concentrations of 2,3,7,8-TCDF were 0.022 ppq in Jarnsjon and 0.026 ppq in Fliseryd. The filtered water, before chlorination and distribution as drinking water, had no detectable tetra-, penta-, or hexa-chlorinated congeners of CDDs or CDFs, but the HpCDDs and OCDD were detected at 120 and 170 ppq, respectively.

A survey was conducted at the Venice lagoon in the north of Italy by the Ministry of Justice and the Ministry of Works to assess the CDD/CDFs contamination produced by industrial and municipal waste water discharges (Ramacci et al., 1998). The results showed that four out of seven waste water samples were characterized by a prevalence of OCDF; two had an almost equal distribution between OCDD and OCDF; and only one collected from a septic tank of the city of Venice presented a prevalence of OCDD.

In Japan, water samples were collected from a coastal area, river, and pond in Matsuyama between October 1996 and September 1997 (Seike et al., 1998). The total concentrations of CDD/CDFs ranged from 15 to 170 pg/L (n = 3) in coastal waster with an average of 51 pg/L, from under the detection limit to 1500 pg/L (n = 22) in river water with an average of 180 pg/L, and from 44 to 530 pg/L (n = 3) in pond water with an average of 260 pg/L. CDD/CDFs in coastal water were relatively lower than from other sources, and were thought to be diluted with seawater and/or deposited to the coastal sediment.

Raw and treated tapwater samples from Japanese water supplies were analyzed by Magara et al. (2000) for CDD/CDFs and PCBs 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189. The average TEQ_{DFP}-WHO_{98} was 0.148 pg/L (ppq) for raw water and 0.019 pg/L (ppq) for treated water. CDFs accounted for about 60 percent of the total TEQ in the treated samples.

3.4.3. Water Observations and Trends

Some general observations for CDD and CDF levels are possible from the limited data available from the various water studies described above:

- CDD/CDFs are seldom detected in drinking water at ppq levels or higher.
- Raw water samples generally have higher concentrations of CDD/CDFs than finished water samples.
- The concentration of CDDs and CDFs in surface water generally increases from the tetra-chlorinated to the octa-chlorinated congener groups.

3.4.4. Water CDD/CDF Profiles and Background TEQ Concentrations

CDD/CDF congener profiles could not be generated for water because of the lack of congener-specific data for treated drinking water. For the background studies reviewed here, only data for OCDD and OCDF were available.

Based on the above studies, a total of 236 samples from Ontario, Canada, and Lockport, New York, were selected as representing background conditions in North America. The "typical" TEQ_{DF}-WHO_{98} level was computed as 0.00056 ppq, assuming that nondetects equal half the detection limit (Jobb et al., 1990). This value is used in Chapter 4 to estimate background exposures to the U.S. population from drinking water consumption. It should be noted, however, that OCDD and OCDF were the only congeners for which background data were available. Of the 214 samples analyzed for OCDD, only 4 were positive, and only 2 out of 22 samples analyzed for OCDF were positive. No appropriate data on drinking water concentrations could be found for Europe, and only one study was available for Japan.

3.5. CONCENTRATIONS IN SEDIMENT

Tables B-8 through B-10 (Appendix B) contain summaries of data from several of the numerous studies in the published literature regarding concentrations of CDDs, CDFs, and dioxin-like PCB congeners in sediment. Several of these studies are discussed in the following paragraphs. It should be noted that the review of sediment data presented here is not based on a comprehensive review of the published studies on CDD/CDFs in sediment. Instead, it is intended to provide a brief overview of sediment levels of CDD/CDFs from a sampling of representative studies. In addition, because the levels of CDD/CDFs and PCBs in sediment layers may be indicative of the cumulative history of contamination at a site (i.e., reservoir sources), the studies presented here represent only

those that analyzed surficial (i.e., recently deposited) sediment samples or the uppermost layers from sediment cores, and not deep sediment core samples.

3.5.1. North American Data

In sediment samples collected from estuaries adjacent to an industrial site in Newark, New Jersey, where chlorinated phenols had been produced, the level of OCDD was many times higher than that of 2,3,7,8-TCDD (Bopp et al., 1991). Studies conducted by Wenning et al. (1992; 1993) in Newark Bay also indicated that OCDD was found in higher concentrations than the lower-chlorinated congeners in this water body. Based on 19 sediment samples, OCDD levels ranged from 310 ppt to 17,000 ppt, and 2,3,7,8-TCDD levels ranged from 2.8 pt to 480 ppt. Observed congener patterns for this area were similar to those found in sediments from several other U.S. and European water bodies. The authors suggest that these similarities are a result of similar municipal and industrial sources in heavily industrialized and populated areas. Based on the results of principal components analyses, the congener profiles for sediments from Newark Bay are closely related to those of several different potential sources, including chemical manufacturing processes and municipal activities. Hudson River sediment samples contained primarily the higher chlorinated (Cl_6 to Cl_8) CDD and CDF congeners (Petty et al., 1982). Concentrations of the HpCDD and OCDD homologues ranged from 5 to 15 ppb, and the OCDD homologue in most instances accounted for more than half of the total CDD residue. Likewise, the HpCDFs and OCDF occurred at the highest levels (ca. 1 ppb).

Surface sediment samples were collected from several estuaries in the United States (Norwood et al., 1989). Sampling sites included Black Rock Harbor in Bridgeport, Connecticut, (an industrialized urban estuary); central Long Island Sound (a relatively clean reference site); Narragansett Bay, Rhode Island, (where chemical industries may have contributed to the input); New Bedford Harbor, Massachusetts, (a section of which is a National Superfund Site because of PCB contamination); and Eagle Harbor, Washington, (the site of a creosote wood treatment facility). Sediments in New Bedford Harbor were reported to be more heavily contaminated with CDFs than sediments from the other sites. In particular, HxCDF congeners were greater by a factor of 40 (although individual data points were not presented) at one of the more contaminated New Bedford Harbor sites. In

contrast, sediments from Eagle Harbor were practically devoid of CDFs and showed a large increase in the HpCDD and OCDD congeners closer to the treatment facility. Narragansett Bay and Black Rock Harbor were similar in both concentration and distribution of CDDs and CDFs, and Black Rock Harbor contained slightly higher levels of the tetra- to hepta-CDD and CDF congeners. Sediment from Long Island Sound was cleaner and had a distribution of CDFs between that of Narragansett Bay and Black Rock Harbor. Sediment with the least contamination was collected in New Bedford Harbor, up-river from the PCB facilities; the highest OCDD concentration (1,400 ppt) was detected in Eagle Harbor.

Sediment samples from Siskiwit Lake, on Isle Royale, Lake Superior, were examined to evaluate the atmospheric input of CDDs and CDFs to the lake (Czuczwa et al., 1984). The water level in Siskiwit Lake is 17 meters higher than that in Lake Superior, and in addition, there are no anthropogenic inputs in the drainage basin of Siskiwit Lake. Consequently, the atmosphere is the only source of anthropogenic chemicals in that lake. OCDD was most predominant, and the HpCDD and HpCDF congeners also were abundant. The study indicated a considerable decrease in concentration of all CDDs and CDFs between 6 and 8 cm of the sediment core depth (i.e., sediment believed to have been deposited about 1940).

Surficial sediments collected from Jackfish Bay on the north shore of Lake Superior contained moderate concentrations of the TCDF and OCDD congeners, with trace concentrations of other congeners (Sherman et al., 1990). The concentration of OCDD was similar to that found in the Siskiwit Lake sediment samples. The OCDF and OCDD profile for a sediment core collected from Moberly Bay was similar to the surficial sediment pattern. These congener groups predominated at all depths where detectable concentrations occurred. In addition, low concentrations of the HpCDD and PeCDF and HpCDF congeners were detected. The concentration profile of the HpCDF congener group showed a relatively high value that dropped abruptly to nondetectable (<60 ppt) below a depth of 10 cm. This abrupt change corresponded to a section date 1973 that reflects an operational change at the pulp mill.

A survey of surficial harbor sediments collected near a wood preserving plant in Thunder Bay, Ontario, Canada, on the north shore of Lake Superior, found the highest concentrations of CDD/CDFs at stations closest to the plant dock, and lower

concentrations at locations further from the source (McKee et al., 1990). No CDDs or CDFs were detected below the surficial layer. TCDD and PeCDD congeners were below analytical detection limits in all samples. However, the concentrations of the HxCDDs to OCDD congeners increased with the degree of chlorination. The maximum concentrations of the HxCDDs to OCDD ranged from 5,700 ppt for the HxCDDs to 980,000 ppt for OCDD. As with the CDD distribution profile, the HxCDFs to OCDF increased with the degree of chlorination.

Sediment levels of CDD/CDFs in British Columbia were found to be higher in samples collected from sites in the receiving environment adjacent to a suspected source (secondary sites) than in areas not expected to be contaminated (background) (Table 3-16) (BC Environment, 1995). These observations are based on a 2-year study conducted during 1990/91 and 1991/92 by British Columbia's Ministry of Environment. Secondary sites were identified as being associated with chemical or combustion sources. Background samples did not contain detectable levels of 2,3,7,8-TCDD, and the mean 2,3,7,8-TCDF concentration was 1.4 ppt. For the purposes of calculating I-TEQ_{DF} values for this study, nondetects were set to zero. Mean I-TEQ_{DF} levels were 32.5 ppt for secondary sites (all sources) and 3.9 ppt for background sites (Table 3-16).

Bottom surficial sediments (0-3 cm) were collected from the sedimentation basins of Lake Ontario to assess the levels of the various PCB congeners (Oliver and Niimi, 1988). Concentrations of 2,3',4,4',5-PeCB (PCB 118); 2,3,3',4,4'-PeCB (PCB 105); and 2,3,3',4,4',5-HxCB (PCB 156) in the sediment were 15, 10, and 2.1 ppb, respectively. A baseline assessment of CDDs and CDFs was performed on the Elk River, a semi-rural area located about 25 miles northwest of Minneapolis-St. Paul, Minnesota (Reed et al., 1990). Sediment samples were collected from Lake Orono, a reservoir on the Elk River, and from an abandoned gravel pit. Although none of the sediment samples contained 2,3,7,8-TCDD, the gravel pit sediments contained measurable concentrations of TCDFs. Only one Lake Orono sample contained measurable concentrations of 2,3,7,8-TCDF (0.31 ppt) and total TCDF (0.54 ppt). Gravel pit samples also contained HpCDDs to OCDD and PeCDFs to OCDF. Lake Orono samples contained HpCDDs, OCDD, and HpCDF congeners. HpCDDs ranged from 7.3 ppt in the lake inlet to 110 ppt in the gravel pit and in the lake near the dam. OCDD concentration ranged from 450 ppt in the gravel pit to 600 ppt in the middle of Lake Orono. The sediment profiles reflected combustion source influences.

The Sheboygan River, a Wisconsin tributary to Lake Michigan, is polluted with PCBs from the mouth to about 14 miles upstream (Sonzogni et al., 1991). That portion of the river is a Superfund site, as well as one of the Great Lakes "Areas of Concern." Sediment cores were collected at Rochester Park, near the original source of the PCBs, about 14 miles upstream from the mouth. The PCB congeners 2,3',4,4',5-PeCB (PCB 118); 2,3,3',4,4'-PeCB (PCB 105); and 3,3',4,4'-TCB (PCB 77) were detected in all samples and ranged from about 5 to 1,500 ppb. Remaining dioxin-like PCB congeners were detected less frequently and ranged from nondetectable to slightly over 100 ppb. The PCB congener 2,3',4,4',5-PeCB (PCB 118) appears to be the most common dioxin-like PCB in environmental samples and was found in the Sheboygan River sediments in the highest weight percent. The eight toxic PCBs detected in this study were present in relatively low concentrations compared to total PCBs or other more abundant congeners.

Sediments collected from Waukegan Harbor in Lake Michigan contained the dioxin-like PCB congeners 3,3',4,4'-TCB (PCB 77) and 2,3,3',4,4'-PeCB (PCB 105) (Huckins et al., 1988). The percentage of 3,3',4,4'-TCB (PCB 77) in the samples averaged 0.16 percent ± 0.15, with concentrations ranging from 13 to 27,500 ppb. The percentage of 2,3,3',4,4'-PeCB (PCB 105) averaged 0.66 percent ± 0.37, with concentrations ranging from 102 to 131,000 ppb. In another Lake Michigan study, sediment samples collected from Green Bay contained concentrations of all 11 dioxin-like PCB congeners (Smith et al., 1990b). The dominant congeners were 2,3,4,4',5-PeCB (PCB 114) and 2,3,3',4,4'-PeCB (PCB 105), with concentrations of 11 and 5.8 ppb, respectively.

Fiedler et al. (1995b) and Rappe et al. (1995b) analyzed sediments samples from a river system in southern Mississippi to determine if the concentrations of CDDs and CDFs in the sediments were influenced by a local pulp and paper mill. The pulp mill, which is located adjacent to the Leaf River and currently uses chlorine dioxide in its bleaching process (elemental chlorine was used from 1984 through 1989), was suspected of contributing to CDD and CDF contamination in the region (Fitzpatrick, 1995). A total of 61 sediment samples were collected from sites located upstream and downstream from the mill. Study results indicated that most CDD and CDF congeners were present in all sediment samples collected, but the predominant congeners were the HpCDDs and OCDD (Rappe et al., 1995b). Congener profiles were generally similar for samples collected from both populated, potentially polluted areas and pristine areas. In addition, for the majority

of sampling sites in the study, the ratio of the sum of CDDs to CDFs ranged from 43 to 1,200. Rappe et al. (1995b) stated that this observation "is notable because, with the exception of sewage sludge, no environmentally significant source has been identified with such a dominance of CDDs." The mean I-TEQ_{DF} concentration observed in this study was 10.6 ng/kg dry weight, and the median I-TEQ_{DF} concentration was 9.90 ng/kg dry weight (Fiedler et al., 1995b). Median values reported in this study were consistent with those of an earlier study conducted by the Mississippi Department of Environmental Quality in 1992 in the same river system.

Rappe et al. (1997a) analyzed sediment core samples from five lakes in southern Mississippi. The sediment cores were collected from five man-made recreational lakes with no known industrial point source of CDD/CDFs and low atmospheric deposition rates. Cores were subdivided into sections to evaluate temporal trends in deposition of CDD/CDFs. I-TEQ_{DF} values for the lake cores ranged from 0.38 to 9.52 ppt (dry weight). 2,3,7,8-TCDD was present at levels below the detection limit in all of the sediment core samples. The higher chlorinated congeners (hexa to octa CDD/CDFs) predominated. OCDD levels ranged from 150 ppt dry weight to 5,500 ppt dry weight, while total CDD levels ranged from 176 to 7,577 ppt dry weight. CDF levels ranged from nondetectable to 14.4 ppt dry weight. As observed in another analysis of sediment cores from the region (Rappe et al., 1997b), the CDD to CDF ratios were very high, ranging from 79.1 to 9,920. The CDD and CDF congener patterns were similar to those observed by Rappe et al. (1995b) in previous sediment studies in the region. No observable trend for levels of CDDs, homologues, or I-TEQ_{DF}s correlating to the age of the strata could be identified.

Rappe et al. (1997b) also studied sediment samples from 15 manmade lakes in the same region of southern Mississippi. Lakes were selected from pristine areas, areas not known to be impacted by industrial point sources of CDDs and CDFs. As in previous studies from this region (Rappe et al., 1995b and Fiedler et al., 1995b), HpCDDs and OCDD were the predominant congeners in these deep lake and sedimentation area samples. OCDD levels ranges from 1,400 to 43,000 ppt dry weight (median 7,700 ppt). The concentration of HpCDDs ranged from 63 ppt to 2,000 ppt dry weight (median 430 ppt). 2,3,7,8-TCDD was detected in 20 of the 27 sediment samples at levels not exceeding 1.0 ppt dry weight. CDDs dominated, and the ratio of CDDs to CDFs ranged from 19 to 764 (79 percent had ratios >100). The I-TEQ_{DF} concentration in the sediment

samples ranged from 2 ppt dry weight to 63.7 ppt dry weight. Rappe et al. (1997b) postulated that the high levels of OCDD found in this region of the United States are due to natural formation. The authors base this theory on the fact that the sediment samples were collected in pristine areas with no known industrial sources of CDD/CDFs and low atmospheric deposition rates. However, they have observed consistently higher than expected OCDD levels and high CDD/CDF ratios in this region, which do not correspond with other levels in the published literature.

In an effort to determine whether incineration of municipal waste influenced CDD/CDF levels in the immediate area of waste incineration facilities, sediment samples were collected from surface water near cities with, and without, operating incinerators throughout Connecticut. A total of 344 sediment samples were collected between 1987 and 1990. The mean total CDD/CDF concentrations for pre-operational and operational status were 3,590 pg/g and 4,523 pg/g, respectively, when nondetects were assumed to be one-half the detection limit (MRI, 1992). Based on the concentration data reported in MRI (1992), mean I-TEQ_{DF} values for pre-operational and operational sediments were 21 pg/g and 24 pg/g, respectively.

Sediment samples collected at the lowermost Tennessee River (Kentucky Dam Tailwater) and Kentucky Lake at the depth of 0-5 cm had total PCB concentrations ranging from the detection limit (1.0 ng/g dry weight) to 26.36 ng/g dry weight (Loganathan et al., 1998). The total PCB concentrations sampled from the lowermost Tennessee River were generally higher that those from Kentucky Lake. The PCB congeners found in the sediment samples included PCB-8, 29, 50, 28, 52, 44, 101, 87, 154, 118, 153, 105, 138, 187, 128, 200, 180, and 170; the dominant congeners were PCB-44 and PCB-101. Of these congeners, only PCBs 118 and 105 are considered to be dioxin-like.

Recently, EPA conducted a time-trend study of dioxin-like compounds in sediment cores (Versar, 1996a; Cleverly et al., 1996). Cores from 11 lakes/reservoirs were collected, sectioned and dated, and analyzed for CDD/CDFs and PCBs 77, 105, 118, 126, 156, 157, and 169. The lakes were located in various geographic locations throughout the United States and were selected to represent background conditions (i.e., no known CDD/CDF sources). Based on the most recently deposited sediments (i.e., the uppermost core sections), total I-TEQ_{DF} concentrations ranged from 0.11 ppt to 15.6 ppt with a mean of 5.3 (TEQ_{DF}-WHO_{98} concentrations ranged from 0.12 ppt to 16.3 ppt, with a mean of

5.3 ppt) when nondetects were set to one-half the detection limit, and from 0.11 ppt to 14.3 ppt with a mean of 4.6 ppt (TEQ_{DF}-WHO_{98} concentrations ranged from 0.12 ppt to 15.6 ppt, with a mean of 4.7 ppt) when nondetects were set to zero (Table 3-17). Chandler Lake, an Arctic lake located in North Slope, Alaska, had the lowest TEQ_{DF} concentration, and Canandaigua Lake in New York and Santeetlah Reservoir in North Carolina, both eastern lakes, had the highest TEQ_{DF}s. In general, the higher chlorinated CDD/CDFs accounted for the largest proportion of total TEQ concentrations. PCB TEQ_P-WHO_{98} and TEQ_P-WHO_{94} ranged from 0.07 ppt for Chandler Lake to 2.2 ppt for Canandaigua Lake, with a mean TEQ_P-WHO_{98} of 0.53 ppt when nondetects were set to either zero or one-half the detection limit. Total CDD/CDF concentrations for these 11 lakes are presented in Table 3-18. Total CDD/CDFs ranged from 9.1 ppt for Chandler Lake, Alaska, to 2,916 ppt for Santeetlah Reservoir, North Carolina, with a mean of 926 ppt. Total PCBs ranged from 34 ppt for Chandler Lake, Alaska, to 2,116 ppt for Canandaigua Lake, new York, with a mean of 489 ppt. Table 3-18 also presents the estimated annual flux of CDD/CDFs to these lakes. Flux was calculated by multiplying sediment concentrations by lake-specific sedimentation rates (g/cm^2-yr), and dividing by lake-specific sediment focusing (redistribution) factors. CDD/CDF Flux ranged from 0.05 pg/cm^2-yr for Chandler Lake to 190 pg/cm^2-yr for Santeetlah Reservoir. PCB flux ranged from 0.19 pg/cm^2-yr for Chandler Lake to 103 pg/cm^2-yr for Santeetlah Reservoir. These data are considered to be the best available data for characterizing sediment CDD/CDF and dioxin-like PCB background concentrations in the United States because they are representative of sites not expected to be impacted from within several geographic regions.

3.5.2. European Data

This section presents a brief overview of some data on European sediments. It is not intended to be a comprehensive review of all available studies on European sediments. No attempt was made to characterize background levels of CDD/CDFs for Europe because of the variability and limited scope of this review.

Sediment samples from the vicinity of a magnesium production plant in Norway were analyzed for CDDs and CDFs (Oehme et al., 1989). The concentration distribution of CDD and CDF congeners was rather homogeneous, except for a slight decrease at a

sampling station downstream of the plant and higher levels in deeper sediments (4-6 and 11-13 cm depth) at that site. TCDF congener profiles were the same as those for magnesium production. In addition, the PeCDF congener profiles were very similar to those found in the wastewater.

Trapped sediments from the archipelago of Stockholm, Sweden, displayed CDD and CDF congener distribution patterns that were very similar to those exhibited in total air and air particulates (Rappe and Kjeller, 1987). HpCDDs, OCDD, and HpCDF were the dominant congener groups in the sediment.

Bottom surface sediment samples collected from the Baltic Sea showed interesting CDD and CDF distribution patterns (Rappe et al., 1989b). Background samples, one between the Swedish and Soviet coasts and the other between the Swedish and Finnish coasts, contained similar levels and distribution profiles. The study indicated that the pattern of the TCDF congeners at these sites was typical of the "incineration pattern" (i.e., patterns resulting from MSW incineration, car exhausts, steel mills, etc.), which also had been found in samples of air and air particulates. However, sediment samples collected at a distance of 4 to 30 km from a pulp mill revealed a congener distribution pattern typical of bleaching mills. TCDFs found in the sediment 4 km from the pulp mill contained only two major congeners. The sediment collected 30 km from the mill displayed the same pattern.

Evaluation of sediments in Hamburg Harbor in Germany revealed high concentrations of the TCDDs through OCDD (mean concentrations of 564, 1112, 2744, 4040, and 7560 ppt, respectively) and the TCDFs through OCDF (mean concentrations of 526, 2980, 4106, 2358, and 2712 ppt) (Gotz and Schumacher, 1990). The average concentration of 2,3,7,8-TCDD was 375.3 ppt. High concentrations of 2,3,7,8-TCDD, especially in the Moorfleeter Canal and the Auserer Vering Canal, were attributed to discharges from an organochlorine pesticide manufacturing plant. Patterns of 2,3,7,8-TCDD and the other HpCDD congeners are characteristic of the patterns resulting from the production of 2,4,5-T and 2,4,6-trichlorophenol. In addition, the pattern of the HpCDF congeners can be linked to emissions from thermal processes employed by chemical industries in the production of chlorinated organic chemicals. High concentrations of hepta- and octa-CDDs/CDFs may also be the result of other industrial combustion processes in the Hamburg area.

The Venice lagoon in the north of Italy, covering a surface of approximately 500 km^2 with a depth of <2 m, has a limited water exchange with its surrounding area. The pollution loading sources includes the effluent of water streams and industrial and municipal waste water discharges, agricultural runoff, and an intense traffic of motorboats. Two sediment studies were conducted at this lagoon. Ramacci et al. (1998) used the data collected by the Ministry of Justice and the Ministry of Works to assess the CDD/CDFs contamination. The sediment samples were collected from various depths, including surficial to 60 cm. The dry weight I-TEQ_{DF} concentrations for various depth were 16.0 pg/g for surficial sediment, 14.3 pg/g and 19.8 pg/g for sediment samples from a depth of 0-20 cm, 6.2 pg/g and 0.5 pg/g for sediment samples from a depth of 20-40 cm, and 6.0 pg/g for the sediment at the depth of 40-60 cm. Di Domenico et al. (1998) collected the data from the top 10-30 cm thick sediment layer of the Venice lagoon bottom in 1992 and 1995. For the area under industrial or prevailing industrial exposure, the concentrations of total CDD/CDFs ranged from 840 pg/g to 29,000 pg/g; the I-TEQ_{DF} concentrations ranged from 12 pg/g to 570 pg/g; and the total PCB concentrations ranged from 53 ng/g to 720 ng/g. For the area exposed to municipal waste water discharges, the concentrations of total CDD/CDFs ranged from 210 pg/g to 1,400 pg/g; the I-TEQ_{DF} concentrations ranged from 4.8 pg/g to 23 pg/g; and the total PCB concentrations ranged from 71 ng/g to 610 ng/g. The CDD/CDF congener profile for sediments from the Venice lagoon appeared to be strongly influenced by the waste water discharges. A prevalence of OCDD and OCDF over other congeners was observed (Ramacci et al., 1998).

Masahide et al. (1998b) examined sediment samples collected from a depth of 0-10 cm in the Districts of Gdansk, Szczecin, and Katowice in Poland in 1993-1994. The dry weight total PCB concentrations sampled in Northern Poland ranged from 1.7 ng/g to 630 ng/g with an average of 110 ng/g. The dry weight total PCB concentrations were 1.7-2.2 ng/g at the area without industrial activity, 78-99 ng/g at the places receiving untreated municipal effluents, and 46-630 ng/g at the sites under the influence of human activities. The dry weight PCB concentrations sampled in Southern Poland ranged from 46 ng/g to 1,300 ng/g with an average of 540 ng/g. This highest concentration was sampled from a pond receiving effluent water from a coal mine in Katowice.

3.5.3. Vietnamese and Japanese Data

Schecter et al. (1989a) collected sediment samples from three rivers in Vietnam and analyzed them for CDD/CDF residues. Rivers included the Red River in the nonindustrialized North, the Saigon River in the industrialized South, and the Dong Nai River in an area sprayed with Agent Orange, a TCDD-contaminated herbicide. Results of these analyses are presented in Table 3-19. The average total concentrations of CDD/CDFs were 240 pg/g dry weight for the Red River, 6,800 pg/g dry weight for the Saigon River, and 1,200 pg/g dry weight for the Dong Nai River. Schecter et al. (1989a) suggested that the total CDD/CDF levels in these Vietnamese rivers is comparable to the total CDD/CDF levels observed in the lake sediments in the United States and Europe (Table 3-19).

In Japan, sediment samples were collected from a coastal area, river, and pond in Matsuyama between April 1995 and December 1997 (Seike et al., 1998). The dry weight total concentrations of CDD/CDFs ranged from 2.0 to 16 ng/g (n = 3) in the coastal area with an average of 8.1 ng/g, from 0.95 to 4.3 ng/g (n = 22) in river water with an average of 2.0 ng/g, and from 0.77 to 3.1 ng/g (n = 3) in pond water with an average of 2.3 ng/g. TCDD and OCDD were the main contributors to total CDD concentrations in all sediment samples, while CDF homologue compositions varied with the samples. Sediment samples were also collected in June-July 1993 at eight sites from upper, mid- and downstream of the Tama River, Japan, which was polluted by industrial and domestic wastewater (Onodera et al., 1998). Total CDD/CDF dry weight concentrations ranged from 27.0 to 231.6 pg/g with an average of 90.7 pg/g. The total I-TEQ_{DF} concentrations ranged from 0.05 to 2.8 pg/g with an average of 1.2 pg/g.

3.5.4. Sediment Observations and Trends

Some general observations for CDD and CDF levels in the United States are possible from the data presented in the various sediment studies above:

- CDD and CDF congener distribution patterns in sediment generally follow those exhibited by the contaminant source.

- The concentration of CDD and CDF congeners in sediment generally increases with the degree of chlorination, but decreases uniformly with distance from the source.

3.5.5. Sediment CDD/CDF Profiles and Background TEQ Concentrations

CDD/CDF homologue group profiles for sediment were calculated as the mean homologue group concentrations divided by the mean total CDD/CDF concentrations. Congener profiles are the ratio of 2,3,7,8-substituted congeners to total CDD/CDFs in sediment. These congener profiles for sediment are presented in Figure 3-5. They are based on data from the recent EPA sediment core study, which evaluated sediment data from 11 non-source-impacted sites throughout the United States (i.e., 1 Alaska site, 3 New York sites, 1 North Carolina site, 1 Georgia site, 3 Utah sites, and 2 Washington sites) (Cleverly et al., 1996; Versar, 1996a). Only the uppermost sediment core samples (i.e., the most recently dated samples) were used in this analysis. The congener that accounts for the highest proportion of total CDD/CDFs is OCDD, with 1,2,3,4,6,7,8-HpCDD and OCDF also accounting for significant portions of total CDD/CDFs (Table 3-20). For the homologue group profile for sediment, OCDD and HpCDD account for the highest proportion of total CDD/CDFs.

Based on data from the uppermost sediment samples from EPA's recent sediment core study (Cleverly et al., 1996; Versar, 1996a) ($n = 11$), the mean background TEQ_{DF}-WHO_{98} level was 5.3 ppt, assuming that nondetects equal half the detection limit (Table 3-21). When nondetects were set to zero, the mean TEQ was 4.7 ppt. These data were considered to be the most appropriate data set for characterizing background CDD/CDF TEQ concentrations, because they are representative of sites not expected to be impacted from various geographic locations in the United States. Thus, the "typical" background concentration in sediment is assumed to be 5.3 ppt TEQ_{DF}-WHO_{98}.

3.6. CONCENTRATIONS IN FISH AND SHELLFISH

Tables B-11 through B-13 (Appendix B) contain summaries of data from the numerous studies in the published literature regarding concentrations of CDDs, CDFs, and dioxin-like PCB congeners in fish and shellfish. It should be noted that some studies reported fish concentrations on a whole weight basis and others reported concentrations

for fish fillets. In the appendix tables and in the data used for calculation of background fish levels, whole weight concentrations were converted to fillet concentrations, assuming that the fillet contained one-half the concentration of the whole fish (U.S. EPA, 1990; Branson et al., 1985). This was necessary for estimating human exposures, because it is assumed that fish fillets, and not whole fish, are ingested by humans. In the following studies, summaries of CDD/CDF and PCB concentrations are presented as reported by the authors.

3.6.1. North American Data

A large quantity of fish data were collected as part of EPA's National Study of Chemical Residues of Fish (NSCRF), more commonly referred to as the National Bioaccumulation Study, during the period of 1986 to 1989 (U.S. EPA, 1992). Based on these data, several summaries were prepared and are presented here. Tables B-11 and B-12 include the dioxin and furan data collected as part of the National Bioaccumulation Study. Samples were collected from a wide variety of sites across the United States, including 314 sites thought to be influenced by point or nonpoint sources and over 30 sites identified as relatively free of influence from point and nonpoint sources. This latter group of sites can be characterized as background per the definition used in this document. Background data are presented in Table 3-22. Using the maximum concentration from each site, the mean I-TEQ_{DF} concentration was 0.59 ppt for the background sites, when nondetects were set at zero, and 1.2 ppt when non-detects were set to one-half the detection limit. For other sites, I-TEQ_{DF} concentrations ranged from 0.7 ppt (POTWs) to 33.9 ppt (Superfund sites). Table B-13 includes similar data for the various PCB congener groups from 362 National Bioaccumulation Study sites. EPA recalculated the background TEQ_{DF}-WHO_{98} concentrations for the background sites using the mean concentration from each site instead of the maximum value for each site. Additional adjustments were included to account for the fact that some samples were analyzed on a whole body basis while others were analyzed on a fillet basis. All concentrations were expressed on a wet weight basis. The background TEQ_{DF}-WHO_{98} concentrations were 0.29 ppt when non-detects were set to zero and 1.3 ppt when non-detects were set to one-half the detection limit. Because the specific PCB congeners could not be identified, it is not known what percentage of these concentrations represent

the PCBs identified as dioxin-like. Of these sites, 20 were identified as background sites. The total PCB (all 209 congeners) mean concentration for these background sites was 46,900 ppt. Because the dioxin-like PCBs consist of only 11 of the 209 possible PCB congeners, it may be that they are a small percentage of the total; however, only congener specific analysis can ultimately confirm this. As discussed at the end of this section (Section 3.6.4), this study was selected as the best basis for estimating background fish levels in the United States.

Fish muscle and hepatopancreas samples of striped bass, blue crabs, and lobsters collected from Newark Bay and the New York Bight all contained high levels (up to 6,200 ppt) of 2,3,7,8-chlorine substituted tetra- and penta-CDDs and CDFs (Rappe et al., 1991). Levels of 2,3,7,8-TCDD were higher than any other New Jersey samples, and the highest sample in this study (found in crab hepatopancreas) may be the highest level of 2,3,7,8-TCDD ever reported for aquatic animals. Crustaceans resembled one another in congener pattern. Specifically, they all contained both a large number and large amounts of CDD and CDF congeners in addition to the 2,3,7,8-chlorine substituted compounds. The striped bass samples, on the other hand, contained primarily the 2,3,7,8-chlorine substituted congeners.

Carp, catfish, striped bass, large mouth bass, and lake trout were collected from sites in the Hudson River and the Great Lakes Basin that were contaminated with industrial chemicals or contained known or suspected levels of PCBs (Gardner and White, 1990). The congener 2,3,7,8-TCDF was detected in 12 fish fillets at levels that ranged from 3 to 93 ppt. A 2,3,7,8-chlorine substituted PeCDF was detected in 14 fish fillets at levels ranging from 4 to 113 ppt. An interesting observation in this study was that 2,4,6-chlorine substituted CDFs were detected in four fish samples, suggesting that those fish may have been exposed to chlorinated phenols. The study indicated that the 2,4,6-chlorine substituted CDFs occurred in the fish at levels similar to those of the 2,3,7,8-chlorine substituted CDFs, but with less frequency.

Composited whole fish samples of lake trout or walleye collected from each of the Great Lakes and Lake St. Clair were analyzed for CDDs and CDFs (De Vault et al., 1989). CDF and CDD concentrations in lake trout were substantially different for each lake and between sites in Lake Michigan, probably reflecting differences in types and amounts of loadings to the lakes. In all of the sampling sites (except Lake Ontario), 2,3,7,8-TCDF

was the dominant CDF congener in lake trout and ranged from 14.8 ppt in Lake Superior to 42.3 ppt in the whole fish samples of Lake Michigan. In Lake Ontario, the dominant congener in lake trout was a 2,3,7,8-chlorine substituted PeCDF. The distribution of CDF congeners in the Lake Erie walleye was very similar to that of the lake trout from Lake Superior. With regard to CDDs, the concentrations of 2,3,7,8-TCDD in the whole fish samples ranged from 1 ppt in Lake Superior to 48.9 ppt in Lake Ontario. With the exception of Lake Ontario, the dominant CDD congener was a 2,3,7,8-chlorine substituted PeCDD. A 2,3,7,8-chlorine substituted HxCDD also contributed significantly to the total CDD concentrations. As with CDFs, the distribution of CDD congeners in the Lake Erie walleye was very similar to that of the lake trout from Lake Superior. Total I-TEQ_{DF}s for these samples ranged from 5.3 ppt to 67.0 ppt on a whole weight basis when nondetected congeners were set to one-half the detection limit.

In another study, CDDs and CDFs were measured in four species of salmonids (lake trout, coho salmon, rainbow trout, and brown trout) collected from Lake Ontario (Niimi and Oliver, 1989a). Levels of 2,3,7,8-TCDD in whole fish ranged from 6 to 20 ppt, and the HxCDD congener group was most dominant in all fish. High levels of OCDD also were detected in lake trout and coho salmon, but not in rainbow trout or brown trout. Although total CDF levels were about 25 percent lower than the total CDD concentrations, the levels of 2,3,7,8-TCDF (which was the dominant component of the TCDF congener group) were the same range as 2,3,7,8-TCDD (6 to 20 ppt). I-TEQ_{DF} concentrations ranged from 7.3 ppt to 22.3 ppt on a whole weight basis, when nondetects were set to zero. The study suggested that, although collection sites can influence chemical levels and congener composition, comparisons of chemical levels and congener frequencies may not be suitable because of differences resulting from localized factors. The study also indicated that the importance of the various CDD and CDF congeners can differ with location (i.e., the same species of fish collected at different locations in a study area may reveal that the most common congener is different at each site).

Travis and Hattemer-Frey (1991) evaluated data generated as part of the National Dioxin Study regarding 2,3,7,8-TCDD concentrations in fish. Fish were collected from 304 urban sites in the vicinity of population centers or areas with known commercial fishing activity, including sites from the Great Lakes Region. Data from that study indicated that concentrations of 2,3,7,8-TCDD in whole fish from urban sites ranged from

nondetectable to 85 ppt. In addition, only 29 percent of the fillets from urban sites had detectable levels of 2,3,7,8-TCDD, with a geometric mean concentration of 0.3 ppt. Whole fish samples from the Great Lakes Region had higher 2,3,7,8-TCDD levels than fish from urban areas (e.g., 80 percent vs. 35 percent detectable levels). In the Great Lakes Region, 2,3,7,8-TCDD concentrations in whole fish samples ranged from nondetectable to 24 ppt, with a geometric mean of 3.8 ppt. These levels were 10 times higher than the concentrations in whole fish from urban areas. Likewise, the mean concentration of 2,3,7,8-TCDD in Great Lakes Region fish fillets (2.3 ppt) was about seven times higher than the levels in the fillets from urban areas (0.3 ppt). As with the whole fish samples, fish fillet samples from the Great Lakes Region had higher 2,3,7,8-TCDD levels than fillets from background urban areas (e.g., 67 percent vs. 29 percent detectable levels). Comparable levels of 2,3,7,8-TCDD were detected in whole bottom feeders and predators from the Great Lakes Region.

In an effort to determine whether incineration of municipal waste influenced CDD/CDF levels in the immediate area of waste incineration facilities, fish samples were collected from surface water near cities with, and without, operating incinerators throughout Connecticut. A total of 550 fish samples were collected between the years of 1987 and 1990. The total CDD/CDF concentrations for pre-operational and operational status were 28.44 pg/g and 58.38 pg/g, respectively, when nondetects were assumed to be one-half the detection limit (MRI, 1992).

Cooper et al. (1995) and Fiedler et al. (1997c) collected fish samples from grocery stores and local fish markets in southern Mississippi. All samples had detectable concentrations of CDD/CDFs. High I-TEQ_{DF} concentrations were observed in farm-raised catfish nuggets (mean = 2.1 ppt/sample I-TEQ_{DF}) and in the parts of the crustacea containing the digestive gland (Cooper et al., 1995). The congener profile for the shellfish samples was similar to that observed for sediments collected in the same area and, reported sewage sludge patterns. For marine fish fillets (i.e., Spanish mackerel and mullet), the mean I-TEQ_{DF} concentration was 0.27 ppt. The meat of marine shellfish (i.e., claw and body of blue crab and whole American oysters) had I-TEQ_{DF} concentrations averaging 0.63 ppt, and freshwater shellfish (i.e., crawfish) had concentrations averaging 1.0 ppt. I-TEQ_{DF} concentrations in fish and shellfish are presented in Table 3-23.

To further examine the high TEQ_{DF} concentrations of the farm-raised catfish from southern Mississippi, Cooper et al. (1997) and Fiedler et al. (1998) performed a follow up to their 1995 study examining catfish feed and pond sediment along with catfish samples from the previously tested facility and other sites in the southeastern United States. The follow-up study also tested for PCB levels. Samples included three catfish fillets and three catfish nugget (i.e., small pieces of fillet) samples from the same store and distribution supplier as sampled in the previous study (Cooper et al., 1995), one catfish fillet from an Alabama supplier, three catfish fillets and one feed and pond sediment sample from a different catfish farm in Mississippi, and two catfish and one catfish feed samples from a site in Arkansas. A summary of the results is presented in Table 3-24. Three farm-raised catfish fillet samples and three catfish nugget samples from Mississippi had lipid-based 2,3,7,8-TCDD levels ranging from 2.1 to 4.7 ppt and total lipid-based TEQ_{DFP}-WHO_{94} ranging from 10.9 to 30.2 ppt. Catfish samples from Arkansas had lipid-based 2,3,7,8-TCDD levels ranging from 27 to 32 ppt and total lipid-based TEQ_{DFP}-WHO_{94} ranging from 41.9 to 44.9 ppt. Similar results were observed in the feed samples. The feed from the Mississippi aquaculture facility, which supplied the food for the Mississippi catfish fillet and nugget samples, contained 2.7 ppt lipid 2,3,7,8-TCDD and a total lipid-based TEQ_{DFP}-WHO_{94} concentration of 10.5 ppt, compared with feed levels from the Arkansas facility that contained 44 ppt lipid 2,3,7,8-TCDD, and a total lipid-based TEQ_{DFP}-WHO_{94} concentration of 61. CDD/CDF congener profiles are also consistent between the catfish and the respective feed suppliers' products with the exception of OCDD and 1,2,3,4,6,7,8-HpCDD. Pond sediment congener profiles were not consistent with the profiles exhibited in the catfish samples, demonstrating significantly lower levels of most 2,3,7,8-substituted CDDs, and higher levels of 2,3,7,8-substituted CDFs. PCB analysis of these same catfish samples demonstrated that for all but one sample, the highest concentrations of PCBs were observed for congeners 153 and 138, respectively. PCB TEQ_{P}-WHO_{94} in the catfish samples (both fillet and nuggets) ranged from 0.45 to 4.9 ppt lipid, with the PCB fraction of the total TEQ_{P}-WHO_{94} ranging from 4 to 16 percent. The feed sample TEQ_{P}-WHO_{94} level from the Mississippi site was 3.31 ppt lipid, while the level from the Arkansas site was 0.19 ppt lipid, and the pond sediment level contained a TEQ_{P}-WHO_{94} level of 0.04 ppt lipid. Rappe et al. (1997c) continued this investigation by evaluating one combined catfish feed sample from Arkansas and its eight ingredients (i.e.,

soybean meal, meat and bone meal, wheat, corn, fish meal, cottonseed meal, and midds). The soybean meal had the highest I-TEQ_{DF} concentration (i.e., 576 pg/g lipid). The 2,3,7,8-TCDD concentration in this ingredient was 370 pg/g lipid. The combined catfish feed sample had a I-TEQ_{DF} concentration of 101 pg/g lipid and a 2,3,7,8-TCDD concentration of 67 pg/g lipid. Rappe et al. (1997c) suggested the ball clay anticaking agent in the soybean meal as the source of CDD/CDFs in this ingredient.

Schecter et al. (1997) analyzed samples of freshwater (n = 10) and marine fish (n = 13) collected from grocery stores in five U.S. cities (Binghamton, New York; Chicago, Illinois; Louisville, Kentucky; Atlanta, Georgia; and San Diego, California). Whole weight mean I-TEQ_{DF} values were 0.69 ppt for composites of freshwater fish and 0.25 ppt for composites of ocean fish, when nondetects were set to one-half the detection limit. Total mean CDD/CDF concentrations were 16.2 ppt (whole weight) for freshwater fish and 3.4 ppt (whole weight) for ocean fish, when nondetects were set to one-half the detection limit. Schecter et al. (2001) reported mean whole weight TEQ_{DFP}-WHO_{98} concentrations for the same fish samples as 1.7 ppt for freshwater fish and 0.39 ppt for ocean fish when nodetects were set to one-half the detection limit, and 1.6 ppt for freshwater fish and 0.16 ppt for ocean fish when nondects were set to zero. Additional detail on the Schecter et al. (1997) study are presented in the section on concentrations in food products (Section 3.7). Schecter et al. (1993a) analyzed five fish collected from a supermarket and found an average of 0.05 ppt of I-TEQ_{DF}.

FDA analyzed fish and shellfish samples collected in 1996 through 1999 as part of a market basket survey. The samples were collected from grocery stores from locations around the country and were analyzed for CDD/CDFs. The results of these analyses have been reported by Jensen and Bolger (2000) and Jensen et al. (2000). The combined results from these two publications are presented in Table 3-25. TEQ_{DF}-WHO_{98}s ranged from 0.22 ppt for pollack to 2.0 ppt for catfish.

Samples from all trophic levels in the Lake Ontario ecosystem were analyzed for PCB congeners (Oliver and Niimi, 1988). Analysis revealed that the PCB concentration increased from water to lower organisms to small fish to salmonids, demonstrating the classical biomagnification process. In addition, the chlorine content of the PCBs increased at the higher trophic levels. PCBs with the highest chlorine content (57 percent) were found in sculpin, small bottom-living fish that feed on benthic invertebrates. TrCBs and

TCBs comprised a much higher percentage of the PCBs in the lower trophic levels than in salmonids and small fish. The percentage of PeCBs and OCPB in all samples was fairly uniform, but the HxCBs and HpCBs comprised a much larger fraction of the PCBs in the small fish and salmonids than in the lower trophic levels.

A study regarding the distribution of PCBs in Lake Ontario salmonids (brown trout, lake trout, rainbow trout, and coho salmon) showed that the PeCBs and HxCBs were dominant in all species (Niimi and Oliver, 1989b). The 10 most common PCB congeners represented about 52 percent of the total content and did not appear to be influenced by species or total concentration. Homologues observed averaged approximately 56 percent chlorine by weight in whole fish and muscle. The analysis of the chlorine content suggested that the more persistent congeners tend to behave as a homogeneous mixture instead of as individual congeners.

Petreas (1991) conducted a study to assess the influence of a bleached pulp and paper mill and other industrial facilities on the PCB congener levels in aquatic species and sediment in northern California. Petreas (1991) collected samples of local fish species, bivalves (freshwater clams that had been transplanted 2 months earlier), and sediment samples at sites upstream, downstream, and within the vicinity of a pulp and paper mill plant. Whole body fish samples were composited, or analyzed individually, based on size. These samples were analyzed for PCBs 77, 126, and 169. Results of an analysis of the raw data from these samples are presented in Table 3-26. Levels of PCBs in fish tissue ranged from 1.2 pg/g for PCB congener 169 to 1,095 pg/g for PCB congener 77. Results of the fish tissue analysis according to sampling location indicated that "no special impact could be attributed to the pulp mill discharge" (Petreas, 1991). Bivalve concentrations ranged from 0.7 pg/g for PCB congener 169 to 102 pg/g for PCB congener 77. Concentrations of PCB congeners 77 and 126 were at least an order of magnitude higher in bivalves than in sediments from the same sampling location, indicating that these congeners bioconcentrate in the aquatic bivalve species evaluated. Bivalve and sediment impacts that could be attributed to facility discharges were not observed in this study.

Krahn et al. (1995) analyzed marine fish and invertebrates collected from several coastal sites of the northeastern United States for dioxin-like PCBs. Samples of winter flounder (muscle tissue), northern lobster (muscle tissue and hepatopancreas), and blue mussel (whole bodies) were analyzed for dioxin-like PCBs. Total mean PCB concentration

ranged from 4 ppt to 351 ppt in muscle tissue from flounder and lobster, and blue mussel whole bodies. Total PCB concentrations in lobster hepatopancreas ranged from 764 to 32,800 ppt. Total mean TEQ_P-WHO_{94} for these PCBs ranged from 0.1 ppt to 6.9 ppt for muscle tissue samples of winter flounder, 0.1 ppt to 3.7 ppt for whole blue mussels, and 0.1 ppt to 5.4 ppt for lobster muscle. Hepatopancreas tissue from lobster showed considerably higher TEQ_P-WHO_{94} concentrations, ranging from 5.2 ppt to 1,820 ppt.

Mes and Weber (1989) analyzed a freshwater fish composite sample and a canned fish composite sample for PCBs 77, 126, and 169. The number of samples included in these composites was not reported. Respective wet weight concentrations of these three PCBs were 36 ppt, 8 ppt, and <1 ppt for freshwater fish, and 8 ppt, 3 ppt, and <1 ppt for canned fish samples. In a later study, Mes et al. (1991) evaluated numerous PCB congeners including dioxin-like PCBs 105, 114, 118, 156, 157, and 189 in foods. A total of five composite freshwater fish, marine fish, and shellfish samples, each composite taken from major Canadian city, were analyzed for these PCBs. The number of samples included in these composites was not reported. Total PCB congener residues for freshwater fish, marine fish, and shellfish were 31.9 ppt, 4.6 ppt, and 0.9 ng/g, respectively, on a wet weight basis, based only on congeners observed in three out of five composites. Schecter et al. (1997) also analyzed freshwater and marine fish samples for dioxin-like PCBs 77, 105, 114, 118, 126, 169, and 180. Concentrations of these congeners ranged from not detected to 1,800 ppt on a whole weight basis in fresh fish, and from 0.20 ppt to 320 ppt in ocean fish. The total whole weight TEQ_P-WHO_{94} was 0.7 ppt for fresh fish and 0.2 for ocean fish, when nondetects were set to one-half the detection limit (Schecter et al., 1997).

3.6.2. European Data

Evaluation of fish in the Baltic Sea (Gulf of Bothnia) and northern Atlantic Ocean in the vicinity of Sweden revealed that concentrations of CDDs and CDFs in composited whole fish herring samples from the Atlantic Ocean were lower than those in the Gulf of Bothnia (Rappe et al., 1989b). Detectable levels of 2,3,7,8-TCDD in salmon muscle were found in both wild homing (4.6 to 19 ppt) and hatchery-reared (0.2 to 0.3 ppt) varieties in the Gulf of Bothnia. In addition, concentrations of the same representative congeners of the Cl_5 to Cl_8 CDD and CDF congener groups found in herring were found in both varieties

of salmon. Levels of those congeners in the muscle of wild salmon, however, were five to ten times higher than the herring levels, while the levels in the hatched salmon essentially were the same as in the herring samples. Perch collected at a distance of 1-6 km from a pulp mill in the southern part of the Gulf of Bothnia contained 2,3,7,8-TCDD and 2,3,7,8-TCDF; the levels were higher in the samples collected closer to the pulp mill. These two compounds have been identified in bleaching effluents from pulp mills, as well as in bleached pulp. Arctic char collected from Lake Vattern, a popular fishing lake in southern Sweden, contained levels of 2,3,7,8-TCDD (6.5 to 25 ppt whole weight), 2,3,7,8-TCDF (21 to 75 ppt whole weight), and representative congeners of the PeCDD and PeCDF homologues. There was a good correlation between the weight of the fish and the levels of CDDs and CDFs. The main general pollution sources of the long, deep, narrow lake are two pulp mills.

Fish (cod, haddock, pole flounder, plaice, flounder, and eel), mussels, and edible shrimp from a fjord area contaminated by wastewater from a magnesium factory in Norway were analyzed for CDDs and CDFs (Oehme et al., 1989). Certain magnesium production processes can result in the formation of substantial amounts of CDDs and CDFs as byproducts. The congener pattern of tetra- and penta-chlorinated CDDs and CDFs released in wastewater during the magnesium production process is very characteristic and is dominated by congeners with chlorine in the positions 1,2,3,7 and/or 8. Fish and shellfish differ in their ability to bioconcentrate CDD and CDF congeners. For example, fish generally only concentrate the most toxic 2,3,7,8-substituted congeners; whereas, shellfish can usually concentrate most of the congeners. Nearly all congeners were present in the shrimp and mussel samples. Although these organisms displayed the very characteristic PeCDF congener pattern of the magnesium production process, some deviations were found in the TCDF congener distribution within those species. For fish, the concentrations of CDDs and CDFs are dependent on the exposure level, fat content, living habit, and the species degree of movement. The highest CDD and CDF levels were found in comparatively high fat-content bottom fish collected close to the source. Cod and haddock (lower fat-content nonstationary fish) had much lower concentrations, even in the vicinity of the magnesium production factory. An interesting note is that the main stream of the fjord follows the west coast; subsequently, cod and eel samples collected along the west coast of the fjord had considerably higher levels of CDDs and CDFs than

those collected from the eastern fjord entrance. Similarly, the level of 2,3,7,8-TCDD in mussels decreased by one order of magnitude from the vicinity of the magnesium production factory to the outer region of the fjord system.

Brown trout, grayling, barbel, carp, and chub collected in the Neckar River in southwest Germany contained much higher levels of 2,3,7,8-TCDF than in eels collected from the same river and the Rhine River (Frommberger, 1991). In addition, eels from both rivers showed very similar patterns for CDD and CDF congener distribution; whereas, the patterns of CDD and CDF distribution generally showed some degree of difference among the other fish collected from the Neckar River. Perch and bream collected from various locations in the vicinity of Hamburg Harbor, however, showed similar patterns in the distribution of the Cl_4 to Cl_8 CDD and CDF congener groups (Gotz and Schumacher, 1990). In general, the levels of CDFs were higher than the level of CDDs in these fish, especially with regard to the TCDFs to HxCDFs. Pooled samples of eels, collected at six different localities in The Netherlands, contained low levels of CDDs and CDFs, the major congeners of which were 2,3,7,8-chlorine substituted (Van den Berg, 1987). Concentrations of the various congeners identified in the eel samples ranged from 0.1 to 9.1 ppt. The sample with the highest concentration of 2,3,7,8-TCDD (9.1 ppt) was collected from Broekervaart in a location that was not far from a chemical waste dump that contained high concentrations of the same congener.

In 1992, Falandysx et al. (1997) examined congener-specific PCB data in fish from the southern part of the Baltic Sea. Eight fish species were collected from the Gulf of Gdańsk near Gdynia. Total PCB levels were high in whole fish samples from this area, ranging from 1.4-million ppt lipid to 11-million ppt lipid. Measurements were performed for 94 PCB congeners. Predominant homologue groups were PeCBs and HxCBs, which constituted 33 to 46 percent and 36 to 46 percent of the total PCB concentrations, respectively. Of the five dioxin-like PCBs examined, levels were highest for PCB 118, and ranged from 160,000 ppt lipid in whole cod samples to 2-million ppt lipid in whole eelpout specimens. Also detected, but in lesser quantities, were TrCBs (0 to 0.9 percent), TCBs (5.5 to 11 percent), HpCBs (7.4 to 13 percent), OCBs (0.23 to 0.53 percent), nonachlorobiphenyls (0 to 0.5 percent), and aldo decachlorobiphenyl (<0.01 to 0.01 percent). A large degree of variability in total PCB levels between species of fish was observed. Total PCB levels in the whole fish samples ranged from 1,400 ng/g lipid weight

(47.6 ng/g wet weight) in cod to 11,000 ng/g lipid weight (48 ng/g wet weight) in pikeperch; 11,000 ng/g lipid weight (332.2 ng/g wet weight) in eelpout. The authors observed that with the relatively similar lipid content of the fish, which varies from 3.02 to 6.26 percent, the interspecies variability in the PCB congener pattern could possibly be attributed to variabilities in "enzyme activity, feeding behavior and trophic niche" (Falandysx et al., 1997).

Lulek et al. (1997) examined five random freshwater fish samples from five different Swiss and French lakes and rivers for 13 dioxin-like PCBs. The sampling locations included two from Lake Geneva, one each from the upper and lower Maggia River in Switzerland, and one from the Saône River in France. The analyzed fish included one each of three different species (i.e., bream, burbot, and arctic char) and two each of a fourth species (i.e., trout). Total PCB levels in the whole fish samples ranged from 1,137,000 ppt lipid (65,980 ppt wet weight) in the trout from the upper Maggia River to 3,235,000 ppt lipid (237,460 ppt wet weight) in the trout from the bottom of the Maggia River to 1,594,000 ppt lipid (254,430 wet weight) in the arctic char, to 2,179,000 ppt lipid (101,970 wet weight) in the burbot of Lake Geneva to 10,590,000 ppt lipid (402,420 ppt wet weight) in the bream of the Saône River. Congener profiles were similar in all species. Total TEQ_P-WHO_{94} concentrations in the whole fish ranged from 104 ppt lipid in the burbot to 523 ppt lipid in the bream (Lulek et al., 1997).

In 1995, the Ministry of Agriculture, Fisheries and Food (MAFF, 1998) sampled trout farms throughout England and Wales. Forty samples, each consisting of several fillets of muscle, were analyzed. When setting nondetects to the limit of detection, lipid-based CDD/CDF concentrations ranged from 2.1 to 13 ppt I-TEQ_{DF} (mean 5.1). Wet weight concentrations ranged from 0.06 to 0.67 ppg I-TEQ_{DF} (mean 0.24). Lipid based PCB concentrations varied from 8.9 to 51 ppt TEQ_P-WHO_{94} (mean 19.0), and wet weight levels ranged from 0.22 to 2.4 ppt TEQ_P-WHO_{94} (mean 0.87). Fat content in the samples ranged from 1.8 to 8.6 percent.

Robinson et al. (2000) analyzed over 100 samples of uncooked marine fish and fish fingers (i.e., fish coated with bread crumbs) for CDD/CDFs and numerous dioxin-like PCB congeners (e.g., 77, 81, 126, 169, 105, 114, 118, 156, 157, 167, 180, 189). Some of these fish were caught in United Kingdom waters; others were imported. The concentration of these compounds varied with fish species, fat content (i.e., fat weight

concentrations were higher in oily fish than in fish with lower fat contents), and sampling month (i.e., lower fat weight concentrations were seen in samples collected during February than in those collected in November and May). The lipid-weight TEQ-WHO_{98} concentrations are shown in Table 3-27. The method used for treating non-detected values in calculating TEQs was not reported. Jacobs et al. (2000) collected 10 samples of farmed Atlantic Salmon from several sites in Scotland and a site in Norway. The samples were analyzed for CDD/CDFs and seven PCB congeners (i.e., 77, 105, 118, 126, 156, 157, 169). TEQ_{DF}-WHO_{98}s ranged from 5 to 18 ppt, on a lipid basis, when non-detects were set to either one-half the detection limit or zero. TEQ_{P}-WHO_{98}s ranged from 9 to 25 ppt on a lipid basis. Lipid contents ranged from 3 to 15 percent. In general, the highest levels were observed in the oldest fish.

3.6.3. Fish Observations and Trends

Some general observations for CDD and CDF levels are possible from the data presented in the various fish and shellfish studies above:

- For fish, the concentrations of CDDs and CDFs are dependent on the exposure level, fat content, living habits, and the degree of movement of the species. Comparatively high fat-content bottom fish, collected close to the contaminant source, generally have the highest CDD/CDF levels; whereas, lower fat content, nonstationary fish have much lower concentrations, even in the vicinity of the contaminant source.

- The National Dioxin Study indicated that the levels of 2,3,7,8-TCDD in fish from the Great Lakes Region were higher than those from urban areas. Comparable levels were detected in whole bottom feeders and predators from the Great Lakes Region.

- With regard to PCBs, concentrations increase from water to lower organisms to small fish to salmonids, and the chlorine content of the PCBs increase at the higher trophic levels.

3.6.4. Fish CDD/CDF Profiles and Background TEQ Concentrations

Example CDD/CDF congener profiles for freshwater fish were generated using data for 10 freshwater fish samples collected from five U.S. States (i.e., New York, Illinois, Kentucky, California, and Georgia), as reported by Schecter et al. (1997). These profiles do not include all of the data used to estimate the background TEQ_{DF}-WHO_{98} concentration

in freshwater fish because congener-specific data were not available for all of the fish data used in calculating the background TEQ concentrations. The CDD/CDF profile for freshwater fish, based on Schecter et al. (1997), was generated by setting nondetects to zero and calculating the ratio of individual congener concentrations to total 2,3,7,8-substituted CDD/CDFs. This was done for consistency with other food profiles presented in this chapter. For marine fish, congener-specific data for mackerel from Mississippi, as reported in Fiedler et al. (1997c), were used to provide an example profile. The example profile for marine fish was based on one mackerel sample. An example shellfish profile was developed using data from Fiedler et al. (1997c), and is based on 13 samples, all presumed to be freshwater species (i.e., crab (n = 6), oyster (n = 3), crayfish (n = 4). Profiles were generated in the same manner as for freshwater fish. Profiles for freshwater fish, marine fish, and shellfish are presented in Table 3-28 and Figure 3-6. In general, CDDs account for a higher percentage of the total 2,3,7,8-substituted CDD/CDFs than CDFs. OCDD is the dominant congener for all three fish groups with 1,2,3,4,6,7,8-HpCDD accounting for the second highest percentage.

Although a comprehensive market basket survey representing the most commonly eaten fish species by the general population would probably provide the best information on background concentrations of CDD/CDFs in fish and corresponding background exposures from fish ingestion, these data are not available from a single source. Thus, the background CDD/CDF TEQ concentrations for freshwater and marine finfish and shellfish were estimated based on data from a variety of studies. These studies included EPA's National Bioaccumulation Study (U.S. EPA, 1992), Fiedler et al. (1997), Jensen and Bolger (2000), and Jensen et al. (2000). These studies were selected because they are based on sampling from grocery stores and/or are based on a National sampling strategy. It should be noted, however, that although the National Bioaccumulation Study data are based on a National sampling, they may be more representative of wild caught fish (i.e., recreational fishing) than fish obtained by the general population at grocery stores. For example, a large percentage of the trout consumed by the general population is likely to be farm-raised. However, because no data were available on farm-raised (or grocery store) trout, the concentration of CDD/CDFs in wild caught trout were used in estimating background fresh and estuarine finfish concentrations. For catfish, which is also primarily farm-raised, grocery store data from FDA's market surveys were used. Concentrations for

several other species (i.e., mullet and mackerel) were based entirely on data collected in the Mississippi area; and may not be entirely representative of levels seen in other locations. Finally, concentrations for some species were averaged over several data sets. In most cases, similar concentrations for these species were observed in the various studies. Species-specific mean concentrations represent the average of the mean concentrations for the various sites where samples were collected, and not the mean of all individual samples. The mean is used to ensure that each site is weighted equally (i.e., heavily sampled sites do not have any greater impact on the overall mean that sites with fewer samples).

Average background concentrations were estimated for freshwater fin- and shellfish, and marine fin- and shellfish by weighting the species-specific fish concentrations according to their species-specific fish consumption rates for the U.S. population (U.S. EPA, 2000). The consumption data are based on an analysis of the USDA's 1994-96 Continuing Survey of Food Intake Among Individuals (CSFII). Weighting was accomplished by multiplying the consumption rates in g/day by the TEQ_{DF}-WHO_{98} concentrations in pg/g. The resulting TEQ intakes in pg/day were then summed by category. Finally, the total TEQ intake (g/day) for the category was divided by the total TEQ consumption rate (g/day) to estimate the weighted average background concentration (pg/g) (Table 3-29).

For consumption categories for which no species-specific concentration data were available, default values were selected to represent that fish category. For example, for freshwater and estuarine finfish, the average TEQ_{DF}-WHO_{98} concentration from U.S. EPA (1992) was used in conjunction with the total consumption rate for those species with no corresponding concentration data. For freshwater/estuarine shellfish, the default value used for the "other" category represents the average concentration for the freshwater/estuarine shellfish species for which concentration data were available. Likewise for marine finfish and shellfish, the default concentration used is the average concentration for species with specific concentration data. This adds a degree of uncertainty to the estimates. Based on this analysis of the available species-specific fish data that are most representative of consumption among the U.S. population, the average background TEQ_{DF}-WHO_{98} concentration in freshwater fish and shellfish was estimated to be 1.0 ppt, assuming non-detects are equal to one-half the detection limit. The

background value for marine fish and shellfish was estimated to be 0.26 ppt TEQ_{DF}-WHO_{98}, when non-detects were set to one-half the detection limit.

The background TEQ_P-WHO_{98} concentration in freshwater fish and shellfish was estimated to be 1.2 ppt, when nondetects were set to one-half the detection limit, based on data from Schecter et al. (1997), Mes and Weber (1989), and Mes et al. (1991). TEQ_P-WHO_{98} for marine fish and shellfish was estimated to be 0.25 ppt when nondetects were set to one-half the detection limit, based on Mes and Weber (1989), Mes et al. (1991), and supermarket data from Schecter et al. (1997), as presented in Section 3.7.2.

3.7. CONCENTRATIONS IN FOOD PRODUCTS

Dietary intake is generally recognized as the primary source of human exposure to CDD/CDFs (Rappe, 1992). Several studies estimated that over 90 percent of the average daily exposure to CDD/CDFs are derived from foods (Rappe, 1992; Henry et al., 1992; Fürst et al., 1991). CDD/CDFs in fatty foods such as dairy, fish, and meat products are believed to be the major contributors to dietary exposures (Rappe, 1992; Henry et al., 1992). Travis and Hattemer-Frey (1991), using a fugacity model, estimated that the food chain, especially meat and dairy products, accounts for 99 percent of human exposure to 2,3,7,8-TCDD.

Analysis of trace levels of CDD and CDF congeners in food has been hindered in the past by lack of sensitive analytical detection methods, extraction difficulties from the high-lipid content food products in which these chemicals are most often found, and the presence of other potentially interfering organochlorine compounds. However, as the analytical difficulties associated with detecting CDD and CDF congeners at ppt levels or lower (Firestone, 1991) were overcome, more food data began to be generated. In recent years, EPA, in association with the U.S. Department of Agriculture (USDA), has conducted several studies of dioxin-like compounds in foods. The results of these studies are presented in the following sections.

Tables B-14 and B-15 (Appendix B) contain summaries of data from the recent published literature regarding concentrations of CDDs and CDFs in food products. Most of the selected studies investigated "background" levels of CDDs and CDFs rather than studies targeted at areas of known contamination. Table B-16 contains a summary of PCB congener concentrations in food products.

Studies summarized in Tables B-14 and B-15 primarily examined CDD and CDF levels in products of animal origin (i.e., fish, meat, eggs, and dairy products). Because of their lipophilic nature, CDDs and CDFs are expected to accumulate in these food groups. Data in the tables indicate that CDDs and CDFs are found at levels ranging from the intermediate ppq up to the low ppt range. As expected, the highest levels reported are those measured in foods with high animal fat content. The highest reported congener concentrations are for the HpCDDs and OCDD. In general, for the less-chlorinated congener groups (i.e., Cl_4 - Cl_6), the CDD and CDF levels are both low and of similar magnitude. However, for the Cl_7 and Cl_8 congener groups, CDDs are higher than CDFs.

3.7.1. Migration of CDD/CDF from Paper Packaging Into Food

In the past, low levels of CDDs and CDFs have been detected in bleached paper. (See discussion in Volume 1.) Because bleached paper is sometimes used for food packaging, concern has been expressed that CDD/CDFs may migrate from the paper into the food.

Using refined and highly sensitive analytical methods, LaFleur et al. (1990) observed the migration of 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 1,2,7,8-TCDF from bleached paper milk cartons into whole milk. After 12 days of exposure, 6.7 percent of the 2,3,7,8-TCDD; 18 percent of the 2,3,7,8-TCDF; and 13 percent of the 1,2,7,8-TCDF in the milk carton leached into the milk. The concentrations of the three congeners in milk were 8.5, 110, and 49 pg/kg for 2,3,7,8-TCDD; 2,3,7,8-TCDF; and 1,2,7,8-TCDF, respectively. [Note: These data are not reported in Appendix B; only data for raw milk are reported.] LaFleur et al. (1990) also analyzed a single background milk sample for 2,3,7,8-TCDD and 2,3,7,8-TCDF. The sample contained 2,3,7,8-TCDD at a concentration of 1.8 pg/kg and nondetectable concentrations of 2,3,7,8-TCDF.

Study results reported by LaFleur et al. (1990) were performed by the National Council of the Paper Industry for Air and Stream Improvement (NCASI) at the request of the U.S. Food and Drug Administration (FDA) as part of a cooperative Federal agency effort to assess the risks posed by dioxin contamination of paper products (i.e., the Federal Interagency Working Group on Dioxin-in-Paper). In addition to assessing the migration of CDDs and CDFs from milk cartons, studies were also conducted to assess the extent of CDD/CDF migration into food from coffee filters, cream cartons, orange juice

cartons, paper cups for hot beverages, paper cups for soup, paper plates for hot foods, dual ovenable trays, and microwave popcorn bags. Migration of CDD/CDFs from the paper into food was observed in all studies. Results of these migration studies and an assessment of the risks to the general population posed by migration from paper are addressed in detail in U.S. EPA (1990). CDD/CDF levels currently found in food due to any leaching of dioxin-like compounds from paperboard containers are expected to be significantly lower than those reported in U.S. EPA (1990) because of process changes implemented by the pulp and paper industry to reduce formation of CDDs and CDFs (59 FR 17384).

In 1990, EPA referred the issue of potential CDD/CDF contamination from bleached food-contact paper products to FDA, because the risks were considered to be unreasonable in accordance with Section 9(a) of TSCA (55 FR 53047). In a 1994 Federal Register notice (59 FR 17384), FDA outlined various options being considered to address this issue, including the voluntary industry program to reduce TCDD in food-contact bleached paper products that had been in effect since 1990. As discussed in Volume 1, the paper industry has made process changes that they expect have generally reduced dioxin levels in bleached paper pulp to less than 2 ppt of I-TEQ_{DF}. Similar or lower levels could be expected in final paper products. NCASI reports that essentially no detectable migration of dioxin to milk occurs from cartons at these levels. According to an industry-wide survey conducted in 1993 by the American Forest and Paper Association, the voluntary specification for 2 ppt or less TCDD has been met by industry (59 FR 17384). This standard was still being met in 1995 (personal communication between G. Schweer, Versar, Inc. and E. Machuga, FDA, October 5, 1995).

3.7.2. North American Food

Until recently, data on measured levels of CDDs, CDFs, and dioxin-like compounds in U.S. food products have generally come from studies of a specific food product(s) in a specific location(s) rather than from large survey studies designed to allow estimation of daily intake of the chemicals for a population. For example, CDD/CDFs have not been routinely monitored for in the U.S. FDA Surveillance Monitoring Program for domestic and imported foods (conversation between Dr. S. Page, FDA, and G. Huse, Versar, Inc., February 8, 1993) nor have they been routinely monitored for by the U.S. Department of

Agriculture (USDA) in the National Meat and Poultry Residue Monitoring Program (conversation between Dr. E. A. Brown, USDA-FSIS, and G. Schweer, Versar, Inc., February 8, 1993).

However, USDA has developed some site-specific, though dated (late 1970s), CDD monitoring data, and recently, EPA and USDA conducted joint statistically-based national studies to evaluate the amount of CDD/CDF residues in animal products. Earlier efforts by USDA to examine CDD/CDFs in animal products were in response to a decline in general health noted by inspectors in several cattle herds in Michigan. Wood products in the local barns and other cattle holding premises, presumed to be treated with pentachlorophenol (PCP), were suspected as the cause of this health decline (Buttrill et al., 1978; Tiernan and Taylor, 1978). PCP was suspected to contain trace CDD and CDF levels as manufacturing contaminants at that time. In response to this incident, USDA performed two national investigations. The first study analyzed peritoneal adipose and liver samples collected from beef cattle in 23 States (Tiernan and Taylor, 1978), while the second study analyzed adipose tissue samples (body region not specified) collected from dairy cattle in 30 States (Buttrill et al., 1978)--neither study specified the cattle breeds for any sample. HxCDD, HpCDD, and OCDD were screened for in the analyses of samples from each study. In the beef cattle study (Tiernan and Taylor, 1978), 220 samples were analyzed: 189 peritoneal adipose samples and 31 liver samples. No residues were detected in any liver samples. A total of 19 (i.e., 10 percent) of the 189 adipose samples were found to contain HxCDD, HpCDD, or OCDD at levels >0.10 ppb (assumed to be on a whole weight basis), while 56 (i.e., 30 percent) contained levels <0.10 ppb (assumed to be on a whole weight basis) that were detectable based on the signal-to-noise ratio of the analytical instrumentation. OCDD accounted for the majority of the samples that positively contained CDDs (i.e., 17 or 9.0 percent), while only 3 samples contained HxCDD and 2 samples contained HpCDD residues. In the dairy cattle study, 358 adipose samples were analyzed (Buttrill et al., 1978). Nine samples (i.e., 2.5 percent) positively contained CDD levels >0.19 ppb or the "level of reliable measurement," while another 30 samples (i.e., 8.4 percent) contained identifiable CDD levels that were below the "level of reliable measurement" (i.e., not positively identified due to low concentration levels). As with the beef cattle study results, OCDD accounted for the majority (eight) of positive samples. HpCDD was identified in only a single sample that also contained OCDD.

HxCDD was also identified in only a single sample. Data from the USDA studies are not useful for estimating CDD/CDF exposure for two reasons. First, the samples were analyzed for only 3 of the 17 CDD/CDF congeners with dioxin-like toxicity, and these were reported on a homolog basis rather than a congener-specific basis. Second, the limit of detection was at or above 0.1 ppb or 100 ppt. Background levels for individual congeners appear to be much less than 100 ppt. For example, the highest congener levels in beef fat analyzed by Fürst et al. (1990) were 5.4 ppt for OCDD.

FDA has also conducted some limited analyses for the higher-chlorinated dioxins in market basket samples collected under FDA's Total Diet Program (Firestone et al., 1986). Food samples found to contain PCP residues >0.05 µg/g were analyzed for 1,2,3,4,6,7,8-HpCDD and OCDD. Also, selected samples of ground beef, chicken, pork, and eggs from the market basket survey were analyzed for these dioxin congeners, regardless of the results of PCP residue analysis. Between 1979 and 1984, 16 ground beef samples, 18 pork samples, 16 chicken samples, and 17 eggs samples with no PCP contamination were collected at various locations throughout the United States and analyzed for 1,2,3,4,6,7,8-HpCDD and OCDD. No dioxin residues were detected in any of the ground beef or egg samples. OCDD was observed at detectable concentrations in only 2 of the 18 pork samples (27 ppt 53 ppt) and 2 of the 16 chicken samples (29 ppt, 76 ppt). One chicken sample with PCP residues >0.05 µg/g had detectable residues of both 1,2,3,4,6,7,8-HpCDD (28 ppt) and OCDD (252 ppt). Egg samples from Houston, Texas, and Mesa, Arizona, with PCP residues >0.05 μg/g, had detectable 1,2,3,4,6,7,8-HpCDD levels ranging from 21 ppt to 588 ppt, and OCDD levels ranging 80 ppt to 1,610 ppt. These levels were attributed to local PCP contamination (Firestone et al., 1986). Milk samples, contaminated with PCP at levels ranging from 0.01 µg/g to 0.05 µg/g PCP, contained no detectable dioxins. It should be noted that these food residue data were not used in this assessment of dioxin exposures in the United States, because the reported limits of detection (10 to 40 ppt) for the FDA analyses were considerably higher than the levels of dioxins observed in foods from more recent studies. Also, the study only analyzed for residues of 2 of the 17 toxic CDD/CDF congeners. Finally, the study focused on samples with PCP contamination and, therefore, was not generally representative of background exposures.

FDA conducted a market basket survey of dairy products and commercial fish and shellfish in 1995/96 (Bolger and Jensen, 1998). Analysis of the foods for CDD/CDFs demonstrated that, other than the catfish samples, few of the food products had quantifiable levels of CDD/CDFs below 1 ppt. Samples containing detectable levels below 1 ppt yielded uncertain results, highly dependent on what value nondetects were set to (i.e., zero, one-half the detection limit, or the detection limit). Consequently, the market basket survey results were not used in calculation of background estimates of CDD/CDFs. Catfish fillet samples did, however, show quantifiable results. Twelve of the 19 catfish samples were suspected of being linked to the use of ball clay as a feed additive. CDD/CDF levels in these fillets ranged from 1.20 to 5.66 ppt I-TEQ_{DF} (mean = 3.11), when nondetects were set to one-half the detection limit and also when nondetects were set to the limit of detection. The seven uncontaminated catfish samples had levels ranging from 0.03 to 0.70 ppt I-TEQ_{DF} (mean = 0.29), when nondetects were set to one-half the detection limit, and 0.05 to 0.71 ppt I-TEQ_{DF} (mean = 0.31), when nondetects were set to the limit of detection.

Jensen and Bolger (2000) and Jensen et al. (2000) reported on additional FDA market basket dairy samples collected during 1996 through 1999. These data are shown in Table 3-30. FDA also analyzed 15 composite egg samples collected in 1997 from California, Ohio, Georgia, New York, Pennsylvania, Oregon, Minnesota, and Wisconsin (two composite samples were collected from each state except Oregion, which had only one composite) (Hayward and Bolger, 2000). Each composite contained 24 eggs. The TEQ_{DF}-WHO_{98} for these samples was 0.07 pg/g whole weight when only the positive samples were included in the TEQ calculation. When all sample results were included in the analysis, the mean TEQ_{DF}-WHO_{98} concentration was 0.013 when non-detects were set to zero and 0.081 when non-detects were setto one-half the detection limit.

Cooper et al. (1995) collected 38 samples of various food items from grocery stores and local fish markets in southern Mississippi during the spring of 1994. Food items "were selected based on their suspected high levels of CDD/CDF to the dietary intake." Thus, locally consumed dairy products, meat, egg, and seafood samples were collected, but items such as vegetables, fruit, grain, and cereal products were not sampled. All 38 samples collected had detectable levels of CDD/CDFs. I-TEQ_{DF} concentrations for each sample are reported in Table 3-31. In general, the levels of

CDD/CDFs in fish and shellfish were higher than the levels in meat and dairy products, and farm-raised catfish had the highest I-TEQ_{DF} concentrations of all the food types analyzed. I-TEQ_{DF} concentrations in meat and dairy products were slightly lower than those reported in other U.S. and European studies (Cooper et al., 1995).

As an extension of previous studies of food samples collected in southern Mississippi, Fiedler et al. (1997d) examined the CDD/CDF I-TEQ_{DF} concentrations of seven restaurant-prepared food dishes. Samples included: a veal chop, chicken strips and fries, blackened amberjack fish fillet, seafood soup, pasta with cheese and cream sauce, cheese sticks, and cheese cake. I-TEQ_{DF} values of CDD/CDFs ranged from 0.0197 ppt to 0.173 ppt on a fresh weight basis and from 0.128 ppt to 1.67 ppt on a lipid basis. The veal chop contained the highest I-TEQ_{DF} levels with 1.67 ppt I-TEQ_{DF} (lipid) and 0.173 ppt (whole weight), and also had measurable quantities of all the analyzed CDD/CDF congeners with the exception of 2,3,7,8-TCDD. 2,3,7,8-TCDD was not detected in quantifiable amounts in any of the restaurant samples. The major fraction of the total I-TEQ_{DF} came from PeCDDs and HxCDDs in most of the samples. The authors observed similar congener patterns in the dairy-based dishes (cheese sticks, pasta with cream sauce, and cheese cake) and in the veal chop sample. Specifically, the ratios between the HxCDDs (1,2,3,4,7,8-, 1,2,3,6,7,8-, and 1,2,3,7,8,9-) were approximately 1:4:1, and the concentration of 1,2,3,7,8-PeCDD and 2,3,4,7,8-PeCDF was approximately the same in dairy-based and veal chop dishes. The authors speculated that a dairy diet for the source cattle would possibly explain the similar pattern in the veal chop and dairy-based dishes. I-TEQ_{DF} levels in the restaurant-prepared seafood dishes were lower than I-TEQ_{DF} levels of store purchased seafood items and farm-raised catfish items from southern Mississippi studied by Cooper et al. (1995). An I-TEQ_{DF} level of 0.5 ppt (lipid) was found by Fiedler et al. (1997d) in restaurant-prepared fish fillet samples, while a mean I-TEQ_{DF} level of 20.5 ppt (lipid) was observed in commercially bought fresh farm-raised catfish nuggets by Cooper et al. (1995) in the same area of southern Mississippi. The restaurant-prepared seafood soup had an I-TEQ_{DF} of 0.646 ppt (lipid), while the I-TEQ_{DF} levels of store purchased fresh crab and crawfish ranged from 5.23 to 40.1 ppt (lipid). Fiedler et al. (1997d) calculated the contribution of the seven restaurant food items to the percentage of daily intake. Based on an assumed average daily dietary CDD/CDF intake of 100 pg I-TEQ_{DF}/person, the veal chop would contribute 46 percent of the daily intake, the chicken

strips 6.7 percent, the fish fillet 7.7 percent, the seafood soup 18 percent, the pasta with cream sauce 51 percent, the cheese sticks 13 percent, and the cheese cake 15 percent.

The California Air Resources Board (CARB) collected multiple samples of seven types of foods from commercial food sources in two urban areas of California (Stanley and Bauer, 1989). Foods were collected randomly, but an emphasis was placed on food stuffs of California origin (Stanley and Bauer, 1989). The types of food stuffs included saltwater fish, freshwater fish, beef, chicken, pork, milk, and eggs. A total of 210 samples were collected in Los Angeles (30 individual samples of each of the 7 types of foods), and 140 samples were collected in San Francisco (20 individual samples of each of the 7 types of foods). Food items were composited before chemical analysis to obtain a sample that was representative of average levels of CDDs and CDFs in the food stuffs, increase the probability of detection, and reduce the cost of chemical analysis. Samples were composited separately for each type of food stuff within each geographical area. Each composite sample contained 6 to 10 individual food samples, and 5 to 8 composite samples were analyzed for each food type. CARB data are summarized in Table 3-32. Beef (ground beef), pork (bacon), chicken, fish, and milk samples were analyzed on a lipid weight basis; however, for the purposes of this report, they were subsequently converted to a wet weight basis by multiplying the lipid weight concentration of CDD/CDFs by the fraction of fat contained in the food product of interest. Assumed lipid contents of 19, 15, and 4 percent for beef, pork and chicken, and milk were used. When nondetects were set to one-half the detection limit, the mean I-TEQ_{DF}s were 0.29 ppt, 0.24 ppt, 0.21 ppt, and 0.06 ppt for beef, pork, chicken, and milk, respectively. When nondetects were set to zero, I-TEQ_{DF}s were 0.03, 0.05, 0.08, and 0.02, respectively. Egg samples were analyzed for CDD/CDFs on a wet weight basis. I-TEQ_{DF}s for eggs were 0.14 ppt, when nondetects were set to one-half the detection limit and 0.004 when nondetects were set to zero.

The NCASI study (as described by LaFleur et al., 1990; and Henry et al., 1992) collected random food samples directly from the shelves of grocery stores located in the southern, midwestern, and northwestern regions of the United States. The samples were analyzed for 2,3,7,8-TCDD and 2,3,7,8-TCDF. These data are summarized in Table 3-33.

Schecter et al. (1993a) conducted complete congener analyses of 18 food samples collected from a supermarket in Binghamton, New York, in early 1990. Samples included

five fish, three types of beef (ground beef, beef sirloin tip, and beef rib steak), one chicken drumstick, one porkchop, one lamb, one ham, one bologna, one heavy cream, and four types of cheese. The following ranges of I-TEQ_{DF} levels on a whole weight basis were found: fish: 0.02 - 0.24 ppt; meat: 0.03 - 1.5 ppt; and dairy products: 0.04 - 0.7 ppt. These data are summarized in Table 3-34.

In a more recent study, Schecter et al. (1997) analyzed food samples collected directly from supermarkets in five U.S. cities: Binghamton, New York; Chicago, Illinois; Louisville, Kentucky; Atlanta, Georgia; and San Diego, California. The types of foods collected included: beef, chicken, ocean fish, fresh fish, and pork. Samples of each food type from the five geographic regions were pooled and analyzed for CDD/CDFs and selected PCBs. Ranges of CDD/CDF I-TEQ_{DF} values were calculated for each food group by assigning either zero or the detection limit to undetected congeners. The following ranges of CDD/CDF I-TEQ_{DF} levels on a lipid weight basis were found: beef: 0.89 - 2.86 ppt; chicken: 0.10 - 5.17 ppt; ocean fish: 2.45 - 21.14 ppt; fresh fish: 12.51 - 16.07 ppt; and pork: 0.64 - 3.97 ppt. These data are summarized in Table 3-35. Using the reported lipid content of these pooled samples to calculate the whole weight concentrations, the whole weight equivalents for these ranges are estimated to be: beef: 0.12 - 0.38 ppt; chicken: 0.005 - 0.28 ppt; ocean fish: 0.035 - 0.30 ppt; fresh fish: 0.60 - 0.78 ppt; and pork: 0.06 -0.36 ppt. PCB concentrations are also presented in Table 3-35. Schecter et al. (2001) reported again on the data collected from supermarkets in five U.S. cites. In this paper, mean TEQ_{DEP}-WHO_{98} concentrations for the same foods as described previously in Schecter et al. (1997) were presented. The whole weight mean TEQ_{DFP}-WHO_{98} concentrations were as follows when non-detects were set to one-half the detection limit: beef: 0.40 ppt; chicken: 0.33 ppt; pork: 0.39 ppt; ocean fish: 0.39 ppt; and fresh fish: 1.7 ppt. When non detects were set to zero, the mean whole weight TEQ_{DFP}-WHO_{98} concentrations were: beef: 0.16 ppt; chicken: 0.14 ppt; pork: 0.12 ppt; ocean fish: 0.16 ppt; fresh fish: 1.6 ppt.

Schecter and Li (1997) also analyzed four kinds of U.S. fast foods (i.e., hamburger, pizza, fried chicken, and ice cream) for CDD/CDFs and dioxin-like PCBs (105, 108, 156, 180). The I-TEQ_{DF} concentrations were similar for hamburger, pizza, and chicken, ranging from approximately 0.01 ppt wet weight, when a value of zero was used for nondetected congeners, to 0.3 ppt wet weight, when the detection limit was used for nondetected

congeners to calculate the total I-TEQ_{DF} value. These values are similar to those observed for other raw food groups and may indicate that cooking does not have a significant effect on the levels of CDD/CDFs in foods. (Further discussion on the effects of cooking can be found in Section 3.7.5.) The I-TEQ_{DF} concentrations for ice cream ranged from 0.03 to 0.49 ppt. Only PCB 180 was detected in hamburger at a concentration of 126 ppt. In pizza, PCB 118 (189 ppt) and PCB 180 (152 ppt) were detected, and in fried chicken, only PCB 118 (250 ppt) was detected. None of the PCB congeners evaluated were quantifiable in ice cream.

Schecter et al. (1989b) compared the levels of CDD/CDFs in cow's milk and infant formulas from Thailand and the United States. Samples of cow's milk and infant formulas were obtained from grocery stores in the Binghamton, New York, area in 1987. Thai formulas were purchased in Bangkok, Thailand, in 1986. In general, the I-TEQ_{DF} levels, on a lipid basis, were lower in infant formula than in cow's milk (Table 3-36). In addition, the formulas that were purchased in the United States had lower I-TEQ_{DF} levels than those purchased in Thailand. On a sample weight basis, the I-TEQ_{DF} level for whole cow's milk was 0.04 ppt (i.e., 1.2 lipid based ppt x 3.4 percent fat). This is similar to I-TEQ_{DF} levels observed for cow's milk in other parts of the United States and in Europe. Using a Nordic model for calculating TEQs, the data for cow's milk and infant formulas were compared to the Nordic-TEQ levels found in human milk samples from various countries. Human milk from industrialized areas (i.e., United States, Germany, and South Vietnam) had higher CDD/CDF Nordic-TEQ levels than either cow's milk or soy-based infant formulas.

U.S. EPA (1991) collected milk samples from several sites in the vicinity of a municipal waste incinerator in Rutland, Vermont, and two background samples from a dairy farm 123 kilometers from the incinerator, where no obvious industrial sources of CDD/CDF were present. All samples were taken from bulk storage tanks at the farms. The report indicated that facility emissions could not be correlated with the levels of CDD/CDF and other contaminants measured in various environmental media. For all milk samples, the majority of the congeners were not detected. It was reported that only OCDD was consistently detected at levels from 0.2 to 2.4 pg/g in the farms near the facility. The levels in milk from the three farms near the facility ranged from about 0.2 to 0.4 pg of I-TEQ_{DF}/g whole milk, and the I-TEQ_{DF} for the background samples collected from the distant farm was 0.12 pg/g. I-TEQ_{DF}s were calculated by U.S. EPA (1991) by

setting the nondetects equal to the detection limit. The 0.12 ppt I-TEQ_{DF} background value estimated by EPA is nearly 2 orders of magnitude higher than the I-TEQ_{DF} for milk based on the NCASI data. (This is probably due largely to the incomplete congener analysis conducted by LaFleur et al., 1990.) Examination of the raw data supporting this study indicated that all of the CDD/CDF congeners in the background sample were nondetectable. Consequently, if nondetects are set to zero, the total background I-TEQ_{DF} for milk would be zero. If half the detection limits are used to calculate the total I-TEQ_{DF} level, the estimated value is 0.07.

Birmingham et al. (1989) analyzed CDD/CDF residues in food collected in Ontario, Canada. Most of the food was grown in Canada, although some was from the United States. They reported analyzing 25 composite samples from 10 food groups. The precise number of samples in each food group was not reported. No TCDD, PeCDD, HxCDD, TCDF, or PeCDF were found at detection limits of 0.1 to 7 ppt. Low ppt levels of some of the higher chlorinated CDD/CDFs were detected in some foods. I-TEQ_{DF} levels were also estimated for the major food groups. However, as shown in Table 3-36, these data were reported on a homolog basis. It is unclear what procedure was used to convert the homolog data to I-TEQ_{DF}. The text implies that nondetects were treated as zero for purposes of estimating I-TEQ_{DF}. In addition to the animal food data shown in Table 3-37, measurements were also made in potatoes, apples, tomatoes, peaches, and wheat. Only OCDD was detected at levels ranging from 0.6 to 8 pg/g fresh weight. The I-TEQ_{DF} totals for vegetables were reported as 0.004 ppt for fruit, 0.002 ppt for vegetables, and 0.0007 ppt for wheat- based products. The procedure used to develop these I-TEQ_{DF} estimates was not clear.

Canada has a food safety program that analyzes total diet samples (i.e., representative food samples of the general population) for chemical substances, The analyses are run on commercially bought and prepared foods. As a part of that program, Ryan et al. (1997) analyzed CDD/CDFs and non-ortho PCBs in 44 food composites from Toronto and also in 44 composite samples from Montreal during the summers of 1992 and 1993, respectively. To optimize specific congener detection, samples of primarily animal origin were analyzed. Food groups included beef (ground beef, beef steak, beef roast), cured pork, organ meat, and poultry, dairy products of varying lipid content (whole milk, 1 percent milk, cream, cheddar cheese, and butter), fish (fresh water and marine),

and cooking fats and salad oils. Congener-specific data were not presented in this report. I-TEQ_{DF} levels and TEQ_{P}-WHO_{94} levels were calculated by setting nondetects to one-half the detection limit. These data were reported on a whole weight basis. TEQ values for each city are summarized in Table 3-38. The highest concentrations of total TEQ_{DFP}-WHO_{94} were found in butter (0.93 ppt in Toronto and 0.62 ppt in Montreal), fresh water fish (0.62 ppt in Toronto and 0.48 ppt in Montreal), oils (0.44 ppt in Toronto and 0.31 ppt in Montreal), and in ground beef (0.39 ppt in Toronto and 0.37 ppt in Montreal). TEQs for dairy products increased with increasing lipid content. Butter (lipid content approximately 70 percent) had a total TEQ_{DFP}-WHO_{94} of 0.93 ppt in Toronto and 0.62 in Montreal, while 1 percent milk (lipid content approximately 0.48 percent) had a TEQ_{DFP}-WHO_{94} of 0.036 ppt in Toronto and 0.025 ppt in Montreal. Fresh water fish, with a total TEQ_{DFP}-WHO_{94} of 0.62 ppt (Toronto) and 0.48 ppt (Montreal), were found to have higher total TEQ_{DFP}-WHO_{94} levels than marine fish (0.28 ppt in Toronto, and 0.12 ppt in Montreal). PCBs constituted 58 percent of the total TEQ_{DFP}-WHO_{94} value in Toronto (0.36 ppt) and 67 percent in Montreal (0.32 ppt). In the meat food group, more of the total TEQ_{DFP}-WHO_{94} was attributable to the CDD/CDF portion than the non-ortho PCB portion. The proportion of total TEQ_{DFP}-WHO_{94} attributable to non-ortho PCBs was greater in the dairy products and fish than in the meat samples.

Mes and Weber (1989) analyzed one composite sample each of beef, butter, cheese, eggs, organ meats, and poultry for PCBs 77, 126, and 169. The number of individual samples included in these composites was not reported. Whole weight concentrations of total PCBs (i.e., the sum of PCB 77, 126, and 169) were as follows: beef - 2 ppt, butter - 24 ppt, cheese - 11 ppt, eggs - 3 ppt, organ meats - 4 ppt, and poultry - 2 ppt. In a later study, Mes et al. (1991) evaluated numerous PCB congeners including dioxin-like PCBs 105, 114, 118, 156, 157, and 189 in foods. Five composite samples of the following food types were collected: milk, various dairy products, various cuts of beef and pork, lamb, organ meats, fish, eggs, luncheon meats, cooking fats, and soup. The number of individual samples included in each of these composites was not reported. Each composite sample was taken from one of five major Canadian cities. Among these foods, total whole weight PCB concentrations were highest for freshwater (31.9 ng/g), canned (9.9 ng/g), and marine (4.6 ng/g) fish, followed by butter (3.0 ng/g)

and cheese (1.7 ng/g). Concentrations were lowest (i.e., <0.1 to 0.1 ng/g) in canned meat soup, margarine, milk, yogurt, and lamb.

Recently, EPA has worked in cooperation with USDA to estimate the levels of CDD/CDFs and dioxin-like PCBs in U.S. food products. Analyses have been conducted for beef, pork, poultry, and milk products. A study of CDD/CDFs in vegetable oils has also been conducted. Data from the completed EPA/USDA studies are used in this Chapter to estimate background levels of CDD/CDFs and dioxin-like PCBs in foods. These studies were designed to be representative of the animal products used in the United States, and are believed to be suitable for calculating national averages.

Beef

EPA conducted a joint study with USDA to evaluate the amount of CDD/CDF residues in beef animals from federally inspected establishments (Winters et al., 1996a). Using a statistically-based sampling plan, 63 back fat samples were collected. Back fat was selected for sampling because: (1) it was assumed to be representative of fat people consume, because it is an extension of the fat reservoir, which, at another point, is the fat that is on rib cuts; (2) it was obtainable with little disruption by the USDA Federal inspectors who collected the samples; and (3) it has high fat content, which would optimize the analytical capability of measuring dioxins in the matrix. The average fat content of the samples was 80 percent. The sampling plan was designed to provide samples representative of the slaughtering establishments, cattle class (i.e., bulls, steer, heifers, beef cows, and dairy cows) and region of the United States in order to provide a national estimate of CDD/CDFs in beef. Tissue samples were analyzed for the residues of the 17 toxic CDD/CDF congeners and for percent lipid content. Limits of detection for the study were 0.05 ppt for the tetra-CDD/CDFs, 0.5 ppt for the penta-, hexa-, and hepta-CDD/CDFs, and 3.0 ppt for OCDD/CDF, on a whole weight basis. Because the samples were 80 percent fat, these whole weight detection limits translate to average lipid-based detection limits of 0.0625 ppt for the tetra-CDD/CDFs, 0.625 ppt for the penta-, hexa-, and hepta-CDD/CDFs, and 3.75 ppt for OCDD/OCDF.

Based on the analytical results, the most frequently detected CDD/CDF congener was 1,2,3,4,6,7,8-HpCDD. This congener was detected in over 70 percent of the samples and most frequently had the highest concentration of all the CDD/CDF congeners.

The second most frequently detected congener was 1,2,3,6,7,8-HxCDD, which was detected in approximately 32 percent of the samples. The most toxic congener, 2,3,7,8-TCDD, occurred in 11 of the 63 samples. Congeners not detected in any of the 63 beef samples included 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 1,2,3,7,8,9-HxCDF, 1,2,3,4,7,8,9,-HpCDF, and OCDF. Of the 17 congeners, 1,2,3,4,6,7,8-HpCDD and OCDD had the highest mean concentrations for the 63 beef samples. Overall, total CDD concentrations were higher than CDF concentrations in 44 of the 45 samples that had detectable CDD/CDF concentrations. Of the 63 samples, 18 (i.e., 28.6 percent) had no detectable CDD/CDFs. When nondetects were set to zero, the mean total CDD concentration accounted for approximately 88 percent of the mean total CDD/CDF concentration, while total CDFs accounted for only 12 percent. When nondetects were set to one-half the detection limit, the mean total CDD concentration accounted for 70 percent of total CDD/CDF concentrations, and CDFs accounted for 30 percent. Based on the cattle classes, both I-TEQ_{DF} and TEQ_{DF}-WHO_{98} concentrations were highest in bulls and lowest in dairy cows.

The mean lipid-based TEQ_{DF}-WHO_{98} value for the 63 beef samples was estimated to be 0.36 ppt (I-TEQ_{DF} = 0.35 ppt), when nondetects were set to zero, and 1.06 ppt (I-TEQ_{DF} = 0.89 ppt), when nondetects were set to one-half the detection limit. These mean values were calculated by statistically extrapolating the sample size for each cattle class to the percentage of the U.S. food supply that they represent. CDDs made up almost 76 percent of the total TEQ_{DF}-WHO_{98}, while CDFs accounted for only about 24 percent, when nondetects were set to zero. When nondetects were set to one-half the detection limit, CDD concentrations accounted for 65 percent of the total TEQ_{DF}-WHO_{98} and CDFs accounted for 35 percent of the TEQ_{DF}-WHO_{98}.

Assuming that the TEQ_{DF}-WHO_{98} concentration in the lipid portion of the back fat samples is equivalent to the TEQ_{DF}-WHO_{98} concentration in the lipid portion of edible cuts of beef, the lipid-based results from this study may be used to estimate the TEQ_{DF}-WHO_{98} concentration of CDD/CDFs in beef that is consumed by the general population. For example, if it is assumed that the average fat content of edible cuts of beef is 17 percent, then the TEQ_{DF}-WHO_{98} concentration in beef consumed by the general population is 0.18 ppt (i.e., 0.17 times 1.06 ppt), when nondetects are set to one-half the detection limit, and 0.06 ppt (i.e., 0.17 times 0.36), when nondetects are set to zero.

The percentage of fat in beef was estimated using food consumption data and fat content data for various beef products provided by David Haytowitz, USDA, to Linda Phillips, Versar, Inc., by personal communication, January 2001. USDA obtained food consumption data from the 1994-96 Continuing Survey of Food Intake Among Individuals (CSFII). The total quantity (in grams) of each food item eaten by the survey population in one survey day was tabulated and weighted to represent the quantity eaten by the entire U.S. population in one day. The fat content of each of these food items was also reported. To estimate the weighted mean percent of fat in beef products that are typically consumed by the U.S. population, the total amount of each beef item was first multiplied by the fraction of fat reported for that item to calculate the amount of beef fat consumed from each beef item. Next, the total amount of beef fat consumed (in grams) was calculated by summing the beef fat intakes for the individual beef items. The total amount of beef consumed was also estimated by summing the beef intake for the individual beef items. Finally, the weighted fraction of beef was estimated by dividing the total beef fat intake by the total beef intake. An abbreviated (i.e., the total number of beef items included in the analysis was 146; only a few beef items were included in the example to demonstrate the methodology) example of this calculation is provided in Table 3-39.

EPA, in cooperation with USDA, also recently analyzed beef samples for dioxin-like PCBs (Winters et al., 1996b; Saunders, 1997). The same samples that were analyzed for CDD/CDFs, as described above, were analyzed for PCBs 77, 118, 105, 126, 156, 157, and 169. Results of these analyses are presented in Table 3-40. Dioxin-like PCB congeners were found to be present in beef fat at an occurrence of greater than 85 percent; however, PCB 77 was found in only 19 percent of the samples. Using a statistical extrapolation of the data to account for the percentage of the different cattle classes in the U.S. food supply, the mean lipid-based total TEQ_P-WHO_{98} concentration for these dioxin-like PCBs was estimated to be 0.49 ppt (TEQ_P-WHO_{98} is also 0.49 ppt), when nondetects were set to either zero or the detection limit. PCB 126 contributed the most to the total TEQ_P-WHO_{98}. Assuming that the average fat content of edible cuts of beef is 17 percent, the PCB concentration in beef consumed by the general population was estimated to be 0.084 ppt TEQ_P-WHO_{98} (i.e., 0.49 times 0.17).

To ensure the relationship between lipid concentrations of dioxin-like compounds in the back fat of cattle is comparable to the level in edible meat products, EPA and USDA collaborated on an additional beef study examining the CDD/CDF/PCB concentrations in various cattle fat reservoirs (Lorber et al., 1997a). Fat matrices under examination included back fat (60 to 90 percent lipid), perirenal (i.e., kidney) fat (70 to 90 percent lipid), muscle tissue (less than 5 percent lipid), and liver (less than 5 percent lipid). Three data sets, cited in Lorber et al. (1997a), were analyzed in the study. The first data set came from a 1995 study in which the 17 dioxin and furan congeners and 6 coplanar PCBs were measured in 5 tissue samples (i.e., back fat, muscle, liver, serum) from animals at 3 research facilities around the United States (Feil et al., 1995). The five selected animals came from research facilities at Pennsylvania State University (PSU), North Dakota State University (NDSU), and Oregon State University (OSU). These animals were raised under the same conditions as cattle raised in routine U.S. feedlot operations, and were slaughtered after about 1-1/2 years. The second data set came from a 1996 dosing study in which four animals were fed high amounts of several, but not all, of the dioxin and furan congeners (Feil et al., 1996). Dosed animals experienced unanticipated exposure to some higher chlorinated congeners that exceeded the dosing levels. The likely source of this exposure comes from the PCP-treated wood in the feeding facilities. Feil et al. (1996) reported the homologue group concentrations in back fat, perirenal fat, muscle tissue, serum, and liver. Lorber et al. (1997a) analyzed the unpublished congener-specific data from this study. The third data set came from a 1995 depletion study of CDD/CDFs in five animals from a herd in Bolsover, Derbyshire, England (Startin et al., 1994). The animals in this herd had very high CDD/CDF concentrations in milk, which was traced to locally contaminated feed.

Results reported below are based solely on analyses of the five animals in the first data set, because they were believed to be representative of a typical food source (i.e., raised under routine feedlot conditions). The animals in the other two studies were not used in the analysis because they experienced high levels of exposure. Examination of total and TEQ_{DF}-WHO_{98} lipid-based concentrations in back fat compared with intramuscular fat concentrations, demonstrated that sampling for CDD/CDFs in back fat can be assumed to be representative of the levels found in edible fat. Assumptions used in this document to estimate CDD/CDF and PCB concentrations in edible beef from back fat are, therefore,

believed valid. This finding is based on examination of the ratios derived by dividing TEQ and total CDD/CDF/PCB concentrations in back fat by the same levels in intramuscular fat as shown in Table 3-41. A ratio of 1.0 indicates that muscle and back fat concentrations are equal. The ratio of total CDD/CDF concentrations in intramuscular fat (ppt lipid) to the same level in back fat (ppt lipid) mostly ranged from 0.5 to 1.5 for the individual CDD/CDF congeners, and the TEQ_{DF}-WHO_{98} ratios ranged from 0.6 to 1.7 (average of 0.9) (Lorber et al., 1997a). PCB comparisons are less straightforward. PCBs 77, 118, and 106 contain total and TEQ_{P}-WHO_{98} concentrations up to 16 times higher in muscle than in back fat. The ratios for PCBs 126, 156, 157, and 169, which ranged from 0.3 to 1.5, however, indicate that back fat levels are comparable to edible fat concentrations.

Pork

In addition to a national survey of CDD/CDFs and dioxin-like PCB residues in beef animals, EPA and USDA recently reported on the completion of a second survey of these compounds in pork (Lorber et al., 1997b). Using a statistically-based sampling plan, 78 belly fat samples were collected from 46 slaughtering establishments. The same justification for collection of back fat samples from beef animals applies to the collection of belly fat samples from the pork animals. These samples averaged 60 percent lipid (standard deviation of 12 percent), similar to the 80 percent lipid of the beef back fat samples. Tissue samples were analyzed for the 17 toxic CDD/CDF congeners and 7 coplanar PCBs, including PCBs 77, 118, 105, 126, 156, 157, and 169. Procedures for analysis were similar to the procedures for beef fat reported in Ferrario et al. (1996a) for CDD/CDFs and for PCBs in Ferrario et al. (1996b). Limits of detection for CDD/CDFs for the study were: 0.1 ppt for the tetras; 0.5 for the pentas, hexas, and hepta; and 1.0 ppt for the octas. Detection limits for the PCBs were: 1.5 ppt for PCB 77, 50.0 ppt for PCB 118, 26.0 for PCB 126, 10.0 for PCB 156, 2.5 ppt for PCB 157, and 0.1 ppt for PCB 169. These were detection limits for the sample matrix, and because the pork samples were about 60 percent lipid, the lipid-based detection limits can be estimated by dividing these detection limits by 0.60.

The sampling plan was designed to be representative of the pork class as a whole, and its three major subclasses: barrows/gilts, sows, and boars/stags. These classes are referred to by their common names: market hogs, sows, and boars, respectively. One

major difference in the pork survey design as compared to the beef survey design was that the two minor classes of pork animal (i.e., the sows and boars) were oversampled in relation to their prevalence in the national slaughter of pork animals as a whole. In the beef survey, the number of animals sampled from each cattle class (which included bulls, steers, heifers, beef cows, and dairy cows) were proportional to their prevalence in the national slaughter, with one exception. The exception was the sampling of two bulls; whereas, sampling in accordance to their prevalence in the class would have required only one sample. Results of the beef survey showed that the concentrations of CDD/CDFs in the bull were 3 to 10 times higher than the other four cattle classes (Winters et al., 1996b). However, it was difficult to draw conclusions and determine the variability in this class because of the small sample size. Based on this experience, an alternate strategy of oversampling the minor swine classes was adopted. This oversampling optimized the ability to distinguish concentration patterns among the three classes, and allowed for an estimate of the variability of the slaughter class estimates. Nationally, market hogs comprise about 95 percent of the total slaughter, with sows comprising about 4 percent and boars 1 percent of the slaughter. In the final sample of 78 animals, 56 were market hogs, 11 were sows, and 11 were boars. These classes represent 71.8 percent, 14.1 percent, 14.1 percent of the total sample size, respectively.

The most toxic congener, 2,3,7,8-TCDD, occurred in only 3 of the 78 samples. Congeners not detected in any of the 78 pork samples included 1,2,3,7,8-PeCDF; 1,2,3,7,8,9-HxCDF; and 1,2,3,4,7,8,9-HpCDF. Overall, CDD concentrations were higher than CDF concentrations. The four most frequently detected congeners were 1,2,3,4,6,7,8-HpCDD; OCDD; 1,2,3,4,6,7,8-HpCDF; and OCDF, all at a frequency of 50 to 60 percent detected. Results also indicated important differences among the swine classes. The TEQ_{DF}-WHO_{98} concentration in sows appeared higher than market hogs: 1.85 ppt (I-TEQ_{DF} = 1.72 ppt) for sows versus 1.44 ppt (I-TEQ_{DF} = 1.26 ppt) for market hogs. This may be due to a longer life span for sows (i.e., >2 years) than for market hogs (i.e., <1 yr). With a longer life, sows accumulate more dioxins and have greater body burdens than market hogs, despite also having the dissipation route of milk excretion. Perhaps the most striking result, however, was for the boar class. While a very small class in terms of exposure (only 1 percent of the pork food supply), older boars were significantly different from all other classes, while younger boars were similar to the

other pork classes. The older boars' lipid concentrations of 6.32 ppt TEQ_{DF}-WHO_{98} (I-TEQ_{DF} = 6.48 ppt) for CDD/CDFs and 0.54 ppt TEQ_{DF}-WHO_{98} (TEQ_{P}-WHO_{94} = 0.54 ppt) for coplanar PCBs were about 5 and 10 times higher than the overall averages for CDD/CDFs and coplanar PCBs, respectively. Like the sows, age is the principal factor that likely explains the higher concentrations. The average age of slaughter for market hogs is less than 1 year, while the old boars live longer than 2 years.

As shown in Table 3-42, the mean lipid-based TEQ_{DF}-WHO_{98} value for the 78 pork fat samples was 1.48 ppt (I-TEQ_{DF} = 1.30 ppt), when nondetects were set equal to one-half the detection limit, and 0.42 ppt (I-TEQ_{DF} = 0.46 ppt), when nondetects were set to zero (Lorber et al., 1997b). Assuming the TEQ_{DF}-WHO_{98} concentration in the lipid portion of belly fat samples is equivalent to the TEQ_{DF}-WHO_{98} concentration in the lipid portion of edible cuts of pork, the lipid-based results of this study can be used to estimate the TEQ_{DF}-WHO_{98} concentrations people are exposed to by eating pork. The average fat content of edible cuts of pork is assumed to be 19 percent (estimated using food consumption data and fat content data for various pork products provided by David Haytowitz, USDA, to Linda Phillips, Versar, Inc., by personal communication, January 2001). Thus, the average TEQ_{DF}-WHO_{98} content of pork consumed by the general population would be 0.28 ppt (i.e., 1.48 ppt times 0.19), when nondetects are set to one-half the detection limit, and 0.080, when nondetects are set to zero. For PCBs, the mean lipid-based TEQ_{P}-WHO_{98} was 0.06 ppt, when nondetects were set to one-half the detection limit, and 0.04 ppt, when nondetects were set to zero (the TEQ_{P}-WHO_{94} are the same as the TEQ_{P}-WHO_{98} for pork) (Table 3-36) (Lorber et al., 1997b). Assuming the average fat content of edible pork cuts is 19 percent, the TEQ_{P}-WHO_{98} concentration in pork consumed by the general population is estimated to be 0.012 ppt (i.e., 0.06 ppt times 0.19), when nondetects are set to one-half the detection limit, and 0.0074 ppt (i.e., 0.04 ppt times 0.19), when nondetects are set to zero.

Poultry and Eggs

EPA and USDA jointly participated in a study of dioxin-like compounds in the U.S. poultry supply (Ferrario et al., 1997). The study is a companion report to the cooperative studies on beef and pork (Winters et al., 1996a; Winters et al., 1996b; and Lorber et al., 1997b), and is the basis for the background TEQ concentrations for poultry. Using a

statistically based sampling plan, 80 abdominal samples were collected from 70 U.S. slaughtering establishments. Abdominal fat was selected for sampling because it has a very high lipid content, thereby optimizing the analytic capability of detecting and quantifying dioxins in the samples. The average fat content of the samples was 80 percent. The sampling plan was designed to be representative of the four poultry classes: young chickens, light fowl, heavy fowl, and young turkeys. Nationally, young chickens account for about 95 percent of total poultry slaughter. In the final sample of 80 animals, 41 (51 percent) were young chickens, 12 (15 percent) were light fowl, 12 (15 percent) were heavy fowl, and 15 (19 percent) were young turkeys. Samples were analyzed for percentage lipid, the same 17 toxic CDD/CDF congeners, and the same coplanar PCBs as the beef and pork samples, as discussed previously. Procedures for analysis of CDD/CDFs are described in Ferrario et al. (1996a) and for analysis of coplanar PCBs in Ferrario et al. (1996b). The detection limits for the study were 0.05 ppt for the tetra-CDD/CDFs; 0.25 ppt for the penta-, hexa-, and hepta-CDD/CDFs; and 0.5 ppt for the OCDD/CDF, on a whole weight basis. The detection limits for PCBs were: 0.80 ppt for PCB 77, 30.0 ppt for PCB 118, 10.0 ppt for PCB 105, 0.10 ppt for PCB 126, 4.0 ppt for PCB 156, 1.0 ppt for PCB 157, and 0.08 ppt for PCB 169. These were detection limits for the sample matrix, and because the poultry samples were about 80 percent lipid, the lipid-based detection limits can be estimated by dividing these detection limits by 0.80.

Laboratory analyses of the samples revealed that two young chicken samples could be classified as outliers by the Dixon and Grubs outlier tests. These two samples demonstrated significantly higher concentration levels of all the dioxin congeners, but CDF and PCB levels were comparable to the results from the other young chickens and other poultry classes. The results are reported below and also used to calculate national background levels; they do not include the data from these two young chicken samples.

The most toxic congener, 2,3,7,8-TCDD, occurred in 67 percent of the young chickens (mean 0.16 ppt lipid-based), 25 percent of the light fowl (mean 0.05 ppt lipid-based), 92 percent of the heavy fowl (mean 0.43 ppt lipid-based), and 73 percent of the young turkeys (mean 0.24 ppt lipid-based). No samples had detectable concentrations of 1,2,3,7,8,9-HxCDF. Ten percent of the young chicken samples had detectable levels of 1,2,3,4,7,8,9-HpCDF; none was detected in the other poultry classes. Overall, CDD concentrations were higher than CDF concentrations, and a larger percentage of the

samples had detectable levels of CDDs than CDFs. The most frequently detected congeners were 1,2,3,4,6,7,8-HpCDD; OCDD; and 2,3,7,8-TCDF, at a detection frequency of 94, 73, and 84 percent, respectively.

The mean lipid-based TEQ_{DF}-WHO_{98} value for the 78 poultry fat samples was 0.77 ppt (I-TEQ_{DF} = 0.65 ppt), when nondetects were set to one-half the detection limit, and 0.48 ppt (I-TEQ_{DF} = 0.42 ppt), when nondetects were set to zero. For PCBs, the mean lipid-based TEQ_{P}-WHO_{98} (and TEQ_{P}-WHO_{94}) value for the same samples was 0.29 ppt, when nondetects were set to either one-half the detection limit or when nondetects were set to zero. Table 3-43 presents a summary of the lipid-based TEQ_{DF}-WHO_{98} results on the basis of poultry class.

Assuming the TEQ_{DFP}-WHO_{98} concentration in the lipid portion of the abdominal fat samples is equivalent to the TEQ_{DFP}-WHO_{98} concentration in the lipid portion of generally consumed poultry, the lipid-based results from this study may be used to estimate the TEQ_{DFP}-WHO_{98} concentration in poultry consumed by the general population. For example, if it is assumed that the average fat content of poultry is 9 percent, then the TEQ_{DF}-WHO_{98} concentration in poultry consumed by the general population would be 0.070 ppt (i.e., 0.09 times 0.77 ppt), when nondetects are set to one-half the detection limit, and 0.043 ppt (i.e., 0.09 times 0.48 ppt), when nondetects are set to zero. The percentage of fat in poultry was estimated using food consumption data and fat content data for various food products provided by David Haytowitz, USDA, to Linda Phillips, Versar, Inc., by personal communication, January 2001). Using the same assumptions, the TEQ_{P}-WHO_{98} concentration in poultry consumed by the general population is estimated to be 0.026 ppt (i.e., 0.09 times 0.29 ppt), when nondetects are set to zero and to one-half the detection limit.

Background TEQ_{DF}-WHO_{98}s for eggs are based on whole weight data for 15 composite egg samples, each containing 24 eggs that were collected in 1997 by FDA from sites in California, Ohio, Georgia, New York, Pennsylvania, Oregon, Minnesota, and Wisconsin as part of a market basket survey (Hayward and Bolger (2000). The estimated total TEQ_{DF}-WHO_{98} for these eggs was 0.081 ppg whole weight, using one-half the detection limit and 0.013 ppt whole weight, when non-detects were set to zero (Table 3-44). Cooper et al. (1995) and Fiedler et al. (1997c) obtained similar results for three egg samples that were analyzed for CDD/CDFs. The estimated total TEQ_{DF}-WHO_{98} for

these eggs was 0.032 ppt (I-TEQ_{DF} = 0.026 ppt), using one-half the detection limit for nondetectable concentrations, and 0.023 ppt (I-TEQ_{DF} = 0.017 ppt), using zero to represent nondetectable concentrations. Schecter et al. (1997) also analyzed eggs. However, many of the congeners were not detected at higher detection limits than those in the Cooper et al. (1995) and Fiedler et al. (1997c) studies. The whole weight I-TEQ_{DF} concentration reported by Schecter et al. (1997) was 0.31 ppt, four to ten times higher than that reported in the other studies. Thus, the Schecter et al. (1997) data were not used in calculating the background estimate for CDD/CDFs. Background TEQ_P-WHO_{98} concentrations were estimated to be 0.1 ppt in eggs (TEQ_P-WHO_{98} was also 0.1 ppt), based on U.S. data from Schecter et al. (1997) and Canadian data from Mes and Weber (1989) and Mes et al. (1991). Schecter et al. (1997) analyzed egg samples (n = 18) for PCBs 118, 126, and 169. Mes and Weber (1989) analyzed one composite egg sample for PCBs 77, 126, and 169, and Mes et al. (1991) analyzed five composite egg samples for PCBs 105, 114, 118, 156, and 157.

Milk and Milk Products

Background TEQ_{DF}-WHO_{98} concentrations in milk were based on data from a recent study conducted by EPA that utilized the Environmental Radiation Ambient Monitoring System (ERAMS) for collecting milk samples (Lorber et al., 1998b). ERAMS has 51 sampling stations in 41 of the 50 U.S. States, and Panama and Puerto Rico. Milk samples from these ERAMS stations collected during four time periods (i.e., April, July, and October 1996, and January 1997) were composited into duplicate composites samples (n = 8) and analyzed for the 2,3,7,8-CDD/CDF congeners and dioxin-like coplanar PCBs 77, 105, 118, 126, 156, 157, and 169 to generate national estimates of the CDD/CDF content of milk. In addition, samples from individual ERAMS stations, collected over the same time period, were analyzed to evaluate geographic or temporal variability in CDD/CDF/PCB concentrations. Composite samples had a mean TEQ_{DF}-WHO_{98} content of 0.98 ppt (I-TEQ_{DF} = 0.82 ppt), when nondetects were set to one-half the detection limit, and 0.97 ppt (I-TEQ_{DF} = 0.81 ppt), when nondetects were set to zero. For PCBs, the lipid-based TEQ_P-WHO_{98} concentration was 0.49 ppt (TEQ_P-WHO_{94} was also 0.49 ppt), when nondetects were set to either one-half the detection limit or zero. These whole milk samples had a mean lipid content of 3.19 percent. However, not all of the milk consumed

is whole milk. Therefore, a weighted mean lipid content was calculated, based on the fat content of whole milk, low fat milk (1.3 percent), and skim milk (0.7 percent), as reported by U.S. EPA (1997), and the proportion of total milk intake accounted for by these milk types (USDA, 1995). Based on adult milk intake rates, the weighted milk fat percentage is 1.8 percent (Table 3-45). Using this weighted lipid content, the whole-weight TEQ_{DF}-WHO_{98} concentration in milk, as consumed, would be 0.018 ppt (i.e., 0.018 times 0.98 ppt) and the TEQ_{P}-WHO_{98} concentration in milk, as consumed, would be 0.0088 ppt (i.e., 0.018 times 0.49 ppt). Congener-specific data for the eight composite samples are presented in Table 3-46. Little evidence of a temporal trend in TEQ_{DF}-WHO_{98} concentrations was observed, based on the results of individual station samples. Results did, however, suggest a geographic trend with CDD/CDF concentrations in milk being highest in the southeastern United States and lowest in the southwestern United States. The TEQ_{DF}-WHO_{98} estimates for U.S. milk obtained by this study are consistent with the levels observed in previous, more limited milk studies (Schecter et al., 1989b; U.S. EPA, 1991).

Additionally, some idea of the total TEQ_{DF} level in milk samples can be gained by assuming that levels in beef fat are similar to levels in milk fat. This assumption implies that the differences in feeding/raising practices of dairy cattle vs. beef cattle do not cause substantial differences in CDD/CDF exposure. Beef contains approximately 20 percent fat, and whole milk is about 4 percent fat. Thus, on a whole food basis, CDD/CDF levels in beef should be about five times higher than in milk. Support for this concept can be seen in the German data presented by Fürst et al. (1990, 1991). These data show that the I-TEQ_{DF} level is 1.35 ppt in milk fat and 1.08 ppt in beef fat. On this basis, the North American data for beef (0.20 ppt of TEQ_{DF}-WHO_{98}) suggest that milk would be about 0.04 ppt of TEQ_{DF}-WHO_{98}. This value is consistent with the TEQ_{DF}-WHO_{98} value obtained from the recent EPA study that utilized the ERAMS for sampling U.S. milk.

Whole weight TEQ_{DFP}-WHO_{98} concentrations for dairy products (other than milk) were derived from the TEQ_{DFP}-WHO_{98} concentrations in milk fat by assuming that the concentration of CDD/CDFs is the same in fat of dairy products as in milk fat. Whole weight TEQ_{DFP}-WHO_{98} concentrations were calculated by multiplying the milk fat TEQ_{DFP}-WHO_{98} concentrations by the fractional fat content of dairy products. However, because the dairy products category included a variety of food types (i.e., cheese, yogurt, milk-

based desserts, etc.), it was first necessary to calculate a fractional fat content value that is representative of the percentage of fat in the diet, on average, that originates from dairy products other than milk. This composite fractional dairy fat value was based on dietary intake data from USDA's 1989-1991 Continuing Survey of Food Intake Among Individuals (CSFII) (USDA, 1995), and fat content data from USDA's Agricultural Handbook Number 8 (USDA, 1979-1984), as reported in EPA's Exposure Factors Handbook (U.S. EPA, 1997), as shown in Table 3-47. The composite percent of fat in dairy products was estimated to be approximately 12 percent (i.e., 11.84 percent). Thus, the whole weight TEQ_{DF}-WHO_{98} concentration in dairy products was estimated to be 0.12 ppt (i.e., 0.98 ppt [milk fat concentration] times 0.12). The whole weight TEQ_{P}-WHO_{98} concentration was estimated to be 0.058 ppt (i.e., 0.49 ppt [milk fat concentration] times 0.12).

These values are similar to I-TEQ concentration estimates for dairy products based on data from Schecter et al. (1992a), Jensen and Bolger (2000), Cooper et al. (1995), Fiedler et al. (1997c) and Schecter et al. (2001). Schecter et al. (1992a) reported on the analysis of 2,3,7,8-substituted CDD/CDFs in U.S. dairy products. Cottage cheese, soft cream cheese, and American cheese samples were selected randomly from New York supermarkets and analyzed on a wet-weight basis. All dairy products sampled had at least 13 detectable congeners out of the 17 evaluated, and only one congener (1,2,3,7,8,9-HxCDF) was not detectable in any of the five dairy products. Whole weight I-TEQ_{DF}s ranged from 0.04 to 0.72 ppt, when nondetects were set to one-half the detection limit. Assuming a fat content of 25 percent for these cheeses, the lipid weight I-TEQ_{DF} content would be 0.16 to 2.9 ppt. This lipid-based concentration range brackets the mean milk fat concentration observed by Lorber et al. (1998b). Jensen et al. (2000) reported whole weight TEQ_{DF}-WHO_{98} values ranging from 0.082 to 0.38 ppt in various dairy products when non-detects were set to one-half the detection limit (Table 3-30). When non-detects were set to zero, TEQ_{DF}-WHO_{98} values ranged from 0.0069 to 0.22 ppt (Table 3-30). Cooper et al. (1995) and Fiedler et al. (1997c) also reported on CDD/CDFs in three samples of cheddar cheese and three samples of butter. Lipid-based I-TEQ_{DF} concentrations ranged from 0.70 to 0.97 ppt in butter and 0.74 to 0.86 ppt in cheddar cheese. Schecter et al. (2001) reported whole weight mean TEQ_{DFP} - WHO_{98} concentrations of 0.47 ppt in cheese, 0.16 ppt in milk, and 1.1 ppt in butter when non-detects were set to one-half the detection limit and 0.022 ppt in milk, 0.17 ppt in cheese,

and 0.82 ppt in butter when nondetects were set to zero. In view of the similarities between the milk fat I-TEQ_{DF} concentrations observed by Lorber et al. (1998b) and the lipid-based I-TEQ_{DF} concentrations observed in dairy products, the use of the national milk fat data to estimate CDD/CDF concentrations in dairy products from various studies is a reasonable approach for estimating background concentrations of dioxin-like compounds for this food group.

Fruits and Vegetables

Data on CDDs and CDFs in U.S. fruit and vegetable products are extremely limited. The Ministry of the Environment, Ontario, conducted a study of CDDs and CDFs in locally produced and imported fruits and vegetables, some of which originated in the United States (Ministry of the Environment, 1988; Birmingham et al., 1989). Samples of fresh apples, peaches, potatoes, tomatoes, and wheat products were analyzed. In general, the minimum detection limits for these analyses were less than 1 ppt. The report indicated that "fruit and vegetable samples were substantially free of PCDD and PCDF residues, especially the more toxic tetra, penta, and hexachlorinated forms" (Ministry of the Environment, 1988). OCDD was the only congener detected in any of the samples. One apple and one peach sample contained detectable OCDD concentrations (8 ppt and 0.6 ppt, respectively). Detectable OCDD concentrations were found at concentrations ranging from 1 to 3 ppt in potatoes and 0.6 to 0.7 ppt in wheat samples. None of the tomato samples contained detectable levels of any CDD or CDF congeners. Based on these results, Birmingham et al. (1989) estimated the I-TEQ_{DF}s for fruits, vegetables, and wheat products to be 0.004 ppt, 0.002 ppt, and 0.0007 ppt, respectively.

As discussed in Volume 3, dioxin contamination of fruits and vegetables is thought to occur primarily via particle deposition or vapor adsorption onto outer layers with little penetration to inner portions. Plant uptake from the soil via the roots is generally considered negligible. However, the work of Hülster and Marschner (1993) indicates that zucchini and pumpkins were exceptions. For these plant species, it appears that root uptake occurs and leads to a uniform concentration within the fruit. The concentration of CDDs and CDFs in zucchini squash grown on "uncontaminated" soil (0.4 ppt I-TEQ_{DF} soil concentration) ranged from 0.5 to 0.7 ppt I-TEQ_{DF} dry weight. These reported values may be converted to whole weight I-TEQ_{DF} concentrations by using an assumed moisture

content of 93.7 percent (USDA, 1979-1984). The resulting range of whole weight concentrations for zucchini is 0.03 to 0.04 ppt I-TEQ_{DF}. Müller et al. (1993) also evaluated CDDs and CDFs in vegetables (carrots, lettuce, and peas) grown at both contaminated plots and control plots. For the control plots, the highest levels of CDDs and CDFs were observed in carrot peels: 0.55 ppt I-TEQ_{DF} dry weight, or 0.07 ppt I-TEQ_{DF} whole weight, assuming a moisture content for carrots of 87.8 percent (USDA, 1979-1984). Lower concentrations were observed in samples from the cortex of the carrots, indicating that the "contamination source for the peel of carrots is the soil" (Müller et al., 1993). Lettuce concentrations ranged from 0.1 to 0.4 ppt I-TEQ_{DF} dry weight. This is equivalent to a whole weight concentration range of 0.005 to 0.018 ppt I-TEQ_{DF}, assuming a moisture content of 95.4 percent for lettuce (USDA, 1979-1984). Concentrations in peas from contaminated plots ranged from 0.04 to 0.12 ppt I-TEQ_{DF} dry weight (0.004 to 0.013 ppt I-TEQ_{DF} whole weight, assuming a moisture content of 88.9 percent). Lower concentrations in peas (i.e., close to the detection limit; exact value not given) were reported for control plots. Similar data for vegetables grown in the United States were not available.

Recently, Tomoaki et al. (2000) reported on the levels of CDD/CDFs and coplanar PCBs in leafy vegetables in Japan. Whole weight TEQ_{DF}-WHO_{98} concentrations were 0.196 pg/g for spinach (n = 7) and 0.094 pg/g for komatsuna (n = 7). Washing followed by boiling reduced the total concentrations to 21 percent, 31 to 38 percent, and 60 to 61 percent of the original concentrations for CDDs, CDFs, and PCBs, respectively. Non-detects were set to zero in the calculations. Kim et al. (2000a) analyzed cabbages and radishes purchased in Korean markets fro CDD/CDFs. TEQ_{DF}-WHO_{98}s were 0.082 ppt for cabbage (n = 15) and 0.0013 ppt for radishes (n = 15) when non-detects were set to zero. Kim et al. (2000b) also evaluated cabbages and radishes, and observed similar results. TEQ_{DF}-WHO_{98}s were 0.042 ppt for cabbages and 0.007 ppt for radishes. Kim et al. (2000b) also analyzed pooled fruit samples (i.e., apples, oranges, and tangerines) and observed an average whole weight TEQ_{DF}-WHO_{98} of 0.006 ppt. The TEQ_{DF}-WHO_{98} was 0.006 ppt for potatoes and 0.012 ppt for rice.

Vegetable Oil

High fat levels in vegetable oil suggest that it may be important to consider as a source of human exposure. Vegetable oils can be made from a variety of plants, including soybeans, corn, olives, peanuts, sunflower seeds, safflower seeds, linseed, and cotton seed. Many of these items are protected from atmospheric deposition, which implies that their CDD/CDF levels would be low. However, Theelen (1991) estimated that vegetable oil could contribute about 10 percent of a person's total daily intake in The Netherlands (14 of 120 pg I-TEQ/d). This estimate was based on the Fürst et al. (1990) study that found nondetects for most congeners, except some of the higher chlorinated congeners of CDD and CDF (detection limit = 0.5 ppt). Half the detection limit was used for the nondetects, and most of the congeners were not detected. Consequently, the actual value could be much lower.

Recently, EPA conducted a study to evaluate the levels of CDD/CDFs in vegetable fats and oils using an adaptation of EPA Method 8290 (Versar, 1996b; Schrock et al., 1996). A total of 30 oil samples collected from various geographical regions of the United States were analyzed for CDD/CDFs. Samples included soybean, corn, peanut, canola, olive, safflower, and sunflower oils, in addition to margarine, solid shortening, and canola oil spray. OCDD was the only analyte detected in all 30 oil samples above background levels found in method blanks. Concentrations of OCDD detected in the oil samples ranged from 3.6 to 33.1 pg/g compared to OCDD method blank levels of 2.8 to 4.4 pg/g. When subtracting out the appropriate method blank concentrations of OCDD from the vegetable oil samples, the range of concentrations was 0.2 to 30.3 ppt, with a mean of 5.6 ppt. Detection limits were generally near 1 pg/g for all analytes and ranged from 0.1 to >2 pg/g. None of the oil samples or blanks with detection limits ranging from 0.2 to 1.8 ppt showed 2,3,7,8-TCDD. Other than OCDD, all detections were at or near the detection limits. Because the occurrences of the CDD/CDFs in vegetable oil were near detection limits and there was only a small percentage of occurrences overall (not including OCDD), an average TEQ_{DF}-WHO_{98} concentration calculated for the case where nondetects were set equal to 0 is evaluated as more meaningful than a TEQ_{DF}-WHO_{98} concentration calculated for nondetects set equal to one-half detection limit. The mean TEQ_{DF}-WHO_{98} calculated at ND = 0 was 0.056 ppt, and this value was used in calculating background exposures. By way of comparison, the mean TEQ_{DF}-WHO_{98} calculated at ND

= ½ detection limit was 1.5 ppt. The difference between the mean concentration calculated both ways is much larger than the difference seen for other food products. This suggests that the detection limits for the vegetable oil were too high to render a calculation of a mean at one-half the detection limit meaningful; for this reason, the mean calculated this way is not used in Chapter 4 for calculating background exposures.

TEQ_P-WHO_{98} concentrations for PCBs were based on data from Mes et al. (1991). A total of five composite samples of cooking fats and salad oils were analyzed for PCBs. The total TEQ_P-WHO_{98} concentration for these samples was 0.037 ppt, whole weight, based on the geometric mean of positive samples.

3.7.3. European Food

One of the most extensive investigations reported to date that involve testing of a variety of randomly selected food samples collected within the framework of official food control have been performed in the Federal Republic of Germany (Beck et al. 1989; Fürst et al., 1990; Malisch, 1998). Detailed results of these studies are included in Appendix B. Fürst et al. (1990) analyzed 107 food samples collected in Germany. The results of this study are presented in Table 3-48. All samples, except some of the milk, were randomly collected during official food monitoring programs. The authors speculated that a source may have been near the areas where the milk samples were collected, because they appeared higher than other milk tested in Germany, which showed levels around 1 ppt I-TEQ_{DF}. In a later report, Fürst et al. (1991) reported that a much larger survey of dairies in Germany had been completed. This survey analyzed 168 samples of milk and milk products collected at dairies prior to bottling in 1990. They found an arithmetic mean of 1.35 pg of I-TEQ_{DF}/g of fat. I-TEQ_{DF}s in these studies were estimated by assuming that nondetects equaled half the detection limits. Except for 1,2,3,7,8,9-HxCDF and 1,2,3,4,7,8,9-HpCDF, the 2,3,7,8-substituted congeners were detected at a frequency of greater than 99 percent in these samples (Fürst, 1995). In a more recent study, Fürst and Wilmers (1995) compared the levels of CDD/CDFs found in dairy products from 1990 to the levels in 120 dairy samples collected in 1994. Over the 4-year period, mean I-TEQ_{DF} concentration in milk fat decreased by almost 25 percent from 1.35 ppt to 1.02 ppt. Similar reductions were noted in human milk fat (Fürst and Wilmers, 1995). Fürst et al. (1991) also provided a summary of the results of several European studies. The data

summaries relevant to background levels in meat and dairy products from Fürst et al. (1991) are presented in Table 3-49. Fürst et al. (1991) report that information on CDD and CDF levels in vegetables and fruits is scarce and that the available data indicate a background of below 1 ppt.

Beck et al. (1989) analyzed 12 food samples collected randomly from food markets in West Berlin, Germany. Chicken, eggs, butter, pork, ocean perch, cod, herring, vegetable oil, cauliflower, lettuce, cherries, and apples were analyzed for CDD/CDFs. CDD/CDFs were detected in samples of animal origin in the ppq to ppt range (fat weight basis). No CDD/CDF congeners were detected at a detection limit of 0.01 ppt (whole weight basis) in samples of plant origin. Mayer (1995) analyzed 27 bulk milk samples (i.e., background) collected from large dairies in Bavaria, Germany, and 160 milk samples from farms in the vicinity of suspected dioxin sources between 1989 and 1993. Background I-TEQ_{DF} concentrations ranged from 0.69 ppt to 1.12 ppt, with a mean of 0.9 ppt on a lipid basis. Nondetected congeners were assumed to equal one-half the detection limit. Few of the potentially impacted samples had I-TEQ_{DF} concentrations exceeding 5 ppt. Malisch et al. (1994) analyzed one background egg sample and one egg sample from a contaminated site in Germany. The mean I-TEQ_{DF} concentrations were 1.2 pg/g fat for the background site and 12.7 pg/g fat for the contaminated site. These results are based on analyses using four different analytical methods, which showed similar results.

Malisch (1998) followed up with a more recent study of intake of food in Germany. In this study, CDD/CDF levels in food from the southwestern part of Germany were measured between 1993 and 1996. Malisch (1998) analyzed 1,414 food samples for CDD/CDF concentrations. The results indicated that the more recent I-TEQ_{DF} concentrations are lower than those previously observed by Fürst et al. (1991) and Fürst et al. (1990) (Table 4-50).

Schmid and Schlatter (1992) found low background levels of CDD/CDFs in milk samples from Switzerland. A total of 28 cow's milk samples and 1 goat's milk sample were collected during 1990 and 1991 from industrial dairies and from both rural alpine sites and potentially impacted sites (i.e., highly industrialized areas, and areas with waste incineration and metal recycling). Due to insufficient analytical sensitivity, 2,3,7,8-TCDD was not detected; thus, an assumed concentration was used for 2,3,7,8-TCDD in

calculating I-TEQ_{DF}s. The lowest I-TEQ_{DF} concentrations were observed in samples from rural and alpine areas. The mean lipid-based I-TEQ_{DF} for these seven milk samples ranged from 0.70 ppt to 3.28 ppt. The goat milk sample had a I-TEQ_{DF} concentration of 0.88 ppt. Based on pooled milk samples from nine industrial dairies in Switzerland, the average lipid-based I-TEQ_{DF} was 1.31 ppt. This is approximately equivalent to a whole weight I-TEQ_{DF} concentration of 0.05 ppt, assuming a lipid content of 4 percent for these samples. No significant differences were observed between samples stored in cardboard containers and those stored in glass bottles. Higher I-TEQ_{DF} concentrations were observed in samples collected from potentially impacted sites (2.02 ppt to 4.85 ppt on a lipid basis).

In 1996, the French Ministry of Agriculture, Fisheries and Food Products (FMAFFP) (1997) undertook a study to investigate "background" levels of CDD/CDFs in the French Republic (FMAFFP, 1997; Defour et al., 1997). This followed a 1993/94 FMAFFP study examining dioxin levels found in French milk samples collected from areas near known polluting industries. In this 1996 study, 40 dairy products, including cheese, butter, milk-based desserts, and cream, were sampled from 34 regions of France. Also, 12 cow's milk samples were collected from different locations in two regions (i.e., Seine-Maritime and Pas-de-Calais). These two regions had shown elevated levels over other regions of the country in the previous study, which targeted areas near pollution sources. The seven milk samples from the Seine-Maritime region had a mean lipid-based I-TEQ_{DF} of 1.77 ppt. The five milk samples from the Pas-de-Calais region had a mean I-TEQ_{DF} of 2.13 ppt. Each of these regions had one sample with a I-TEQ_{DF} greater than 3.0 ppt; whereas, the remaining samples clustered together at levels around 1.5 ppt and 1.9 ppt, respectively. The congener profiles of the milk samples showed a predominance of OCDD, and the furans typically were higher than the dioxins. Table 3-51 presents the mean I-TEQ_{DF} levels of the dairy products tested by the FMAFFP. The lipid-based I-TEQ_{DF} values of the eight butter samples ranged from 0.51 ppt to 2.10 ppt (mean of 1.01 ppt). The lipid-based I-TEQ_{DF} values of the 20 cheese samples ranged from 0.54 ppt to 1.44 ppt (mean of 1.11 ppt). The 12 fresh cream and milk-based desserts had lipid-based I-TEQ_{DF} values ranging from 0.78 ppt to 3.15 ppt (mean of 1.34 ppt). The sample from the Nord region had an I-TEQ_{DF} value of 3.15 ppt, which was significantly higher than the other cream or milk-based dessert samples, possibly reflecting industrial sources in the region. The mean value of the remaining 11 samples was 1.18 ppt I-TEQ_{DF}.

Theelen et al. (1993) collected food products from various locations in The Netherlands and analyzed them for 2,3,7,8-chlorine substituted dioxins, furans, and planar PCBs. Meat samples were collected from slaughter houses throughout The Netherlands. Fish, mixed meats, and cheeses were gathered at various grocery stores. Mixtures of foods in these categories were prepared based on the proportion of the average annual consumption rate that different food items in these categories represented. The food industry provided purified oils and fats. Mixtures of these items were also prepared in proportion to their annual use in The Netherlands. The concentrations of CDD/CDFs in these food products are presented in Table 3-52.

Food samples were collected in 1996 from both local markets and supermarkets from Catalonia, Spain (Domingo et al., 1999). A total of 35 food samples were collected and analyzed for CDD/CDF concentrations. The food samples included various types of beef, pork, chicken, lamb, fish, seafood, canned fish, milk and dairy products, vegetables, cereals, fruits, fats and oils, and eggs. The lipid-based and wet-weight I-TEQ_{DF} concentrations in these foods are presented in Table 4-53. As shown in Table 4-53, both the lipid-weight and wet-weight I-TEQ_{DF} concentrations were highest in fish and seafood. It is interesting to note that reported concentrations of CDD/CDFs in fruits, vegetables, and cereals were similar to those observed for meat and dairy products. However, the number of samples collected from each food group was not reported, and the method used for treating non-detects in calculating total I-TEQ_{DF}s was not reported.

CDDs and CDFs have been studied in dairy products in Spain. Ramos et al. (1999) analyzed butter samples for CDD/CDFs/PCBs and estimated TEQ_{DFP}-WHO_{94}s. Eight of the best known brands of butter were purchased from Spanish supermarkets. A total of 21 samples were analyzed. The results of the study indicated that the I-TEQ averages were 0.41 ppt for CDDs, 0.70 ppt for CDFs, and the TEQ_{P}-WHO_{94} average was 0.09 ppt for PCBs. The most toxic CDD congener, 2,3,7,8-TCDD, was found at detectable levels in 15 of the 21 samples analyzed and the most toxic CDF congener, 2,3,7,8-TCDF, was found in all samples. Ramos et al. (1999) did not report whether non-detects were set to zero or one-half the detection limit in calculating TEQs.

In the early 1990s, the United Kingdom's Ministry of Agriculture, Fisheries, and Food (MAFF) conducted a survey of CDD/CDFs in foods collected as part of their Total Diet Study (MAFF, 1992). Food samples were collected in 1988 from two UK locations:

Port Talbot and Stonehaven, selected to represent an urban/industrial site and a rural site, respectively. Additional samples were collected in Norwich. Selected food items included: meat and meat products, milk products, fish, fats and oils, eggs, and fruits and vegetables. I-TEQ_{DF}s were calculated by setting nondetects to either zero or to the limit of detection to provide a range of possible I-TEQ_{DF} values for each food item. Results of these analyses are presented in Table 3-54 in terms of total I-TEQ_{DF}s. Higher I-TEQ_{DF} concentrations were found in fatty food products, such as fish, meats, and fats and oils, than in food items with lower fat contents, such as fruits and vegetables. For some food items, higher I-TEQ_{DF} concentrations were observed at the urban/industrial area than at the rural site. Milk samples were collected from farms in rural/remote areas that were not expected to be impacted and from farms closer to urban/industrialized areas. In addition, retail milk samples were collected in 1990 from several UK locations during both winter and summer months. The results of these analyses are presented in Table 3-55. After laboratory procedures were developed for the fractionation of ortho and nonortho substituted chlorobiphenyls, Kroskos et al. (1996) analyzed frozen aliquots of the same 1990 milk samples for PCB congeners. The mean concentration for seven congeners (PCBs 28, 52, 101, 118, 138, 153, and 180) was 0.26 μg/kg whole milk or 6.7 μg/kg on a lipid basis assuming a typical fat content of 3.9 percent for cow's milk. The mean TEQ_P-WHO_{94} concentration of PCBs 77, 118, 126, 169, and 180 in the milk samples was 0.06 ppt whole milk. PCB 118 and 126 accounted for 98 percent of the total PCB TEQ (Kroskos et al., 1996). Additional MAFF analyses of Total Diet Study samples examining temporal trends in dietary intake are summarized in Chapter 6.

Foxall et al. (1995) analyzed samples of fruits and vegetables from urban and rural areas in Wales and England for CDD/CDF and PCB residues. The study was initiated as a result of concerns over elevated CDD/CDF and PCB concentrations in the air and soil in the vicinity of a chemical waste incinerator. Samples were collected from gardens at five sites within a 1.5-mile radius of the incinerator and from five similar sites in three rural areas for comparison. The produce evaluated included apples, courgettes, lettuce, and potatoes. Median I-TEQ_{DF} concentrations ranged from 0.3 ppt to 0.4 ppt for the four fruit and vegetable products, when nondetects were set to the limit of detection. In addition, no significant differences were observed between CDD/CDF and PCB concentrations in produce taken from urban and rural sites. The authors noted that CDD/CDF

concentrations in produce directly exposed to atmospheric deposition (i.e., apples and lettuces) are not significantly different from root vegetables (Foxall et al., 1995).

The Ministry of Agriculture, Fisheries, and Food (MAFF) also analyzed commercially available cow's milk for dioxins and PCBs in samples collected in 1995 from 12 locations in England (MAFF, 1997a). The locations were chosen to be representative of the different regions. Full fat milk purchased in glass bottles was tested. Lipid-based CDD/CDF concentrations ranged from 0.67 to 1.4 ppt I-TEQ_{DF}. Lipid-based PCB levels ranged from 0.75 to 2.3 ppt TEQ_P-WHO_{94}. Concentration levels of dioxins found in the 1995 samples were lower than those found in a comparable MAFF survey conducted on milk collected during 1990 (MAFF, 1992). (See Section 6.5, Temporal Trends in Food Products, for details.)

In a Lancaster University study, Stewart and Jones (1996) also examined PCBs in cow's milk from rural and urban dairy farms in the northwest of England. Sites were chosen to be representative of farms providing milk for human consumption. Stewart and Jones (1996) sampled pooled milk taken from 10 herds between 1993 and 1994. The sum of the lipid based levels of PCBs 77, 105, 118, 126, 156, 169, 170, and 180 ranged from 1.2 to 2.1 ppt TEQ_P-WHO_{94}.

The Ministry (MAFF) has also studied dioxin levels in samples of cow's milk from individual farms located around known emission sources in the United Kingdom annually since 1993. Additionally, beginning in 1994, the samples were analyzed for PCBs. Between 1993 and 1995, MAFF collected samples from 93 farms in the vicinity of 29 industrial sites (MAFF, 1997b). The concentration of dioxins in the cow's milk (for sample years 1993-1995) ranged from 0.87 to 11 ppt TEQ milk fat. In all but two of the samples, dioxin levels were within or below the normal range of 1.1 to 7.1 ppt I-TEQ milk fat previously described for the United Kingdom (MAFF, 1992). Two samples with slightly elevated results were obtained from farms in the vicinity of a municipal waste incinerator, which closed in 1996 due to noncompliance of plant emission standards. PCB levels (sample years 1994-1995) ranged from 1.1 to 9.3 ppt TEQ_P-WHO_{94} lipid. In 1996, the Ministry sampled 26 farms in the vicinity of 7 industrial sites and found dioxin levels ranging from 0.81 to 8.6 ppt TEQ_P-WHO_{94} milk fat. PCB concentrations ranged from 1.2 to 8.0 ppt TEQ_P-WHO_{94} milk fat (MAFF, 1997c).

The Ministry (MAFF) also analyzed 40 samples of cow's milk obtained from 20 dairies and farms in Northern Ireland during 1993 and 1994 (MAFF, 1997d). Sites were chosen to be representative of all the regions of Northern Ireland, and the samples were collected in polypropylene containers. Lipid-based dioxin concentrations in the retail samples from dairies ranged from 0.74 to 2.7 ppt I-TEQ_{DF} lipid (mean = 1.2 ppt I-TEQ_{DF}), and the concentrations in individual farm samples ranged from 0.84 to 3.0 ppt I-TEQ_{DF} lipid (mean = 1.2 ppt I-TEQ_{DF}). I-TEQ_{DF}s were calculated by setting nondetects to the limit of detection.

Vartiainen and Hallikainen (1994) conducted a survey of CDD/CDFs in cow's milk from Finland's largest dairies, eggs from major Finnish producers, and meat (pork and bovine) from major Finnish slaughter houses. Twenty samples in each food category were analyzed for CDD/CDFs. Low levels of CDD/CDFs were observed in cow's milk. Based on Nordic TEF_{DF}s (N-TEF_{DF}s), the mean lipid-based Nordic TEQ_{DF} (N-TEQ_{DF}) concentrations were 0.83 ppt for milk stored in glass bottles, 1.17 ppt for milk stored in paper milk cartons, and <0.5 ppt for meats. Whole-weight N-TEQ_{DF} concentrations in eggs averaged 0.12 ppt. The method used for treating nondetects in calculating these mean N-TEQ_{DF}s was not described in the paper. Also, use of N-TEQ_{DF}s instead of I-TEQ_{DF}s adds uncertainty to the interpretation of these data.

Himberg (1993) analyzed Finnish food samples for dioxin-like PCBs 77, 105, 126, and 169 to estimate the average daily intake of these PCBs. A total of 34 food samples were collected from food stores in the city of Helsinki. Concentrations of these PCBs in foods are presented in Table 3-56. Concentrations were higher in fish than meat by approximately one order of magnitude. Van Rhijr et al. (1993) analyzed 39 cow's milk samples from various agricultural, industrial, and impacted sites in The Netherlands for dioxin-like PCBs 77, 126, and 169 and CDD/CDFs. Mean lipid-based I-TEQ_{DF}s ranged from 0.8 to 1.8 for agricultural sites, 2.7 ppt for an industrial site, and 3.6 ppt to 7.7 ppt for sites near municipal waste incinerators. Lipid-based average TEQ_{P}-WHO_{94} ranged from 1.1 ppt to 1.9 ppt for agricultural sites, 2.1 ppt for the industrial site, and 1.8 pt to 4.5 ppt for sites near municipal waste incinerators.

3.7.4. Eastern European and Asian Food

Schecter et al. (1990, 1992b) analyzed foods collected from sites within the former Soviet Union between 1988 and 1990 for CDD/CDF residues. A total of 31 samples were collected from markets and restaurants in four cities (i.e., Moscow, Irkutsk, Novosibirsk, and Baikalsk). Fish samples were collected from local rivers in these areas. The study compared CDD/CDF levels from Moscow, which represented an area that had been industrialized for a long period of time, and Siberian cities, where industrialization had occurred more recently. Fathead minnow samples were collected from Lake Baikal in Baikalsk, because it was believed that they may have been impacted by a nearby pulp and papermill. Results of these analyses are presented in Table 3-57. I-TEQ_{DF}s ranged from 0.02 to 0.7 ppt wet weight for samples from Moscow, 0.04 to 0.8 ppt wet weight for samples from Irkutsk, 0.005 to 0.8 ppt wet weight for samples from Novosibirsk, and 0.9 to 1.4 ppt wet weight for samples from Baikalsk. Schecter et al. (1993b) analyzed foods from the same cities within the former Soviet Union for PCBs and organochlorine pesticides. PCB 180 was the only PCB congener analyzed for which a TEF_P-WHO_{94} had been developed. Foods analyzed included pork, poultry, fish, beef, lamb, and cheese. PCB 180 in these samples ranged from less than 0.001 to 0.007 ppm on a lipid basis.

Amirova et al. (1997) reported on the results of a 1996 examination of I-TEQ_{DF} levels in 17 foods purchased from food stores in Ufa, a town in the agricultural region of Bashkortostan in Russia. Foods were selected that contained high fat contents, such as dairy products, fish, beef, port, poultry, and vegetable oil (Amirova et al., 1997). The highest I-TEQ_{DF} concentrations, on a lipid basis, were found in freshwater fish (9.2 ppt), cream (5.45 ppt), and milk (3.32 ppt). Using data on the food consumption patterns of both rural and urban regions of the Republic of Bashkortostan, the dietary intake of I-TEQ_{DF}s for the urban population of Bashkortostan was calculated to be 2.31 pg/kg/day, while the rural population was estimated to have a lower level of 1.15 pg/kg/day.

Olie et al. (1989) analyzed food and wildlife samples from North and South Vietnam for CDD/CDF residues. Samples were collected between 1985 and 1987 from markets, fishermen, and women in the fields. The collection protocol used non-random sampling and did not provide a statistically representative sample of foods in these regions of the country. However, based on the limited number of samples collected, the study results suggest that food samples collected in the South contain higher levels of

CDD/CDFs than samples collected in the North. The authors suggest that these differences may be due, in part, to differences in the level of industrialization in these regions (i.e., the South is more industrialized than the North), and the spraying of South Vietnam with Agent Orange during the Vietnamese War (Olie et al., 1989). Concentrations of CDD/CDF in North Vietnamese food and wildlife samples ranged from 0.26 ppt I-TEQ_{DF} wet weight (catfish) to 3.30 ppt I-TEQ_{DF} wet weight (chicken fat) and 3.51 ppt I-TEQ_{DF} wet weight (cow fat) (Olie et al., 1989). For these same food products (i.e., catfish and chicken fat; cow fat was not analyzed), I-TEQ_{DF} concentrations in South Vietnamese food samples were higher (i.e., 5.68 and 31.54 ppt I-TEQ_{DF} wet weight, respectively) than those observed in samples collected from North Vietnam. The highest I-TEQ_{DF} concentrations in South Vietnamese wildlife were observed in turtle ovaries (85.71 ppt I-TEQ_{DF} wet weight). Schecter et al. (1990) reported the levels of PCBs in samples of pork and chicken collected in Vietnam. PCB 180 was the only PCB congener analyzed for which a TEF_P-WHO_{94} had been developed. PCB 180 ranged from less than 2.0 to 2.0 ppb on a lipid basis in pork and 3.0 to 4.0 ppb on a lipid basis in chicken.

3.7.5. Effects of Cooking and Trimming, or Processing on Residue Levels in Foods

Data on the effects of cooking on the levels of dioxin-like compounds in food products are limited, and the available data on this subject are somewhat contradictory. Cooking losses of dioxin-like compounds are reported in the literature in two ways. One method calculates losses by comparing total residues in a sample before cooking to total residues after cooking (i.e., by comparing total micrograms of dioxin-like compounds in raw and cooked foods). The other method calculates losses on the basis of the sample weight (i.e., by comparing the concentrations of residues in raw and cooked food). Losses of total residues are often accompanied by similar losses of water and/or fats. Thus, although total residues are reduced by cooking, concentrations based on the uncooked and cooked sample weights show little difference. Because dietary doses of dioxin-like compounds are calculated on the basis of dioxin residues in uncooked foods and intake rates of as-eaten (i.e., cooked) foods, changes in the concentrations of dioxin-like compounds from cooking would be relevant to these calculations. In contrast, losses of total residues, although an interesting phenomena, would have less effect on the

results of these estimates. This section summarizes some of the data on the effects of cooking on dioxin-like residues in foods, as reported in the scientific literature.

Stachiw et al. (1988) evaluated changes in the residue levels of 2,3,7,8-TCDD in fish from cooking. Restructured carp fillets (i.e., fabricated fish products that use mechanically deboned fish) from Saginaw Bay, Michigan, measuring either 7.5-cm or 10-cm diameters, with a uniform thickness of 1 cm, were roasted (covered or uncovered) or charbroiled to internal end temperatures of 60°C, 70°C, or 80°C. Both spiked samples (i.e., spiked to levels approximating 100 ppt) and control samples (i.e., unspiked, containing levels ranging from 37 to 45 ppt) were tested for residues of 2,3,7,8-TCDD before and after cooking. Samples were also tested for total cooking losses (i.e., losses of fat and moisture). Cooking losses ranged from approximately 5 to 20 percent, depending on the cooking method. Results of the TCDD residue analyses indicated that both cooking methods resulted in significant reductions of total 2,3,7,8-TCDD residues (Table 3-58). Reductions of total TCDD residues by cooking ranged from 34.2 percent to 67.5 percent for control samples and 44.2 percent to 70.6 percent for spiked samples (Stachiw et al., 1988). These percentage reductions were not significantly different for control vs. spiked samples. Thus, the concentration of TCDD in the raw samples did not appear to have a significant impact on the percent reduction by cooking. However, increasing the end point temperature and surface area of the sample resulted in significantly increased losses. Also, TCDD losses were two to eight times greater than total cooking losses (i.e., fat and moisture losses) (Stachiw et al., 1988). When TCDD levels were evaluated on a ppt whole weight concentration basis, reductions ranged from 24 to 60 percent for control samples and 38 to 65 percent for spiked samples.

In a similar study, Zabik et al. (1979) compared the reductions in PCBs in lake trout achieved by various cooking methods. Samples of fat trout from Lake Superior, Michigan, were analyzed before and after broiling, roasting, or microwave cooking. Significant total residue losses of xenobiotics were observed for all cooking methods (i.e., 26 to 53 percent for PCBs). However, when PCB losses were calculated on a wet weight concentration (ppm) basis, losses ranged from 5 to 16 percent, depending on the cooking method. On a fat weight concentration basis (ppm), PCB losses ranged from 16 to 40 percent, depending on the cooking method. In a later study, Zabik et al. (1982) found

that cooking was not an effective means of reducing the total residues or concentrations of xenobiotics in the edible tissue of carp from Saginaw Bay.

Poston et al. (1994) and Moya et al. (1997) found that total PCB levels in winter flounder from New Bedford Bay, Massachusetts, were reduced by one cooking method, but not others. Significant reductions in total PCB residues was observed in deep fried fish, but not in fillets pan fried or broiled. Similar results were obtained on an individual congener basis. Deep frying reduced total PCB levels 47 percent. However, deep-fried fillets also showed a weight loss of approximately 40 percent. Pan fried fillets showed a much lower percent reduction in total PCB residues. Water losses were also significantly lower for these two cooking methods (i.e., 7 percent and 15 percent, respectively) (Moya et al., 1997).

Smith et al. (1973) reported that the total residue levels of PCBs (Aroclor 1248 and 1254) in chinook and coho salmon steaks from Lake Michigan were reduced only slightly by baking and poaching; however, Cichy et al. (1979) observed significant losses (38 to 43 percent) of PCBs in Michigan lake trout that were irradiated and broiled. Losses were calculated by comparing the total micrograms of PCBs in raw and cooked fish. Pan-frying of white croaker fillets from Santa Monica Bay and Orange County, California, resulted in total PCB (Aroclor 1242 and 1254) losses of 65 percent and 28 percent, respectively (Puffer and Gossett, 1983). Trotter et al. (1989) found that, on the basis of concentration, PCB levels in cooked and uncooked bluefish were similar. However, when the results of cooked samples were corrected for moisture losses and compared to raw samples based on total residue levels, PCBs were found to be reduced by 27 percent.

Based on a study of Atlantic bluefish collected near Long Island, New York, Armbruster et al. (1989) concluded that trimming resulted in the largest reductions in PCB residues in fish. Armbruster et al. (1989) reported that trimming bluefish fillets resulted in an average total PCB residue reduction of 59.4 percent and that baking, broiling, frying, or poaching resulted in further losses averaging only 7.5 percent. The magnitude of reduction observed for the various cooking methods (combined with trimming) did not differ significantly. In addition, Armbruster et al. (1989) analyzed oil drippings released during cooking, and found that the total PCB residues in the oil did not account for the total losses of PCBs that occurred during cooking. Based on these results, Armbruster et al. (1989) concluded that "PCB losses by vaporization during the various cooking

procedures may have constituted the major portion of the mean total (7.5 percent) loss from cooking." Skea et al. (1979) also reported that trimming resulted in significantly greater reductions in PCB concentrations in fish than cooking. Skea et al. (1979) evaluated the effects of trimming and various cooking methods on the residue levels of PCB, Mirex, and DDT in brown trout and smallmouth bass collected from Lake Ontario. PCB results from this study are summarized in Table 3-59 according to the percent reduction in concentration (μg/g) and total reduction of PCB residues (i.e., calculated by comparing the total micrograms of PCBs in raw and cooked fish). Trimming alone resulted in total percent reductions of approximately 80 percent. Of the cooking methods, deep fat frying resulted in the greatest additional reductions in PCB residues Skea et al. (1979).

Zabik (1974) found that cooked chicken pieces had significantly lower concentrations of PCBs than raw pieces. Ten hens that had been fed PCB Aroclor 1254 were slaughtered, split in half, and cut into several pieces (i.e., drumsticks, breasts, thigh, etc.). Pieces obtained from one-half of the chicken were analyzed raw, and pieces from the other half were analyzed after stewing or pressure cooking. The two cooking methods resulted in similar losses of PCBs (Table 3-60). Cooking resulted in greater losses from abdominal adipose tissue and thigh skin. These pieces also had the highest fat content. Recovery of PCBs was calculated by comparing the levels of Aroclor in cooked chicken and broth to the levels in raw chicken. Percentage recoveries ranged from 60 to 95 percent.

Schecter et al. (1996) studied the effects of cooking on CDD/CDF levels in hamburger. Ground beef was purchased from a supermarket in Binghamton, New York, and divided into eight samples. Four samples were analyzed for CDD/CDFs uncooked, and the other four samples were broiled and then analyzed for CDD/CDFs. Cooking produced a 42 to 49 percent decrease in I-TEQ$_{DF}$s per hamburger. However, this decrease was identical to the decrease in weight due to cooking. Thus, reduction in CDD/CDFs in hamburger are due to loss of fat and water during cooking. The I-TEQ$_{DF}$s calculated on a whole weight concentration basis were 0.128 to 0.134 ppt for uncooked samples and 0.116 to 0.145 ppt for cooked samples. These results indicated little change in total I-TEQ$_{DF}$ concentrations from cooking, despite the significant losses observed on the basis of total residue level.

Schecter et al. (1999) recently extended their studies to examine the effect of broiling on CDD, CDF, and co-planar PCB levels in hamburger, bacon, and catfish. The samples were again purchased from a supermarket in Binghamton, New York, and each food type was divided into nine samples. Five samples of each food type were broiled in an electric oven (one of each cooked food type sample was consumed to guarantee edibility), and the other four samples were analyzed uncooked. Reductions of approximately 50 percent in the total CDD/CDF/PCB TEQ levels (using I-TEFs for CDD/CDFs and TEF_P-WHO_{94} for PCBs) were observed in the broiled samples. However, after adjusting for moisture losses due to broiling (i.e., looking at concentration on a weight basis), the following TEQ concentrations of CDD/CDF/PCBs were observed: (1) TEQ concentrations in the hamburger remained the same (about 0.155 ppt); (2) TEQ concentrations in the bacon increased 84 percent (from 0.079 ppt uncooked to 0.145 ppt cooked); and (3) TEQ concentrations in the catfish decreased by 34 percent (from 0.577 ppt uncooked to 0.378 ppt cooked).

Petroske et al. (1997) studied the effect of pan frying on CDD/CDF concentrations in ground beef. Samples were collected from four control animals and four dosed (16 congeners) cattle in a dioxin/furan feeding experiment. Muscle tissue (rib eye) and back fat from the cattle were blended into patties containing approximately 20 percent fat. The patties were then cooked in a stainless steel frying pan to an internal temperature of 74°C. During the cooking process, the fats, juices, and volatiles that formed were collected on an inverted funnel placed over the frying pan, draining back into the pan. These volatiles were analyzed along with the cooked patties. Analysis of the samples showed significant reductions in total congener residue levels (pg/patty) after pan frying (assuming the fats and juices are not consumed). Decreases after cooking ranged from approximately 21 to 50 percent for the control samples and approximately 31 to 50 percent for the dosed animals. The majority of reductions after pan frying, for both types of sample, were in the 40 to 50 percent range, which is similar to the reductions observed by Schecter et al. (1996; 1999) after broiling. The findings were not analyzed on a concentration (i.e., ppt per unit weight) basis, however. Consistent with the findings of Stachiw et al. (1988), the concentration of CDDs and CDFs in the raw samples did not appear to have a significant impact on the percent reduction by pan frying. Taking into consideration the CDD/CDFs found in the volatiles and juices released during the cooking

process, between 6 and 16 percent of the dosed CDD/CDF congeners were unaccounted for after cooking. Unaccounted losses were greater for the lower chlorinated dioxin congeners than for the more highly chlorinated congeners, while the opposite was observed with the furans. Petroske et al. (1997) hypothesized that "pan frying of ground beef patties, and likely non-patty ground beef significantly reduces the quantity of dioxin and furan congeners consumed if the fat and juices are discarded, while congeners releases as volatiles may pose a secondary mode of human exposure."

As indicated previously, Tomoaki et al. (2000) found that washing followed by boiling significantly reduced the concentrations of CDD/CDFs and PCBs on leafy vegetables. Concentrations were reduced to approximately 20 percent, 30 to 40 percent, and 60 percent of the original concentrations of CDDs, CDFs, and PCBs, respectively.

To evaluate the potential for contamination of foods with CDD/CDFs during the curing process, Mayer (1998) examined CDD/CDFs levels in 41 smoked ham samples produced in southern Germany, and compared the results to CDD/CDFs in 21 untreated pork samples. Only the results from samples of the outer layer of the smoked ham, about 1 cm thickness, were included in the comparison because it was assumed that CDD/CDFs derived from the curing smoke would be concentrated in this surface. I-TEQ_{DF} concentrations ranged from 0.08 pg/g fat to 85 pg/g fat, with an average of 6.2 pg/g fat in the smoked ham samples. In comparison, the I-TEQ_{DF} concentrations in the untreated pork samples were between 0.09 pg/g fat and 1.2 pg/g fat, with an average of 0.31 pg/g fat. The median I-TEQ_{DF} levels for these two groups were approximately the same; 0.33 pg/g fat for the outer parts of smoked ham samples and 0.31 pg/g fat for the untreated pork samples. Most pork samples had lipid-based I-TEQ_{DF} concentrations below 0.5 pg/g. A total of 61 percent of the smoked ham samples, compared to 90 percent of the untreated pork samples, had I-TEQ_{DF} concentrations lower than 0.5 pg/g fat. Mayer (1998) also presented I-TEQ_{DF} levels based on all edible parts of the smoked ham samples. The results indicated that 30 samples had I-TEQ_{DF} concentrations lower than 0.04 pg/g; 8 samples showed levels between 0.06 and 0.35 pg/g; and 3 samples were highly contaminated with I-TEQ_{DF}s ranging from 1.7 to 3.7 pg/g. CDD/CDF homologue group profiles illustrated that smoked ham with low CDD/CDF contamination had a similar profile to that of untreated pork. Smoked ham with elevated levels of CDD/CDFs had a similar profile to that of highly contaminated ham, but a quite different profile to that of untreated

pork. Mayer (1998) indicated that the curing process may be a source of CDD/CDFs in smoked ham.

Results of the preceding studies suggest that processes such as smoke curing may increase CDD/CDFs in foods. Cooking may significantly reduce total residues of dioxin-like compounds in foods. However, the data reported on the basis of concentration are somewhat contradictory. Schecter et al. (1996, 1999) observed that concentrations of dioxin-like compounds in beef were not significantly affected by cooking, but the effects of cooking were more significant in bacon and fish. Skea et al. (1979) also observed significant concentration changes of PCBs in fish. In contrast, the Zabik et al. (1979, 1982) studies did not show significant losses of PCB concentrations in fish from cooking. Therefore, based on the existing data, it is not possible to draw conclusions with regard to reductions in food concentrations of dioxin-like compounds from cooking. As a result, potential reductions in concentrations from cooking are not accounted for in Chapter 4 for the purpose of estimating dietary intake of dioxin-like compounds.

3.7.6. Food Observations and Trends

Some general observations for CDD/CDF levels are possible from the data presented in the various food product studies above:

- TEQ concentrations of CDD/CDFs and PCBs are similar in the studies from the United States and Europe.
- CDD/CDF levels in the higher chlorinated congeners (i.e., HpCDDs and OCDD) are present in higher concentrations than the lower chlorinated congeners. In the higher chlorinated congeners, CDD levels are present in greater concentrations than the CDFs.
- PeCDD is frequently the highest contributors to total TEQs in foods.
- Food products of animal origin (i.e., fish, meat, eggs, and dairy products), which have a high fat content, have a higher concentration of CDD/CDFs than those food products that have lower lipid contents.
- Generally, of all the food products, fish and shellfish contain the highest levels of CDD/CDFs.

3.7.7. Food CDD/CDF Congener Profiles and Background TEQ Concentrations

The 2,3,7,8-substituted congener profile for various foods are presented in Table 3-61 and Figures 3-7 through 3-10. These profiles are calculated as the ratio of individual congener concentrations to the sum of concentrations for all of the 2,3,7,8-substituted congeners and are based on data from the studies discussed previously and footnoted on Table 3-53. Profiles for beef, milk, and dairy products are similar, with 1,2,3,4,6,7,8-HpCDD and OCDD dominating the profiles in nearly equal proportions. In contrast, OCDD is the single dominant congener in both chicken, eggs, and pork.

U.S. food data on CDD/CDFs are summarized in Table 3-62. Background TEQ_{DF}-WHO_{98} estimates are presented first assuming that nondetects equal half the detection limits and second assuming that nondetects equal zero. Large national surveys conducted by EPA/USDA (i.e., beef, pork, poultry, and milk) provide an adequate basis for estimating the concentrations of dioxin-like compounds believed to be representative of background levels in U.S. foods. For some food groups, however, the small sample size and high number of nondetects provide an uncertain basis for estimating national background levels. Overall, the general agreement between the national U.S. estimates and the food level estimates for Canada and Europe provides some reassurance that the U.S. values are reasonable. For the purposes of calculating background exposures to CDD/CDFs via dietary intake, the upper-range background TEQ_{DF}-WHO_{98} (i.e., those calculated using one-half the detection limit for the nondetects) were used, except for vegetable oil. (See Chapter 4.)

North American food data on PCBs are summarized in Table 3-63. These data are used in Chapter 4 to estimate background dietary exposures to PCBs.

3.8. SUMMARY OF CDD/CDF AND PCB LEVELS IN ENVIRONMENTAL MEDIA AND FOOD

This chapter summarizes data on CDD/CDF and PCB levels in environmental media and food with emphasis on "background levels." Data representative of background conditions in environmental media are considered to be those collected in rural, pristine, and urban (soil and air only) areas not believed to be impacted by any local sources (e.g., incinerators).

The mean background levels for the various environmental media and foods presented in this chapter are summarized in Table 3-64. These total background level TEQ_{DFP}-WHO_{98} are used in Chapter 4 to estimate typical exposure levels in the United States. Standard deviations of the total mean TEQ_{DF}-WHO_{98} for each media were also calculated to depict the "range" of probable CDD/CDF levels in various media. For media for which complete congener-specific data for multiple samples from the same study (i.e., beef, pork, poultry, milk, dairy, and sediments) were available, means and standard deviations were calculated by conventional methods. However, for media for which mean total TEQ_{DF}-WHO_{98} were calculated by summing congener-specific TEQ_{DF}-WHO_{98} from multiple studies (e.g., soil, air), the use of typical methods for calculating standard deviations was not possible. Therefore, standard deviations were based on the standard deviation of the congener that contributed most to the total TEQ_{DF}-WHO_{98}. The percentage deviation from the mean for that congener was applied to the total mean TEQ_{DF}-WHO_{98} for all congeners combined. The congeners selected for use in the standard deviation estimates are presented in Table 3-65. The data in this table indicate that the pentachlorinated dioxins and furans were frequently the highest contributors to total TEQ_{DF}-WHO_{98} in foods and other environmental media in the United States. Standard deviations for fish could not be calculated because of the weighing method used in developing the average background concentration for fish. Media levels presented in Table 3-61 are shown graphically in Figure 3-11. Table 3-61 illustrates that of all the food products, levels (whole weight basis) of CDD/CDF/PCBs are highest in freshwater fish.

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Table 3-1. Mean CDD/CDF Ambient Air Concentrations from Sites Located Upwind and Downwind of an Industrial Site

	Upwind (Background)			Downwind		
	No. of Positive Samples	Mean Concentration nd = ½ LOD[a] (pg/m^3)	Mean Concentration nd = 0[b] (pg/m^3)	No. of Positive Samples	Mean Concentration nd = ½ LOD[a] (pg/m^3)	Mean Concentration nd = 0[b] (pg/m^3)
2,3,7,8-TCDD	0/3	0.0070	0	0/3	0.0070	0
1,2,3,7,8-PeCDD	0/3	0.0070	0	1/3	0.17	0.16
1,2,3,4,7,8-HxCDD	0/3	0.0070	0	3/3	0.24	0.24
1,2,3,6,7,8-HxCDD	1/3	0.015	0.010	3/3	0.39	0.39
1,2,3,7,8,9-HxCDD	1/3	0.015	0.010	2/3	0.062	0.060
1,2,3,4,6,7,8-HpCDD	3/3	0.41	0.41	2/3	2.0	2.0
OCDD	15/16	1.1	1.1	14/14	3.0	3.0
2,3,7,8-TCDF	0/3	0.090	0.090	3/3	1.5	1.5
1,2,3,7,8-PeCDF	0/3	0.0050	0	3/3	0.25	0.25
2,3,4,7,8-PeCDF	0/3	0.0070	0	2/3	0.69	0.68
1,2,3,4,7,8-HxCDF	1/3	0.023	0	2/3	0.11	0.11
1,2,3,6,7,8-HxCDF	1/3	0.010	0.010	3/3	0.45	0.45
2,3,4,6,7,8-HxCDF	1/3	0.018	0.010	1/3	0.76	0.76
1,2,3,7,8,9-HxCDF	0/3	0.0070	0	1/3	0.038	0.038
1,2,3,4,6,7,8-HpCDF	1/3	0.053	0.050	3/3	2.1	2.1
OCDF	12/16	0.089	0.071	8/15	0.62	0.59
TOTAL I-TEQ_{DF}	--	0.038	0.019	--	0.84	0.83
TOTAL TEQ_{DF}-WHO_{98}	--	0.041	0.020	--	0.92	0.91

[a] Nondetects assumed to be one-half the detection limit in calculating the mean.
[b] Nondetects assumed to be zero in calculating the mean.

Source: Smith et al. (1989).

Table 3-2. Congener-Specific, Homologue, Total, and TEQ Concentrations for the Four Clusters of Air Samples (pg/m^3)

Congener	1994 Impacted Air (n = 2)	1994 Urban (n = 8)	1995 Urban (n = 6)	Rural (n = 3)
2,3,7,8-TCDD	0.019	0.003	0.007	0.003
1,2,3,7,8-PCDD	0.062	0.012	0.008	0.005
1,2,3,4,7,8-HxCDD	0.081	0.017	0.011	0.008
1,2,3,6,7,8-HxCDD	0.095	0.028	0.024	0.009
1,2,3,7,8,9-HxCDD	0.086	0.029	0.020	0.013
1,2,3,4,6,7,8-HpCDD	0.633	0.248	0.205	0.227
OCDD	1.765	1.062	0.807	0.904
2,3,7,8-TCDF	0.051	0.012	0.017	0.003
1,2,3,7,8-PCDF	0.121	0.024	0.022	0.007
2,3,4,7,8-PCDF	0.169	0.028	0.020	0.010
1,2,3,4,7,8-HxCDF	0.205	0.038	0.063	0.014
1,2,3,6,7,8-HxCDF	0.302	0.056	0.058	0.016
1,2,3,7,8,9-HxCDF	0.006	0.003	0.003	0.003
2,3,4,6,7,8-HxCDF	0.189	0.033	0.027	0.009
1,2,3,4,6,7,8-HpCDF	0.939	0.165	0.165	0.061
1,2,3,4,7,8,9-HpCDF	0.131	0.027	0.038	0.014
OCDF	0.411	0.124	0.159	0.067
TCDD	0.761	0.097	0.110	0.015
PCDD	0.939	0.158	0.082	0.027
HxCDD	1.193	0.331	0.252	0.188
HpCDD	1.290	0.533	0.416	0.494
TCDF	1.793	0.374	0.378	0.083
PCDF	2.373	0.420	0.294	0.122
HxCDF	2.044	0.363	0.361	0.134
HpCDF	1.542	0.287	0.325	0.144
TOTAL	14.11	3.75	3.18	2.18
I-TEQ_{DF}	0.26	0.050		0.022
TEQ_{DF}-WHO_{98}	0.29	0.055		0.024

Note: Non-detects assumed to be one-half the detection limit.
Source: OEPA (1995).

Table 3-3. Background Air Concentrations of CDD/CDFs at Mohawk Mountain, Connecticut

Parameter	Sample Period			
	Oct. 29-Nov. 29, 1993 (pg/m^3)	Jan. 20-Feb. 18, 1994 (pg/m^3)	Apr. 26-May 26, 1994 (pg/m^3)	Jul. 26-Aug. 25, 1994 (pg/m^3)
2,3,7,8-TCDD	0.001	(0.000)	(0.001)	(0.000)
Total TCDD	0.032	0.017	0.012	0.007
1,2,3,7,8-PeCDD	0.004	0.002	0.002	(0.001)
Total PeCDD	0.043	0.027	0.022	0.009
1,2,3,4,7,8-HxCDD	0.007	0.004	0.002	(0.001)
1,2,3,6,7,8-HxCDD	0.010	0.005	0.003	0.002
1,2,3,7,8,9-HxCDD	0.011	0.005	0.002	(0.001)
Total HxCDD	0.122	0.072	0.032	0.020
1,2,3,4,6,7,8-HpCDD	0.159	0.065	0.029	0.016
Total HpCDD	0.317	0.133	0.061	0.033
OCDD	0.451	0.196	0.155	0.056
2,3,7,8-TCDF	0.004	0.003	0.002	0.004
Total TCDF	0.134	0.090	0.095	0.112
1,2,3,7,8-PeCDF	0.004	0.003	0.003	0.003
2,3,4,7,8-PeCDF	0.006	0.005	0.004	0.004
Total PeCDF	0.078	0.057	0.057	0.073
1,2,3,4,7,8-HxCDF	0.008	0.008	0.004	0.004
1,2,3,6,7,8-HxCDF	0.007	0.006	0.003	0.004
2,3,4,6,7,8-HxCDF	0.009	0.008	0.004	0.004
1,2,3,7,8,9-HxCDF	0.004	0.003	0.001	(0.001)
Total HxCDF	0.078	0.060	0.041	0.041
1,2,3,4,6,7,8-HpCDF	0.035	0.028	0.012	0.016
1,2,3,4,7,8,9-HpCDF	0.006	0.005	0.001	0.002
Total HpCDF	0.070	0.049	0.020	0.029
OCDF	0.028	0.027	0.011	0.011

( ) = Parameter not detected at the indicated detection limit.

Source: CDEP (1995).

Table 3-4. Ambient Air Concentrations Near a Roadway in Phoenix, Arizona

Parameter	Average I-TEQ_{DF} (pg/m^3)	Average TEQ_{DF}-WHO_{98}
2,3,7,8-TCDD	0.0077	0.0077
1,2,3,7,8-PeCDD	0.0254	0.0508
1,2,3,4,7,8-HxCDD	0.0096	0.0096
1,2,3,6,7,8-HxCDD	0.0220	0.0220
1,2,3,7,8,9-HxCDD	0.0182	0.0182
1,2,3,4,6,7,8-HpCDD	0.0295	0.0295
OCDD	0.0096	0.00096
2,3,7,8-TCDF	0.0033	0.0033
1,2,3,7,8-PeCDF	0.0026	0.0026
2,3,4,7,8-PeCDF	0.0562	0.0562
1,2,3,4,7,8-HxCDF	0.0147	0.0147
1,2,3,6,7,8-HxCDF	0.0127	0.0127
2,3,4,6,7,8-HxCDF	0.0215	0.0215
1,2,3,7,8,9-HxCDF	0.0078	0.0078
1,2,3,4,6,7,8-HpCDF	0.0076	0.0076
1,2,3,4,7,8,9-HpCDF	0.0010	0.0010
OCDF	0.0003	0.00003
TOTAL TEQ	0.2499	0.2664

Source: Hunt et al. (1997).

Table 3-5. Average Dioxin/Furan/PCB Concentrations at Nine NDAMN Sites, Collected for Six Sampling Moments (n = 53)

Parameter	Mean Concentration (pg/m^3)	
	ND = zero	ND = ½ DL
Dioxins		
2,3,7,8-TCDD	0.00070	0.00071
1,2,3,7,8-PeCDD	0.0040	0.0041
1,2,3,4,7,8-HxCDD	0.0053	0.0053
1,2,3,6,7,8-HxCDD	0.010	0.010
1,2,3,7,8,9-HxCDD	0.0096	0.0096
1,2,3,4,6,7,8-HpCDD	0.13	0.14
OCDD	0.45	0.45
Furans		
2,3,7,8-TCDF	0.0017	0.0017
1,2,3,7,8-PeCDF	0.0019	0.0019
2,3,4,7,8-PeCDF	0.0032	0.0032
1,2,3,4,7,8-HxCDF	0.0038	0.0038
1,2,3,6,7,8-HxCDF	0.0035	0.0035
2,3,4,6,7,8-HxCDF	0.0045	0.0045
1,2,3,7,8,9-HxCDF	0.0014	0.0014
1,2,3,4,6,7,8-HpCDF	0.020	0.020
1,2,3,4,7,8,9-HpCDF	0.0026	0.0026
OCDF	0.017	0.017
Total Concentration (pg/m^3)	0.68	0.68
Total Concentration (pg TEQ/m^3)	0.012	0.012
Congener Groups		
Total TCDF	0.068	0.068
Total TCDD	0.017	0.017
Total PCDF	0.041	0.041
Total PCDD	0.033	0.033
Total HxCDF	0.047	0.047
Total HxCDD	0.13	0.13
Total HpCDF	0.035	0.035
Total HpCDD	0.30	0.30
Total CDD/CDF (pg/m^3)	0.67	0.67
PCB 77	0.053	0.053
PCB 118	0.82	0.82
PCB 105	0.30	0.30
PCB 126	0.0055	0.0055
PCB 156	0.049	0.049
PCB 157	0.011	0.011
PCB 169	0.00060	0.00062
Total PCBs (pg/m^3)	1.2	1.2
Total Concentration (pg TEQ/m^3)	0.00071	0.00071

Table 3-6. Annual Mean PCB Concentrations in Ambient Air, Ontario, Canada (pg/m^3)

PCB Congener	No. of Positive Samples	Annual Mean Concentration (pg/m^3)
105	63/143	0.16
114	79/143	1.2
118	122/142	2.3
156	13/143	0.07
170	53/143	0.48
180	111/143	1.1
189	3/143	0.01
TOTAL TEQ_{DF}-WHO_{94}	--	0.00094
TOTAL TEQ_{DF}-WHO_{98}	--	0.00088

Source: Hoff et al. (1992).

Table 3-7. Annual Average Dioxin-Like PCB Concentrations in Ambient Air in Germany (pg/m^3)

	Köln	Duesburg[a]	Essen	Dortmund
PCB 77	3.0	4.5-4.8	2.6	4.5
PCB 126	0.27	0.50-0.62	0.24	0.48
PCB 169	0.02	0.05	0.06	0.07
TOTAL (77 + 126 + 169)	3.3	5.2-5.4	2.9	5.1

[a] Two sites were sampled at this location.

Source: Hiester et al. (1995).

Table 3-8. Mean Background CDD/CDF Profiles for Air

2,3,7,8-Substituted CDD/CDFs	Rural Background[a]		Urban Background[b]		CDD/CDF Homologue Group	Rural Background[a]		Urban Background[c]	
	Concentration (pg/m^3)	Fraction of Total CDD/CDFs	Concentration (pg/m^3)	Fraction of Total CDD/CDFs		Concentration (pg/m^3)	Fraction of Total CDD/CDFs	Concentration (pg/m^3)	Fraction of Total CDD/CDFs
2,3,7,8-TCDD	0.00059	0.00050	0.00065	0.00012	TCDD	0.016	0.014	0.017	0.0030
1,2,3,7,8-PeCDD	0.0038	0.0032	0.0039	0.00071	PeCDD	0.032	0.026	0.041	0.0075
1,2,3,4,7,8-HxCDD	0.0051	0.0043	0.011	0.0020	HxCDD	0.13	0.11	0.23	0.042
1,2,3,6,7,8-HxCDD	0.0092	0.0077	0.025	0.0046	HpCDD	0.30	0.25	0.89	0.16
1,2,3,7,8,9-HxCDD	0.0090	0.0075	0.028	0.0051	OCDD	0.47	0.39	1.9	0.34
1,2,3,4,6,7,8-HpCDD	0.14	0.11	0.56	0.10	TCDF	0.073	0.061	1.2	0.22
OCDD	0.47	0.39	1.9	0.34	PeCDF	0.050	0.042	0.69	0.13
2,3,7,8-TCDF	0.0017	0.0014	0.22	0.040	HxCDF	0.055	0.046	0.28	0.052
1,2,3,7,8-PeCDF	0.0022	0.0019	0.057	0.010	HpCDF	0.045	0.038	0.18	0.032
2,3,4,7,8-PeCDF	0.0038	0.0032	0.021	0.0039	OCDF	0.022	0.018	0.091	0.017
1,2,3,4,7,8-HxCDF	0.0045	0.0037	0.044	0.0080					
1,2,3,6,7,8-HxCDF	0.0041	0.0034	0.067	0.012					
1,2,3,7,8,9-HxCDF	0.0013	0.0011	0.00077	0.00014					
2,3,4,6,7,8-HxCDF	0.0048	0.0040	0.020	0.0037					
1,2,3,4,6,7,8-HpCDF	0.024	0.020	0.13	0.023					
1,2,3,4,7,8,9-HpCDF	0.0035	0.0029	0.0070	0.0013					
OCDF	0.022	0.018	0.092	0.017					
TOTAL	0.71	0.59	3.1	0.57	TOTAL	1.2	1.000	5.4	1.0

NOTE: Non-detects are assumed to be zero.

[a] Based on data from OEPA (1995) CDEP (1988), and Cleverly et al. (2000).
[b] Based on data from CDEP (1988, 1995); Smith et al. (1989); Maisel and Hunt (1990); Hunt et al. (1990); and OEPA (1995).
[c] Based on data from CDEP (1988, 1995); Smith et al. (1989, 1990a); Maisel and Hunt (1990); Hunt et al. (1990); and OEPA (1995).

See Table 3-8 for sampling locations and numbers of samples from these studies.

Table 3-9. TEQ_{DF}-WHO_{98} Concentrations of CDD/CDFs in Air in the United States (pg/m^3)
(ND = 1/2 LOD)

Reference	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	2,3,7,8-HxCDDs	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PeCDF	2,3,4,7,8-PeCDF	2,3,7,8-HxDCFs	2,3,7,8-HpCDFs	OCDF	Total
RURAL BACKGROUND												
CDEP, 1995 Mohawk Mt., CT (n = 4)	0.00038	0.0021	0.0013	0.00067	0.000021	0.00033	0.00016	0.0024	0.0019	0.00026	0.0000019	0.010
Ohio EPA, 1995 Rural Ohio (n = 3)	0.0029	0.0052	0.0031	0.0023	0.000090	0.00028	0.00033	0.0048	0.0041	0.00076	0.0000067	0.024
Cleverly et al., 2000 Arkadelphia, AR (n = 6)	0.00050	0.0027	0.0019	0.0010	0.000046	0.00012	0.000050	0.00082	0.00075	0.00013	0.0000012	0.008
Cleverly et al., 2000 Bixby, OK (n = 5)	0.00074	0.0047	0.0026	0.0013	0.000045	0.00028	0.00016	0.0024	0.0020	0.00032	0.0000021	0.015
Cleverly et al., 2000 Clinton Crops, NC (n = 4)	0.00045	0.0029	0.0016	0.00072	0.000024	0.00029	0.00014	0.0025	0.0021	0.00032	0.0000027	0.011
Cleverly et al., 2000 Everglades, FL (n = 4)	0.00030	0.0013	0.0012	0.00087	0.000034	0.000069	0.000039	0.00071	0.00062	0.00011	0.00000076	0.005
Cleverly et al., 2000 Lake Dubay, WI (n = 6)	0.00043	0.0025	0.0018	0.0010	0.000033	0.00016	0.000096	0.0018	0.0014	0.00022	0.0000017	0.009
Cleverly et al., 2000 Lake Scott, KS (n = 6)	0.00033	0.0015	0.0010	0.00057	0.000024	0.000040	0.000023	0.00039	0.00034	0.000057	0.00000047	0.004
Cleverly et al., 2000 McNay, IA (n = 6)	0.0012	0.0058	0.00032	0.0017	0.000061	0.00012	0.000086	0.0015	0.0012	0.00026	0.0000021	0.015
Cleverly et al., 2000 Monmouth, IL (n = 4)	0.0012	0.0088	0.0065	0.0036	0.000097	0.00024	0.00015	0.0025	0.0020	0.00037	0.0000027	0.026
Cleverly et al., 2000 Penn Nursery, PA (n = 12)	0.0011	0.0064	0.0026	0.0013	0.000043	0.00023	0.00012	0.0018	0.0015	0.00027	0.0000019	0.015
MEAN	0.00087	0.0040	0.024	0.0014	0.000047	0.00020	0.00012	0.0020	0.0016	0.00028	0.0000022	0.0129
SD	0.00073	0.0023	0.0015	0.00085	0.000025	0.000094	0.000079	0.0011	0.0010	0.00018	0.0000016	--
WEIGHTED MEAN	0.00084	0.0042	0.0024	0.0013	0.000045	0.00019	0.00011	0.0018	0.0015	0.00026	0.0000020	0.0126

Table 3-9. TEQ_{DF}-WHO_{98} Concentrations of CDD/CDFs in Air in the United States (pg/m^3) (continued)
(ND = 1/2 LOD)

Reference	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	2,3,7,8-HxCDDs	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7, 8-PeCDF	2,3,4,7, 8-PeCDF	2,3,7,8-HxDCFs	2,3,7,8-HpCDFs	OCDF	Total
URBAN BACKGROUND												
CDEP, 1988 Wallingford, CT (n = 28)	0.0019	0.0063	0.0086	0.0029	0.00055	0.0072	0.00039	0.010	0.012	0.0029	0.000022	0.053
CDEP, 1995 Connecticut (n = 20)	0.00012	0.0063	0.0036	0.0014	0.000044	0.00093	0.00046	0.0080	0.0065	0.00081	0.0000055	0.029
Hunt and Maisel, 1990 Bridgeport, CT (n = 7)	0.012	0.024	0.015	0.0048	0.00021	0.0078	0.0016	0.024	0.024	0.0025	0.000021	0.115
Hunt et al., 1990 W. Long Beach, CA (n = 2)	0.0075	0.032	0.0046	0.0034	0.00029	0.025	0.00078	0.00275	0.012	0.00081	0.000037	0.088
Hunt et al., 1990 Reseda, CA (n = 7)	0.0080	0.034	0.026	0.024	0.00054	0.0028	0.0016	0.015	0.026	0.0024	0.000012	0.140
Hunt et al., 1990 San Bernadino, CA (n = 5)	0.013	0.12	0.015	0.0059	0.00031	0.0038	0.020	0.019	0.028	0.0029	0.000016	0.232
Hunt et al., 1990 El Toro, CA (n = 7)	0.010	0.018	0.0075	0.0014	0.00011	0.0015	0.0017	0.018	0.016	0.00098	0.0000076	0.076
Hunt et al., 1990 N. Long Beach, CA (n = 6)	0.013	0.017	0.020	0.0079	0.00014	0.0018	0.0019	0.020	0.023	0.0031	0.000015	0.110
Maisel and Hunt, 1990 Los Angeles, CA (n = 1)	0.0048	0.020	0.012	0.0025	0.00019	0.0021	0.0039	0.034	0.048	0.0010	0.0000056	0.132
Ohio EPA, 1995 Franklin Co., OH (n = 14)	0.0048	0.010	0.0066	0.0023	0.00010	0.0014	0.0012	0.012	0.014	0.0020	0.000014	0.055
Smith et al., 1989 Niagra Falls, NY (n = 3)	0.0070	0.0070	0.0037	0.0041	0.00011	0.0090	0.00025	0.0035	0.0058	0.00053	0.0000089	0.041
Smith et al., 1990a Albany, NY (n = 3)	0.048				0.000057	0.094					0.000028	0.142
Smith et al., 1990a Binghampton, NY (n = 1)	0.030				0.00014	0.018					0.000015	0.048
Smith et al., 1990a Utica, NY (n = 2)	0.058				0.00012	0.12					0.000031	0.173
MEAN	0.016	0.027	0.011	0.0055	0.00021	0.021	0.0031	0.015	0.020	0.0018	0.000017	0.120
SD	0.017	0.032	0.007	0.0063	0.00016	0.035	0.0054	0.010	0.011	0.00094	0.0000093	
WEIGHTED MEAN	0.008	0.018	0.010	0.0045	0.00026	0.009	0.0019	0.013	0.015	0.0020	0.000015	0.081

Table 3-10. Mean PCDD and PCDF Concentrations in Canadian Soil from 1987 (ppt)[a]

Homologue Group	Soil Near Sludge Incinerator (n = 12)	Urban Background (n = 11)	Rural Background (n = 26)
TCDDs	69 (ND-430)	ND	ND
PeCDDs	81 (ND-540)	ND	ND
HxCDDs	9 (ND-70)	ND	ND
HpCDDs	43 (ND-300)	31 (ND-140)	ND
OCDDs	570 (ND-1,500)	1,461 (ND-11,000)	30 (ND-100)
Total CDDs	772 (ND-2,770)	1,492 (ND-11,140)	30 (ND-100)
TCDFs	ND	29 (ND-120)	ND
PeCDFs	ND	1 (ND-10)	ND
HxCDFs	ND	7 (ND-35)	ND
HpCDFs	ND	9 (ND-60)	ND
OCDFs	43 (ND-230)	16 (ND-160)	ND
Total CDFs	43 (ND-230)	65 (ND-262)	ND

[a] Data collected in 1987 in Ontario Canada; range presented in parentheses.

Source: Pearson et al. (1990).

Table 3-11. Dioxin/Furan Levels in Four Background Soil Samples from Elk River, Minnesota (ppt)[a]

Congener	Tilled (n = 2)	Untilled (n = 2)
2,3,7,8-TCDD	ND	ND
Total TCDD	ND	ND
1,2,3,7,8-PeCDD	ND	ND
Total PeCDD	ND-38	ND
1,2,3,4,7,8-HxCDD	ND	ND
1,2,3,6,7,8-HxCDD	ND	ND-14
1,2,3,7,8,9-HxCDD	ND-8.7	ND-9.9
Total HxCDD	12-99	29-53
1,2,3,4,6,7,8-HpCDD	37-360	78-300
Total HpCDD	62-640	150-530
OCDD	340-3300	680-2300
2,3,7,8-TCDF	ND	ND
Total TCDF	ND-1.2	ND
1,2,3,7,8-PeCDF	ND	ND
2,3,4,7,8-PeCDF	ND	ND
Total PeCDF	ND-41	18-45
1,2,3,4,7,8-HxCDF	ND	ND
1,2,3,6,7,8-HxCDF	ND	ND
2,3,4,6,7,8-HxCDF	ND	ND-7.1
1,2,3,7,8,9-HxCDF	ND	ND
Total HxCDF	6.7-86	20-150
1,2,3,4,6,7,8-HpCDF	11-80	26-72
1,2,3,4,7,8,9-HpCDF	ND	ND
Total HpCDF	30-260	30-82
OCDF	ND-270	60-120

[a] ND = Nondetected. Detection limits vary from 0.75 ppt to 2.9 ppt on a congener-specific basis.

Source: Reed et al. (1990).

Table 3-12. Dioxin/Furan Levels in British Columbia Soils

Sample Category[a]	Dioxin and Furan Concentrations (pg/g)[b]		I-TEQ_{DF} (pg/g)[b,c]	
	Range	Mean[d]	Range	Mean[d]
Background Soil • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND[e] ND - 32.0	 ND (53) 3.2 (53)	0.0 - 57.0	5.0 (53)[f]
Primary Soil (all sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND - 85.0 ND - 520.0	 5.2 (31) 47.9 (31)	0.0 - 2580.0	252.3 (31)
Primary Soil (chemical sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND - 85.0 ND - 520.0	 8.4 (18) 60.3 (18)	0.0 - 2580.0	418.5 (18)
Primary Soil (combustion sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND - 3.5 ND - 160.0	 0.8 (13) 30.7 (13)	0.0 - 125.7	22.3 (13)
Secondary Soil (all sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND - 550.0 ND - 550.0	 5.4 (137) 25.1 (137)	0.0 - 18721.8	241.7 (137)
Secondary Soil (chemical sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND - 550.0 ND - 550.0	 15.4 (47) 60.7 (47)	0.0 - 18721.8	668.6 (47)
Secondary Soil (combustion sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	 ND - 5.6 ND - 180.0	 0.09 (90) 6.5 (90)	0.0 - 472.6	18.7 (90)

[a] Background samples were believed to be indicative of ambient levels of dioxins and furans in the environment. Primary samples were collected immediately at a potential source of contamination. Secondary samples were collected from areas directly impacted by the primary source and could be used to indicate movement of contaminants.

[b] Concentrations in picograms/gram (pg/g) dry weight.

[c] I-TEQ_{DF}s are the sum of seventeen 2,3,7,8-substituted dioxins and furans after the concentration of each individual dioxin or furan is multiplied by its International Toxicity Equivalency Factor (I-TEF_{DF}). For samples with nondetected levels of a dioxin or furan, zero was used as the concentration for the I-TEQ_{DF} calculation.

[d] Numbers in parentheses indicate the number of samples (n) used to calculate mean.

[e] ND = Not Detected.

[f] When the total TEQ was recalculated using TEF_{DF}-WHO_{98}s, the TEQ_{DF}-WHO_{98} was 4.4 pg/g.

Source: BC Environment (1995).

Table 3-13 Number of Positive Soil Samples and CDD/CDF Concentrations in Background, Urban, and Impacted Sites Near a Waste-to-Energy Facility in Ohio

	Background		Urban		Impacted	
	No. of Positive Samples	Mean Conc. (ppt) (nondetects = ½ LOD)	No. of Positive Samples	Mean Conc. (ppt) (nondetects = ½ LOD)	No. of Positive Samples	Mean Conc. (ppt) (nondetects = ½ LOD)
2,3,7,8-TCDD	2/3	0.39	15/18	2.27	3/3	28.5
1,2,3,7,8-PeCDD	0/3	0.14	18/18	6.58	3/3	180.0
1,2,3,4,7,8-HxCDD	1/3	0.35	18/18	6.14	3/3	142.3
1,2,3,6,7,8-HxCDD	3/3	0.82	18/18	10.9	3/3	137.8
1,2,3,7,8,9-HxCDD	3/3	1.23	18/18	10.8	3/3	201.6
1,2,3,4,6,7,8-HpCDD	3/3	17.7	18/18	190.1	3/3	765.2
OCDD	3/3	160.9	18/18	1560.2	3/3	1495.4
2,3,7,8-TCDF	0/3	0.45	18/18	4.12	3/3	85.9
1,2,3,7,8-PeCDF	0/3	0.17	17/18	5.50	3/3	139.6
2,3,4,7,8-PeCDF	1/3	0.21	17/18	7.56	3/3	199.9
1,2,3,4,7,8-HxCDF	1/3	0.19	15/18	8.06	3/3	196.8
1,2,3,6,7,8-HxCDF	3/3	0.52	17/18	8.12	3/3	209.1
1,2,3,7,8,9-HxCDF	0/3	0.15	6/18	0.51	3/3	11.6
2,3,4,6,7,8-HxCDF	3/3	0.64	18/18	6.99	3/3	156.7
1,2,3,4,6,7,8-HpCDF	3/3	4.06	18/18	41.7	3/3	641.0
1,2,3,4,7,8,9-HpCDF	1/3	0.27	16/18	3.82	3/3	57.9
OCDF	3/3	10.72	18/18	44.3	3/3	184.5
Mean Total I-TEQ_{DF}, ppt (nondetects = ½ LOD)	--	1.4	--	19.2	--	356.0
Mean Total I-TEQ_{DF}, ppt (nondetects = 0)	--	1.1	--	19.2	--	356.0
Mean Total TEQ_{DF}-WHO_{98}, ppt (nondetects = ½ LOD)	--	1.3	--	21.0	--	444.5
Mean Total TEQ_{DF}-WHO_{98}, ppt (nondetects = 0)	--	0.92	--	21.0	--	444.5

Table 3-14. Mean Background CDD/CDF Profiles for Soil

2,3,7,8-Substituted CDD/CDFs	Rural Background[a]		Urban Background[b]		CDD/CDF Homologue Groups	Rural Background[c]		Urban Background[d]	
	Concentration (ppt)	Fraction of Total CDD/CDFs	Concentration (ppt)	Fraction of Total CDD/CDFs		Concentration (ppt)	Fraction of Total CDD/CDFs	Concentration (ppt)	Fraction of Total CDD/CDFs
2,3,7,8-TCDD	0.017	0.00019	0.87	0.00027	TCDD	2.1	0.0031	32	0.012
1,2,3,7,8-PeCDD	0.28	0.00030	2.4	0.00077	PeCDD	3.9	0.0057	19	0.0074
1,2,3,4,7,8-HxCDD	0.53	0.00057	2.7	0.00086	HxCDD	21	0.030	34	0.013
1,2,3,6,7,8-HxCDD	3.7	0.0039	5.3	0.0017	HpCDD	96	0.14	170	0.068
1,2,3,7,8,9-HxCDD	2.4	0.0025	5.1	0.0016	OCDD	470	0.68	2,100	0.83
1,2,3,4,6,7,8-HpCDD	72	0.077	99	0.031	TCDF	7.3	0.011	37	0.014
OCDD	630	0.68	2,700	0.86	PeCDF	10	0.015	37	0.014
2,3,7,8-TCDF	1.3	0.0014	2.3	0.00073	HxxCDF	18	0.027	22	0.0085
1,2,3,7,8-PeCDF	0.34	0.00037	1.8	0.00058	HpCDF	31	0.046	41	0.016
2,3,4,7,8-PeCDF	0.52	0.00056	3.2	0.0010	OCDF	28	0.041	36	0.014
1,2,3,4,7,8-HxCDF	1.0	0.0011	4.0	0.0013					
1,2,3,6,7,8-HxCDF	0.66	0.00071	3.6	0.0011					
1,2,3,7,8,9-HxCDF	0.40	0.00043	0.75	0.00024					
2,3,4,6,7,8-HxCDF	0.77	0.00083	2.6	0.00080					
1,2,3,4,6,7,8-HpCDF	18	0.019	17	0.0053					
1,2,3,4,7,8,9-HpCDF	0.59	0.00064	1.5	0.00046					
OCDF	40	0.043	23	0.0073					
TOTAL	770	0.83	2,900	0.91	TOTAL	680	1.00	2,600	1.00

[a] Based on data from Reed et al. (1990), BC Environment (1995), U.S. EPA (1996), MRI (1992), Tewhey Associates (1997), Rogowski et al. (1999), and Rogowski and Yake (1999)..

[b] Based on data from U.S. EPA (1996) NIH (1995); and Rogowski et al (1999).

[c] Based on data from Reed et al. (1990), Birmingham (1990), Pearson et al. (1990), BC Environment (1995), U.S. EPA (1985), U.S. EPA

Table 3-15. TEQ_{DF}-WHO_{98} Concentrations of CDD/CDFs in North American Soil (ppt)
(nondetects = 0)

Reference	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	2,3,7,8-HxCDDs	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PeCDF	2,3,4,7,8-PeCDF	2,3,7,8-HxDCFs	2,3,7,8-HpCDFs	OCDF	Total
RURAL BACKGROUND												
BC Environment, 1995 British Columbia (n=53) background	0	0.16	1.7	1.4	0.068	0.32	0.016	0.090	0.22	0.44	0.0077	4.41
Birmingham, 1990 Ontario (n=30) rural, background	--	--	--	--	0.070	--	--	--	--	--	0	--
MRI, 1992* Connecticut (n=34) background	0.61	0.87	0.67	0.55	0.081	0.48	0.090	1.2	1.0	0.18	0.0026	5.74
Pearson et al., 1990 Ontario (n=43) rural, background	--	--	--	--	0.0038	--	--	--	--	--	0	--
Reed et al., 1990 Minnesota (n=4) semi-rural, background	0	0	0.82	1.9	0.17	0	0	0	0.18	0.47	0.011	3.58
Rogowski and Yake, 1999 Washington (n=54) agricultural	0	0	0.014	0.029	0.0024	0.025	0.0011	0.0078	0.023	0.011	0.00062	0.12
Rogowski et al., 1999 Washington (n=16) rangeland and forest	0.024	0.52	0.55	0.20	0.012	0.067	0.0031	0.27	0.14	0.02	0.00056	1.8
Tewhey Associates, 1997 Maine (n=8) background	0.28	0.43	0.65	0.70	0.097	0.040	0.010	0.25	0.28	0.15	0.0040	2.89
U.S. EPA, 1985 Illinois (n=13) residential, background	0.15	--	--	--	--	--	--	--	--	--	--	--
U.S. EPA, 1985 Minnesota (n=4) natural, background	0	--	--	--	--	--	--	--	--	--	--	--
U.S. EPA, 1985 Ohio (n=22) residential, background	1.1	--	--	--	--	--	--	--	--	--	--	--
U.S. EPA, 1985 Ohio (n=5) residential, background	--	--	--	--	0.24	--	--	--	--	--	0	--
U.S. EPA, 1985 Minnesota (n=3) natural, background	--	--	--	--	0.014	--	--	--	--	--	0	--

Table 3-15. TEQ_{DF}-WHO_{98} Concentrations of CDD/CDFs in North American Soil (ppt) (continued)
(nondetects = 0)

Reference	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	2,3,7,8-HxCDDs	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PeCDF	2,3,4,7,8-PeCDF	2,3,7,8-HxDCF	2,3,7,8-HpCDFs	OCDF	Total
U.S. EPA, 1996 Ohio (n=3) background	0.30	0	0.23	0.18	0.016	0	0	0.028	0.12	0.042	0.0011	0.92
U.S. EPA, 2000b Colorado (n=62) agricultural, open space	0.027	0.27	0.19	0.25	0.016	0	0.0077	0.25	0.14	0.036	0.00087	1.2
MEAN	0.23	0.28	0.60	0.66	0.060	0.12	0.016	0.26	0.27	0.17	0.0024	2.7
S.D.	0.33	0.29	0.48	0.64	0.073	0.17	0.028	0.36	0.30	0.18	0.0034	
WEIGHTED MEAN	0.19	0.28	0.61	0.55	0.038	0.15	0.019	0.29	0.27	0.15	0.0022	2.6
URBAN BACKGROUND												
Birmingham, 1990 Ontario (n=47) urban, background	--	--	--	--	0.16	--	--	--	--	--	0.0059	--
Nestrick et al., 1986 Michigan (n=20) urban/indus. bckgrd.	2.1	--	--	--	--	--	--	--	--	--	--	--
NIH, 1995 Maryland (n=37) urban	0.056	0.098	0.34	0.60	0.63	0.028	0.0070	0.14	0.27	0.039	0.00067	2.21
Pearson et al., 1990 Ontario (n=29) urban, background	--	--	--	--	0.25	--	--	--	--	--	0.0050	--
Rogowski et al., 1999 Washington (n=14) urban	0.35	0.71	0.77	0.48	0.033	0.30	0	0.93	0.44	0.061	0.0019	4.1
U.S. EPA, 1985 Michigan (n=6) public areas	--	--	--	--	0.51	--	--	--	--	--	0.032	--
U.S. EPA, 1996 Ohio (n=18) urban	2.2	6.5	2.8	1.90	0.16	0.37	0.27	3.8	2.6	0.45	0.0044	21.0
U.S. EPA, 2000b Colorado (n=99) commercial, industrial, residential background	0.86	1.8	1.7	1.8	0.089	0	0.043	1.1	0.84	0.36	0.0073	8.6
MEAN	1.1	2.3	1.4	1.2	0.26	0.17	0.079	1.5	1.0	0.23	0.0082	9.3
S.D.	0.89	2.5	0.95	0.65	0.21	0.16	0.11	1.4	0.90	0.18	0.010	--
WEIGHTED MEAN	0.92	1.8	1.4	1.4	0.28	0.046	0.056	1.1	0.83	0.27	0.0062	8.0

* Calculated using nondetects = ½ LOD. Proportion of nondetects ranged from 3 to 11 percent of samples per each analyte, with the exception of 2,3,7,8-TCDD and 1,2,3,7,8-HxCDF, which had 56 and 49 percent nondetects, respectively.

Table 3-16. CDD/CDF Levels in British Columbia Sediments

Sample Category[a]	Dioxin and Furan Concentrations (pg/g)[b]		I-TEQ_{DF}s (pg/g)[b,c]	
	Range	Mean[d]	Range	Mean[d]
Background Sediment • 2,3,7,8-TCDD • 2,3,7,8-TCDF	ND[e] ND - 17.0	ND (12) 1.4 (12)	0.0 - 24.4	3.9 (12)
Secondary Sediment (all sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	ND - 2.7 ND - 33.0	0.2 (21) 3.5 (21)	0.0 - 172.0	32.5 (21)
Secondary Sediment (chemical sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	ND - 2.7 ND - 33.0	0.2 (14) 3.8 (14)	0.0 - 172.0	42.1 (14)
Secondary Sediment (combustion sources) • 2,3,7,8-TCDD • 2,3,7,8-TCDF	ND - 1.1 ND - 12.0	0.2 (7) 3.0 (7)	0.0 - 63.6	13.2 (7)

[a] Background samples were believed to be indicative of ambient levels of dioxins and furans in the environment. Secondary samples were collected from areas directly impacted by the primary source, and could be used to indicate movement of contaminants.

[b] Concentrations in picograms/gram (pg/g) dry weight.

[c] I-TEQ_{DF}s are the sum of 17 2,3,7,8-substituted dioxins and furans after the concentration of each individual dioxin or furan is multiplied by its International Toxicity Equivalency Factor (I-TEF_{DF}). For samples with nondetected levels of a dioxin or furan, zero was used as the concentration for the I-TEQ_{DF} calculation.

[d] Numbers in parentheses indicate the number of samples (n) used to calculate mean.

[e] ND = Not Detected.

Source: BC Environment (1995).

Table 3-17. TEQ_{DF} Concentrations (ppt) and Ratios of 2,3,7,8-Substituted CDD/CDF Concentrations to Total CDD/CDF Concentrations for the Most Recent Sediment Core Sampling Periods for 11 U.S. Lakes

Lake	I-TEQ_{DF} (ppt)		TEQ_{DF}-WHO_{98} (ppt)		Ratio of 2,3,7,8-CDD/CDFs to Total CDD/CDFs		Range of Dates Represented by Uppermost Core Section
	n = ½ LOD	nd = 0	n = ½ LOD	nd = 0	n = ½ LOD	nd = 0	
Chandler Lake, AK	0.11	0.11	0.12	0.12	0.47	0.47	1956-1993
Canandaigua Lake, NY	15.0	14.3	16.3	15.5	0.66	0.63	1981-1991
Skaneateles Lake, NY	10.1	9.1	10.8	9.7	0.73	0.71	1984-1991
Great Sacandaga Reservoir, NY	6.4	4.9	6.1	4.8	0.75	0.49	1974-1983
Santeetlah Reservoir, NC	15.6	13.1	15.4	13.0	0.70	0.64	1974-1983
Blue Ridge Reservoir, GA	5.6	4.8	4.9	4.2	0.75	0.71	1974-1983
Deer Creek Reservoir, UT	1.2	1.0	1.0	0.83	0.86	0.85	1973-1982
Echo Lake, UT	0.82	0.68	0.67	0.50	0.91	0.90	1973-1982
Panguitch Lake, UT	0.91	0.76	0.82	0.60	0.74	0.73	1976-1985
Ozette Lake, WA	1.2	1.1	1.3	1.2	0.56	0.56	1977-1985
Beaver Lake, WA	0.98	0.86	0.97	0.80	0.60	0.59	1974-1985
Mean	5.3	4.6	5.3	4.7	0.70	0.66	--

Source: Cleverly et al. (1996); Versar (1996a).

Table 3-18. CDD/CDF and PCB Concentrations and Flux for 11 U.S. Lakes/Reservoirs

	Total Concentration (pg/g, dry weight)[a]		Flux (pg/cm^2-yr)[a]	
	CDD/CDFs	Dioxin-Like PCBs	CDD/CDFs	Dioxin-Like PCBs
Chandler Lake, AK	9.1	34.0	0.051	0.19
Canandaigua Lake, NY	1790.6	2115.5	86.9	102.7
Skaneateles Lake, NY	1338.4	974.6	58.6	42.7
Great Sacandaga Reservoir, NY	1257.4	865.7	82.0	56.5
Santeetlah Reservoir, NC	2916.2	522.0	190.0	34.0
Blue Ridge Reservoir, GA	1785.8	218.0	158.6	19.4
Deer Creek Reservoir, UT	255.3	303.6	46.4	55.2
Echo Lake, UT	236.9	125.9	39.5	21.0
Panguitch Lake, UT	265.4	76.0	15.5	4.5
Ozette Lake, WA	203.4	103.0	7.9	4.0
Beaver Lake, WA	132.0	39.0	31.6	9.3
Mean	926.4	488.8	65.2	31.8

[a] Nondetects set to one-half the detection limit.

Source: Cleverly et al. (1996); Versar (1996a).

Table 3-19. Average Total Concentrations of CDD/CDFs for Sediments (pg/g)

Vietnamese River Sediments		Lake Sediments	
Site	Concentration	Site	Concentration
Saigon River	6,800	Lake Huron	1,240
Dong Nai River	1,200	Lake Michigan	1,600
Red River	240	Lake Erie	2,150
		Lake Ontario	11,000
		Siskiwit Lake	730
		Lake Zurich	1,500
		Lake Balderg	1,500
		Lake Lugano	2,000

Source: Schecter et al. (1989a).

Table 3-20. Mean Background Profiles for Sediment[a]

2,3,7,8-Substituted CDD/CDFs	Concentration (ppt)	Fraction of Total CDD/CDFs	CDD/CDF Homologue Groups	Concentration (ppt)	Fraction of Total CDD/CDFs
2,3,7,8-TCDD	0.26	0.0003	TCDD	6.5	0.007
1,2,3,7,8-PeCDD	0.95	0.0010	PeCDD	9.1	0.0100
1,2,3,4,7,8-HxCDD	1.8	0.0020	HxCDD	43.3	0.0468
1,2,3,6,7,8-HxCDD	4.7	0.0051	HpCDD	199.1	0.2149
1,2,3,7,8,9-HxCDD	4.1	0.0044	OCDD	400.5	0.4323
1,2,3,4,6,7,8-HpCDD	100.6	0.1086	TCDF	25.7	0.0278
OCDD	400.5	0.4323	PeCDF	17.9	0.0193
2,3,7,8-TCDF	1.6	0.0017	HxCDF	38.0	0.0411
1,2,3,7,8-PeCDF	0.91	0.0010	HpCDF	82.8	0.0893
2,3,4,7,8-PeCDF	1.5	0.0016	OCDF	103.6	0.1118
1,2,3,4,7,8-HxCDF	1.9	0.0020			
1,2,3,6,7,8-HxCDF	0.003	0.0000			
1,2,3,7,8,9-HxCDF	0.02	0.0000			
2,3,4,6,7,8-HxCDF	1.7	0.0018			
12,3,4,6,7,8-HpCDF	0.01	0.0000			
1,2,3,4,7,8,9-HpCDF	2.1	0.0023			
OCDF	83.0	0.0896			
TOTAL	605.4	0.6536		926.40	1.0

[a] Based on Cleverly et al. (1996); Versar (1996a).

Table 3-21. TEQ_{DF}-WHO_{98} Concentrations of CDD/CDFs in North American Sediment (ppt)
(nondetects = ½ LOD)

Location	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	2,3,7,8-HxCDDs	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PeCDF	2,3,4,7,8-PeCDF	2,3,7,8-HxDCFs	2,3,7,8-HpCDFs	OCDF	Total
Chandler Lake, AK Cs date = 1952	0.016	0.025	0.010	0.002	0.0003	0.018	0.003	0.022	0.021	0.002	0.00002	0.012
Canadaigua Lake,NY Cs date = 1981	0.782	3.91	3.512	2.720	0.069	0.844	0.153	2.635	1.274	0.369	0.011	16.3
Skaneateles Lake, NY Cs date = 1984	0.687	2.610	1.672	1.320	0.072	0.404	0.147	2.385	1.189	0.262	0.005	10.8
Great Sacandaga Reservoir, NY Cs date = 1974	0.098	0.726	0.613	0.487	0.054	0.382	0.098	1.610	0.983	0.989	0.023	6.1
Santeetlah Reservoir, NC Cs date = 1974	0.390	2.160	4.054	4.310	0.099	0.210	0.043	0.685	1.861	1.554	0.039	15.4
Blue Ridge Reservoir, GA Cs date = 1974	0.279	0.682	0.854	1.470	0.087	0.090	0.023	0.327	0.517	0.596	0.025	4.9
Deer Creek Reservoir, UT Cs date = 1973	0.106	0.124	0.161	0.173	0.018	0.073	0.017	0.182	0.154	0.037	0.001	1.0
Echo Lake, UT Cs = 1973	0.042	0.055	0.127	0.143	0.010	0.012	0.005	0.100	0.138	0.029	0.010	0.67
Panguitch Lake, UT Cs = 1976	0.025	0.124	0.169	0.195	0.016	0.027	0.014	0.137	0.090	0.025	0.0007	0.82
Ozette Lake, WA Cs = 1977	0.246	0.345	0.270	0.143	0.009	0.066	0.007	0.111	0.100	0.015	0.0003	1.3
Beaver Lake, WA Cs = 1974	0.299	0.125	0.163	0.104	0.006	0.021	0.007	0.163	0.094	0.008	0.0002	0.99
Mean	0.270	0.990	1.055	1.006	0.040	0.195	0.047	0.760	0.584	0.353	0.010	5.31
S.D.	0.250	1.249	1.368	1.318	0.035	0.246	0.055	0.932	0.607	0.485	0.012	5.83

Source: Cleverly et al. (1996); Versar (1996a).

Table 3-22. Background Data for Fish from the National Bioaccumulation Study

Congener	No. of Background Sites	Concentration Range[a] (pg/g)	Mean Conc.[a] (pg/g)	Standard Deviation[a] (pg/g)	Median Conc.[a] (pg/g)
2,3,7,8-TCDD	34	0.06 - 2.26	0.56	0.38	0.50
2,3,7,8-TCDF	34	0.10 - 13.73	1.61	2.51	0.90
1,2,3,7,8-PeCDD	33	0.15 - 2.67	0.77	0.54	0.54
1,2,3,7,8-PeCDF	34	0.10 - 1.90	0.43	0.31	0.39
2,3,4,7,8-PeCDF	34	0.10 - 1.39	0.50	0.36	0.42
Total HxCDDs	30	ND - 3.57	0.39	0.8	ND
Total HxCDFs	29	ND - 2.59	0.22	0.66	ND

Source: U.S. EPA (1992).

[a] Concentrations are picograms per gram (pg/g) wet weight. The mean, median, and standard deviation were calculated using one-half the detection limit for samples that were below the detection limit. In cases where multiple samples were analyzed per site, the value used represents the highest concentration.

Note: ND = nondetect.

Table 3-23. Levels of CDD and CDF I-TEQ_{DF}s in Fish From the Southern Mississippi Region

Food Sample	Number of Observations	I-TEQ_{DF} pg/g sample[a]
Catfish (farm-raised) Nuggets[b]	3	1.19, 2.64, 2.57
Mullet Fillet	2	0.089, 0.027
Spanish Mackerel Fillet	1	0.72
American Oyster Meat	3	0.62, 0.53, 0.60
Blue Crab		
Claw Meat	3	0.06, 0.10, 0.09
Body (soft-shell)	3	1.09, 1.14, 1.44
Crawfish		
Tail Muscle	2	0.033, 0.087
Head and Digestive Gland	2	2.34, 1.55

[a] One-half the detection limit was used in calculating the I-TEQ_{DF}s.

[b] Nuggets are small pieces of fillet.

Source: Cooper et al. (1995).

Table 3-24. Summary of CDD, CDF, and PCB Analyses in Farm Raised Catfish from the Southeastern United States[a]

Sample Type	Number of Observations	I-TEQ_{DF} (mean) pg/g lipid	TEQ_{P}-WHO_{98} (mean) pg/g lipid [b]	TEQ_{DFP}-WHO_{98} (mean) pg/g lipid
Catfish Nuggets from Mississippi[c]	3	9.7	1.43	11.13
Catfish Fillet from Mississippi[c]	3	22.67	2.66	25.33
Catfish Fillet from Alabama	1	13	0.92	13.92
Catfish Fillet from Mississippi Agriculture Facility	3	7.93	0.86	8.79
Catfish Fillet from Arkansas Agriculture Facility (8% fish meal)	2	40	3.42	43.42
Feed - Mississippi (4% fish meal)	1	7.2	3.31	10.51
Feed - Arkansas (8% fish meal)	1	61	0.19	61.19
Sediment from Mississippi Agriculture Facility	1	3.5	0.04	3.54

[a] One-half the detection limit was used in calculating the TEQs.
[b] Includes PCB 28, 52, 77, 101, 105, 118, 126, 138, 153, 156, 169, and 180.
[c] Purchased from same store and distributed by same supplier as those collected and analyzed in Cooper et al. (1995).

Source: Cooper et al. (1997) and Fiedler et al. (1998).

Table 3-25. FDA Fish and Shellfish Data for 1995-1999 Combined
(TEQs Based on 17 2,3,7,8-substituted dioxin and furan congeners)

	Year	N	Average TEQ ND = 0	Average TEQ ND = DL/2	N Total	Weighted Average ND = DL/2
Salmon	1998	20	0.54	0.63	39	0.57
	1999	19	0.39	0.51		
Catfish (all)	1996	19	2.1	2.1	30	2.0
	1999	11	1.8	1.9		
Rockfish/ striped bass	1999	16	1.1	1.1	26	1.2
	1998	10	1.2	1.2		
Pollack	1999	9	0.04	0.19	19	0.22
	1998	10	0.00	0.24		
Tuna	1996	16	0.00022	0.055		
Cod	1996	18	0.00045	0.15		
Lobster	1998	8	0.13	0.31	16	0.26
	1999	8	0.02	0.21		
Crawfish	1998	10	0.05	0.26	20	0.23
	1999	10	0.05	0.19		
Crab	1998	10	0.26	0.36	38	0.36
	1999	10	0.20	0.36		
Blue crab	1996	18	0.34	0.35		
Shrimp	1996	19	0.0016	0.074		
Scallops	1999	11	0.00	0.16		
Oyster	1996	15	0.44	0.44		

Sources: Jensen and Bolger (2000) and Jensen et al. (2000).

Table 3-26. Levels of PCBs in Fish Tissue, Bivalves, and Sediment at a Site Near a Pulp and Paper Mill

Congener		Upstream	Mill Vicinity	Downstream
Fish Tissue (Whole Body)				
PCB77	range (pg/g, wet wt.)	26.0-120.6	14.2-1095.3	30.2-80.6
	mean (pg/g, wet wt.)	56.0	555.7	51.3
	mean TEQ (pg/g, wet wt.)	0.028	0.277	0.026
PCB126	range (pg/g, wet wt.)	12.3-30.5	17.7	13.8-17.4
	mean (pg/g, wet wt.)	20.7	17.7	15.3
	mean TEQ (pg/g, wet wt.)	2.07	1.77	1.53
PCB169	range (pg/g, wet wt.)	1.2-2.8	1.4	1.6-2.0
	mean (pg/g, wet wt.)	2.0	1.4	1.7
	mean TEQ (pg/g, wet wt.)	0.020	0.014	0.017
Total TEQ_P-WHO_{94}		2.12	2.06	1.57
Bivalves				
PCB77	range (pg/g, wet wt.)	101.7	-	-
	mean (pg/g, wet wt.)	101.7	-	-
	mean TEQ (pg/g, wet wt.)	0.05	-	-
PCB126	range (pg/g, wet wt.)	19.4	11.5	-
	mean (pg/g, wet wt.)	19.4	11.5	-
	mean TEQ (pg/g, wet wt.)	1.94	1.15	-
PCB169	range (pg/g, wet wt.)	-	0.7	3.3
	mean (pg/g, wet wt.)	-	0.7	3.3
	mean TEQ (pg/g, wet wt.)	-	0.007	0.033
Total TEQ_P-WHO_{94}		1.99	1.16	0.03
Sediment				
PCB77	range (pg/g, wet wt.)	9.5	-	27.8
	mean (pg/g, wet wt.)	9.5	-	27.8
	mean TEQ (pg/g, wet wt.)	0.005	-	0.009
PCB126	range (pg/g, wet wt.)	0.9-1.1	-	1.38
	mean (pg/g, wet wt.)	1.0	-	1.38
	mean TEQ (pg/g, wet wt.)	0.10	-	0.14
PCB169	range (pg/g, wet wt.)	1.5	-	0.5
	mean (pg/g, wet wt.)	1.5	-	0.5
	mean TEQ (pg/g, wet wt.)	0.015	-	0.005
Total TEQ_P-WHO_{94}		0.12	-	0.16

NOTE: Results of sample analyses that showed interference or had recoveries below 40 percent or above 120 percent (acceptability range specified by this study was 40 to 120 percent recovery) were not included in the data set used here. Half the detection (or quantification) limit was used for samples below the detection (or quantification) limit. TEF_P-WHO_{94}s used in calculating the TEQ_P-WHO_{94}s.

Source: Derived from Petreas (1991).

Table 3-27. TEQ_{DFP}-WHO_{98} Concentrations in Marine Fish
(pg/g lipid)

Fish Type	n	CDD/CDFs		PCBs	
		Mean	Range	Mean	Range
UK Landed					
Cod	17	9	2.1 - 24	17	3.3 - 76
Haddock	16	6.9	1.1- 14	7.4	2.2 - 22
Plaice	10	25	3.6 - 43	42	9.5 - 55
Whiting	14	8.3	2.0 - 20	23	2.4 - 91
Herring	10	24	13 - 38	59	12 - 110
Mackarel	13	3.8	1.0 - 9.0	14	2.5 - 31
Salmon	11	6.5	4.6 - 11	19	12 - 30
Fish Fingers	12	0.7	0.3 - 2.4	1.6	1.3 - 6.2
Imported					
Cod	13	6.1	1.4 - 18	9.7	2.0 - 32
Haddock	10	4.6	1.9 - 8.5	5.4	1.9 - 12
Plaice	3	20	16 - 27	33	21 - 57
Salmon	1	3.4	3.4	12	12
Red fish	2	14	12, 16	43	42, 44

Source: Robinson et al. (2000).

Table 3-28. Mean CDD/CDF Profiles for Fish

2,3,7,8-Substituted CDD/CDFs	Freshwater Fish[a]		Marine Fish[b]		Shellfish[b]	
	Concentration Whole Weight (ppt)	Fraction of Total CDD/CDFs	Concentration Whole Weight (ppt)	Fraction of Total CDD/CDFs	Concentration Whole Weight (ppt)	Fraction of Total CDD/CDFs
2,3,7,8-TCDD	0.15	0.016	0.18	0.028	0.15	0.014
1,2,3,7,8-PeCDD	0.25	0.028	0.45	0.068	0.41	0.040
1,2,3,4,7,8-HxCDD	0.15	0.016	0.23	0.036	0.36	0.035
1,2,3,6,7,8-HxCDD	0.26	0.028	1.2	0.19	0.67	0.066
1,2,3,7,8,9-HxCDD	0.20	0.022	0.34	0.052	0.62	0.061
1,2,3,4,6,7,8-HpCDD	1.1	0.12	1.4	0.21	2.3	0.23
OCDD	5.9	0.65	2.0	0.30	8.6	0.84
2,3,7,8-TCDF	0.70	0.077	0.29	0.044	0.67	0.066
1,2,3,7,8-PeCDF	0	0	0.092	0.014	0.089	0.0087
2,3,4,7,8-PeCDF	0.37	0.040	0.13	0.020	0.17	0.017
1,2,3,4,7,8-HxCDF	0	0	0.066	0.010	0.18	0.017
1,2,3,6,7,8-HxCDF	0	0	0.055	0.0084	0.077	0.0075
1,2,3,7,8,9-HxCDF	0	0	0	0	0.018	0.0018
2,3,4,6,7,8-HxCDF	0	0	0.032	0.0048	0.066	0.0065
1,2,3,4,6,7,8-HpCDF	0	0	0.055	0.0084	0.24	0.024
1,2,3,4,7,8,9-HpCDF	0	0	0	0	0.012	0.0011
OCDF	0	0	0.047	0.0072	0.066	0.0065
TOTAL	9.1	1.0	6.6	1.0	10.2	1.0

[a] Based on data from Schecter et al. (1997).

[b] Based on data from Fiedler et al. (1997c).

Table 3-29. Background CDD/CDF TEQs in Fish and Shellfish, Consumption Rates, and Intakes (Ages 18+ years)

Fish Class	Species	Consumption Rate (g/day)	N	CDD/CDF TEQ Conc. (Pg/g fresh wt.)	CDD/CDF TEQ Intake (pg/day)
Estuarine Finfish	Flounder (e)(f)	0.58	3	1.8	1.0
	Catfish-nonfarmed(h)	0	0		
	Trout-nonfarmed (e,h)	0	0		
	Rockfish/Striped Bass (d)	0.043	26	1.2	0.052
	Salmon (d)	0.042	39	0.57	0.024
	Mullet (a)	0.034	2	0.068	0.0023
	Other				
	Flatfish	0.39	0		
	Perch	0.19	0		
	Croaker	0.13	0		
	Herring	0.12	0		
	Anchovy	0.042	0		
	Smelts	0.0074	0		
	Eel	0.0038	0		
	Sturgeon	0.00017	0		
	Total Other*	0.88	0	1.3	1.1
Freshwater Finfish	Catfish-farmed (b,d,h)	0.90	30	2.0	1.8
	Trout-farmed (e,h)	0.41	6	1.9	0.78
	Perch (e) (walleye)	0.17	3	1.2	0.20
	Carp (e)	0.14	4	1.2	0.17
	Pike (e) (pickerel)	0.035	3	0.49	0.017
	Salmon (d)	0.00083	39	0.57	0.00047
	Other				
	Whitefish	0.012	0		
	Cisco	0.0012	0		
	Smelts, Rainbow	0.00050	0		
	Sturgeon	0.00017	0		
	Total Other*	0.014	0	1.3	0.018
Total Freshwater/Est. Finfish		**3.3**	**116**	**1.6**	**5.3**
Freshwater/Estuarine Shellfish	Shrimp (b,c)	2.0	19	0.080	0.16
	Crab (b,d)		38	0.36	
	Crab (a)		6	0.84	
	Crab Average (i)	0.30	33	0.37	0.11
	Oyster (b,d)		15	0.45	
	Oyster (a)		3	0.69	
	Oyster Average (i)	0.15	18	0.47	0.070
	Scallop (d)	0.0011	11	0.16	0.00018
	Crawfish (a)		4	1.0	
	Crayfish (e)		1	1.0	
	Crayfish (d)		20	0.23	
	Crayfish (i)	0.0090	25	0.30	0.0027
	Other				
	Clam	0.014	0		
	Snails	0.0017	0		
	Total Other**	0.0157	0	0.43	0.0068
Total Freshwater/Est. Shellfish		**2.5**	**106**	**0.14**	**0.35**
Unknown Freshwater/Est. Species	Fish***	0.14	0	1.3	0.18
Total Fresh./Est. Fish		**5.9**	**222**	**1.0*** **	**5.8**
Marine Finfish	Tuna (c)	3.1	16	0.060	0.19
	Cod (c)	1.4	18	0.15	0.21
	Salmon (d)	1.3	39	0.57	0.74
	Pollack (d)	0.25	19	0.22	0.055
	Mackerel (a)	0.11	1	0.95	0.10

Fish Class	Species	Consumption Rate (g/day)	N	CDD/CDF TEQ Conc. (Pg/g fresh wt.)	CDD/CDF TEQ Intake (pg/day)
Marine Finfish (continued)	Other				
	Porgy	0.36	0		
	Haddock	0.31	0		
	Whiting	0.26	0		
	Squid	0.17	0		
	Perch	0.13	0		
	Sardine	0.12	0		
	Sea Bass	0.10	0		
	Swordfish	0.098	0		
	Pompano	0.084	0		
	Octopus	0.073	0		
	Flatfish	0.045	0		
	Halibut	0.035	0		
	Snapper	0.032	0		
	Whitefish	0.012	0		
	Smelt	0.0066	0		
	Shark	0.0046	0		
	Roe	0.0011	0		
	Total Other*****	1.8	0	0.39	0.72
Total Marine Finfish		**8.0**	**93**	**0.25**	**2.0**
Marine Shellfish	Scallop (d)	0.19	11	0.16	0.030
	Lobster (d)	0.19	16	0.26	0.049
	Crab (d)	0.16	38	0.36	0.058
	Other				
	Clams	0.70	0		
	Mussels	0.070	0		
	Conch	0.0021	0		
	Snails	0.0017	0		
	Total Other*****	0.77	0	0.26	0.20
Total Marine Shellfish		**1.3**	**65**	**0.26**	**0.34**
Unknown Marine Species	Seafood (g)***	0.080	0	0.39	0.031
	Fish***	0.220	0	0.39	0.09
Total Marine Fish and Shellfish		**9.6**	**158**	**0.26****	**2.5**
TOTAL FISH		**15.5**	**292**(j)	**0.53**	**8.3**

(a) Fiedler et al., 1997
(b) Jensen and Bolger, 2000
(c) Jensen (2000); personal communication by facsimile
(d) Jensen et al., 2000, with additional clarification by personal communication with FDA
(e) U.S. EPA, 1992
(f) Classified as marine by U.S. EPA, 1992
(g) Assumed to be marine, based on recommendation by EPA, Office of Water
(h) Catfish and trout were assumed to be entirely farm-raised
(i) Calculated as the average over all locations assuming that Jensen et al. (2000) and Jensen and Bolger (2000) collected samples at different locations and Fiedler et al. (1992) collected samples from one location.
(j) Total N does not equal the sum of Ns of total freshwater/estuarine fish and total marine fish because the same data are used in both categories for salmon, scallop, and crab. Thus, the N for these data were not double counted.
* For freshwater/estuarine species for which species-specific concentration data were not available, the average value from U.S. EPA, 1992 was used
** For freshwater/estuarine shellfish species for which species-specific data were not available, the average value from the species with known concentrations was used.
*** For unclassified fish, 39% of the consumption was assumed to be freshwater/estuarine and 61% was assumed to be marine, based on recommendations by EPA, Office of Water.
**** This concentration is a species-specific ingestion-weighted average value.
***** For marine species for which species-specific concentration data were not available, the average value for the available species shown here was used.

NOTE: Data from U.S. EPA, 1992 for the following species were not used here, except in the average freshwater/estuarine fish concentration, because corresponding consumption data were not available: freshwater bass, crappie, dolly varden, redhorse, rockbass, sucker, and sunfish.

Table 3-30. FDA Dairy Data for 1995-1999 Combined
(WHO_{98} TEQs Based on 17 2,3,7,8-substituted dioxin and furan congeners)

	Year	N	Average TEQ (ppt) ND = 0	Average TEQ (ppt) ND = DL/2	N Total	Weighted Average ND = DL/2
Ice cream	1996	40	0.058	0.10		
Yogurt	1996	20	0.0069	0.082		
Butter	1996	22	0.060	0.31		
Milk	1996	44	0.029	0.061		
Cream	1998	19	0.22	0.27		
American cheese	1996	30	0.067	0.10	169	0.13
Various (romano, Mozz)		19				
Swiss cheese		14				
Cheddar cheese		39				
Cottage cheese		24				
Cream cheese		25				
Mozzarella cheese	1998	18	0.21	0.38		
Eggs	1998	20	0.05	0.17		

Sources: Jensen and Bolger (2000) and Jensen et al. (2000).

Table 3-31. I-TEQ$_{DF}$s in Foods From Southern Mississippi

Food Sample	Number of Observations	I-TEQ$_{DF}$ pg/g sample[a]
Catfish (farm-raised) Nuggets	3	1.19, 2.64, 2.57
Mullet Fillet	2	0.089, 0.027
Spanish Mackerel Fillet	1	0.72
American Oyster Meat	3	0.62, 0.53, 0.60
Blue Crab		
Claw Meat	3	0.06, 0.10, 0.09
Body (soft-shell)	3	1.09, 1.14, 1.44
Crawfish		
Tail Muscle	2	0.033, 0.087
Head and Digestive Gland	2	2.34, 1.55
Butter	3	0.683, 0.770, 0.552
Milk	3	0.025, 0.026, 0.012
Cheddar Cheese	3	0.300, 0.247, 0.254
Eggs	3	0.038, 0.020, 0.019
Ground Beef	3	0.196, 0.254, 0.152
Chicken	3	0.043, 0.085, 0.053
Chicken Liver	3	0.031, 0.064, 0.070
Sausage	3	0.178, 0.221, 0.282

[a] One-half the detection limit was used in calculating the I-TEQ$_{DF}$s.

Source: Cooper et al. (1995).

Table 3-32. Summary of Dioxin/Furan Food Data Collected in the California State Air Resources Board Study

Congener	Beef		Pork		Chicken	
	Fraction of composite samples that were positive	Concentration range of positive samples (pg/g)[a,b]	Fraction of composite samples that were positive	Concentration range of positive samples (pg/g)[a,b]	Fraction of composite samples that were positive	Concentration range of positive samples (pg/g)[a,b]
2,3,7,8-TCDD	0/8	-	0/8	-	3/8	0.31-1.67
1,2,3,7,8-PeCDD	0/8	-	0/8	-	0/8	-
1,2,3,4,7,8/1,2,3,6,7,8-HxCDD	3/8	0.72-3.96	2/8	2.83-3.50	1/8	2.29
1,2,3,7,8,9-HxCDD	0/8	-	0/8	-	2/8	2.14-4.30
1,2,3,4,6,7,8-HpCDD	7/8	3.53-8.95	8/8	3.04-45.50	7/8	1.10-35.20
OCDD	7/8	7.75-11.90	8/8	13.70-254.0	7/8	2.61-96.20
2,3,7,8-TCDF	3/8	0.63-1.56	0/8	-	1/8	0.67
1,2,3,7,8-PeCDF	0/8	-	0/8	-	0/8	-
2,3,4,7,8-PeCDF	0/8	-	0/8	-	0/8	-
1,2,3,4,7,8-HxCDF	0/8	-	0/8	-	0/8	-
1,2,3,6,7,8-HxCDF	0/8	-	0/8	-	0/8	-
1,2,3,7,8,9-HxCDF	0/8	-	0/8	-	0/8	-
2,3,4,6,7,8-HxCDF	0/8	-	0/8	-	0/8	-
1,2,3,4,6,7,8-HpCDF	4/8	0.48-1.15	7/8	1.57-10.60	6/8	1.01-24.60
1,2,3,4,7,8,9-HpCDF	0/8	-	0/8	-	0/8	-
OCDF	0/8	-	5/8	1.24-9.36	2/8	3.79-26.00

Table 3-32. Summary of Dioxin/Furan Data Collected in the California State Air Resources Board Study (continued)

Congener	Eggs		Milk		Fish (freshwater & saltwater)	
	Fraction of composite samples that were positive	Concentration range of positive samples (pg/g)[c]	Fraction of composite samples that were positive	Concentration range of positive samples (pg/g)[a,b]	Fraction of composite samples that were positive	Concentration range of positive samples (pg/g)[a,b]
2,3,7,8-TCDD	0/8	-	1/8	1.46	8/10	0.73-9.78
1,2,3,7,8-PeCDD	0/8	-	0/8	-	6/10	1.67-23.6
1,2,3,4,7,8/1,2,3,6,7,8-HxCDD	0/8	-	1/8	0.59	7/10	1.19-84.1
1,2,3,7,8,9-HxCDD	0/8	-	0/8	-	4/10	3.91-38.9
1,2,3,4,6,7,8-HpCDD	0/8	-	7/8	2.08-4.25	5/10	3.15-201
OCDD	1/8	1.30	6/8	2.23-6.12	10/10	4.37-1490
2,3,7,8-TCDF	1/8	0.011	8/8	1.30-6.11	10/10	0.83-28.2
1,2,3,7,8-PeCDF	0/8	-	0/8	-	0/10	-
2,3,4,7,8-PeCDF	0/8	-	0/8	-	0/10	-
1,2,3,4,7,8-HxCDF	0/8	-	0/8	-	0/10	-
1,2,3,6,7,8-HxCDF	0/8	-	0/8	-	0/10	-
1,2,3,7,8,9-HxCDF	0/8	-	0/8	-	0/10	-
2,3,4,6,7,8-HxCDF	0/8	-	0/8	-	0/10	-
1,2,3,4,6,7,8-HpCDF	1/8	0.065	1/8	0.70	2/110	2.21-92.9
1,2,3,4,7,8,9-HpCDF	0/8	-	0/8	-	1/10	13.3
OCDF	0/8	-	0/8	-	0/10	0

[a] Concentration reported on a lipid weight basis.
[b] For some of the concentrations reported, the ratio of characteristic ions were outside the qualitative identification data quality objectives.
[c] Concentration reported on a whole weight basis.

Source: Stanley and Bauer (1989).

Table 3-33. Summary of U.S. Food Data from NCASI Study

Food	Number of Samples	2,3,7,8-TCDD Level[a] (Food basis, pg/kg)	2,3,7,8-TCDD Level[a] (Lipid basis, pg/kg)	2,3,7,8-TCDF Level[a] (Food basis, pg/kg)	2,3,7,8-TCDF Level[a] (Lipid basis, pg/kg)
Milk	1	1.8	48	ND	ND
Half & Half	2	7.2; 8.7	55; 67	NR	NR
Ground beef	3	17; 18; 62	71; 141; 352	ND(3.8); ND(4.8); 5.2	ND(16); ND(27); 41
Corned beef hash	14	7.2-20	54-144	ND(5.9); ND(17); 4.7-12	ND(39); ND(120); 33-103
Beef hot dogs	3	12; 15; 37	44; 56; 128	ND(7.7); 11; 11	ND(28); 38; 41
Ground pork	3	ND(5.8); ND(6.5); ND(6.5)	ND(18); ND(22); ND(27)	13; 13; 20	45; 53; 62
Chicken broth	3	1.1; 1.3; 1.5	(lipid content unknown)	NR	NR
Coffee	2	ND(0.2); 0.08	NR	NR	NR
Orange juice	3	ND(0.3); ND(0.3); ND(0.4)	NR	NR	NR

NOTE: ND = Not detected; NR = Not reported

[a] Values in parentheses are detection limits.

Sources: Henry et al. (1992); LaFleur et al. (1990).

Table 3-34. Summary of Schecter et al. (1993a) Data on U.S. Foods

	CDD/CDF I-TEQ_{DF} (pg/g)[a] Assuming ND = 0.5 DL	CDD/CDF I-TEQ_{DF} (pg/g)[a] Assuming ND = 0	Number of Samples[b]
Haddock Fillet	0.03	0.02	2
Crunchy Haddock	0.13	0.13	1
Perch	0.24	0.24	1
Cod	0.023	0.012	1
Ground Beef	1.5	1.5	1
Beef Rib Sirloin Tip	0.04	0.04	1
Beef Rib Steak	0.65	0.65	1
Pork Chop	0.26	0.26	1
Cooked Ham	0.029	0.024	1
Lamb Sirloin	0.4	0.4	1
Lebanon Bologna	0.12	0.11	1
Chicken	0.03	0.03	1
Cottage Cheese	0.04	0.04	1
Blue Cheese	0.73	0.70	1
Cream Cheese	0.38	0.38	1
American Cheese	0.31	0.31	1
Heavy Cream	0.35	0.33	1

ND = nondetect; DL = detection limit

[a] Concentrations reported on whole food, wet weight basis.
[b] Samples collected from a supermarket in New York.

Source: Schecter et al. (1993a).

Table 3-35. CDD/CDFs and PCBs in Foods from Five Regions of the United States

Congener	Beef N = 9	Chicken N = 7	Ocean Fish N = 13	Fresh Fish N = 10	Pork N = 7
% Lipid	13.13	5.33	1.43	4.83	9.18
CDD/Fs (pg/g, lipid-based)					
2,3,7,8-TCDF	0.488	ND (1.88 EMPC)[a]	ND (11.6 EMPC)[a]	14.4	1.97
2,3,7,8-TCDD	ND (.19)[b]	ND (.467)[b]	2.3	3.09	ND (.349 EMPC)[a]
1,2,3,7,8-PeCDF	ND (.95)[b]	ND (2.34)[b]	ND (8.74)[b]	ND (7.59 EMPC)[a]	ND (1.36)[b]
2,3,4,7,8-PeCDF	ND (.95)[b]	2.6	ND (8.74)[b]	7.56	ND (1.36)[b]
1,2,3,7,8-PeCDD	ND (.95)[b]	ND (2.34)[b]	ND (8.74)[b]	5.2	ND (1.36)[b]
1,2,3,4,7,8-HxCDF	ND (1.22 EMPC)[a]	ND (2.34)[b]	ND (10.8)[b]	ND (3.36 EMPC)[a]	ND (1.47 EMPC)[a]
1,2,3,6,7,8-HxCDF	ND (2.15 EMPC)[a]	ND (2.84 EMPC)[a]	ND (16.6 EMPC)[a]	ND (19.9 EMPC)[a]	ND (6.46 EMPC)[a]
2,3,4,6,7,8-HxCDF	ND (.95)[b]	ND (2.34)[b]	ND (9.51)[b]	ND (2.58)[b]	ND (1.36)[b]
1,2,3,7,8,9-HxCDF	ND (.95)[b]	ND (2.91)[b]	ND (14.5)[b]	ND (2.58)[b]	ND (1.36)[b]
1,2,3,4,7,8-HxCDD	ND (1.39 EMPC)[a]	ND (2.34)[b]	ND (8.74)[b]	3.01	ND (1.36)[b]
1,2,3,6,7,8-HxCDD	4.92	ND (2.34)[b]	ND (8.74)[b]	5.31	1.81
1,2,3,7,8,9-HxCDD	1.04	ND (2.34)[b]	ND (8.74)[b]	4.11	ND (1.36)[b]
1,2,3,4,6,7,8-HpCDF	ND (10.8 EMPC)[a]	ND (5.49 EMPC)[a]	ND (48.7 EMPC)[a]	ND (31 EMPC)[a]	ND (20.2 EMPC)[a]
1,2,3,4,7,8,9-HpCDF	ND (.95)[b]	ND (2.34)[b]	ND (8.74)[b]	ND (2.72)[b]	ND (1.36)[b]
1,2,3,4,6,7,8-HpCDD	20.9	8.09	11.7	23.5	17.1
1,2,3,4,6,7,8,9-OCDF	ND (3 EMPC)[a]	ND (4.67)[b]	ND (17.5)[b]	ND (5.17)[b]	ND (3.26 EMPC)[a]
1,2,3,4,6,7,8,9-OCDD	32.7	20.2	31.6	122	87.1
I-TEQ_{DF}s (pg/g)					
lipid-based min.	0.89	0.10	2.45	12.51	0.64
lipid-based max.	2.86	5.17	21.14	16.07	3.97
whole-weight min.	0.12	0.005	0.035	0.60	0.06
whole-weight max.	0.38	0.28	0.30	0.78	0.36
PCBs (ng/g, lipid-based)					
# 118	0.717	3.70	22.3	36.3	--
# 114	--	--	--	--	--
# 153	0.629	2.08	27.4	39.3	0.785
# 105	--	1.47	8.34	12.4	--
# 138	--	0.747	30.2	37.4	1.07
# 128	--	--	--	5.59	--
# 156	--	--	--	7.27	--
# 180	--	4.32	11.8	12.6	--

[a] Nondetected due to an interference. An estimated maximum possible concentration (EMPC) is given as the detection limit.
[b] Nondetected, with the curve based detection limit in pg/g.
[c] Calculated using a value of zero for nondetected congeners.
[d] Calculated using the detection limit value for nondetected congeners.

Source: Schecter et al. (1997).

Table 3-36. I-TEQ$_{DF}$ Levels in Cow's Milk and Infant Formula from the United States and Thailand

Product/Origin	Lipid-based I-TEQ$_{DF}$ (ppt)	Fat Content (%)
Cow's Milk/NY	1.2	3.4
2% Cow's Milk/NY	0.1	1.9
Ultra Pasteurized Heavy Cream/NY	0.38	39.1
Similac Formula/NY	0.004	-[b]
Isomil Formula/NY	0.003	3.2
Prosoybee Formula/NY	0.005[a]	2.5
Laclasoy UHT Soy Milk/Thailand	0.23	2.9
Thai-Danish UHT/Thailand	0.32	3.5

[a] Contamination from cap liner.
[b] Not available.

Source: Schecter et al. (1989b).

Table 3-37. Maximum CDD/CDF Levels in Foods Collected in Canada (pg/g fresh weight) as Reported by Birmingham et al. (1989)

	Eggs	Beef	Milk Products	Pork	Chicken
TCDD	ND	ND	NR	ND	ND
PeCDD	ND	ND	NR	ND	ND
HxCDD	ND	ND	NR	ND	ND
HpCDD	ND	ND	NR	ND	15
OCDD	8[a]	24[a]	NR	ND	210
TCDF	ND	ND	NR	ND	ND
PeCDF	ND	ND	NR	ND	ND
HxCDF	5[a]	ND	NR	ND	ND
HpCDF	7[a]	ND	NR	ND	ND
OCDF	12[a]	ND	NR	ND	ND
I-TEQ_{DF}	0.59	0.29	0.11	0.03	0.39

NR = Not Reported.
ND = Not Detected; detection limits ranged from 0.1 to 0.7 pg/g.
[a] Data for foods of U.S. origin collected in Canada.

Source: Birmingham et al. (1989).

Table 3-38. Summary of TEQ Levels in Toronto (1992) and Montreal (1993)*

Food Category	Composite Sample	CDD/CDF (ppt) I-TEQ_{DF}		Non-Ortho PCB (ppt) TEQ_{P}-WHO_{94}		Σ CDD/CDF/PCB TEQ (ppt)	
		Toronto	Montreal	Toronto	Montreal	Toronto	Montreal
Meat	Beef Ground	0.32	0.32	0.067	0.045	0.39	0.37
	Beef Steak	0.18	0.17	0.017	0.016	0.19	0.18
	Beef Roast	0.087	0.14	0.014	0.018	0.10	0.16
	Pork Cured	0.045	0.044	0.007	0.004	0.053	0.049
	Organ Meat	0.29	0.37	0.034	0.052	0.32	0.42
	Poultry	0.066	0.043	0.010	0.019	0.076	0.062
Dairy	Whole Milk	0.038	0.031	0.033	0.096	0.072	0.041
	1% Milk	0.024	0.021	0.012	0.004	0.036	0.025
	Cream	0.079	0.076	0.066	0.062	0.145	0.138
	Cheese Cheddar	0.24	0.20	.015	0.16	0.39	0.36
	Butter	0.50	0.33	0.42	0.29	0.93	0.62
Fish	Fresh Water	0.26	0.16	0.36	0.32	0.62	0.48
	Marine	0.033	0.013	0.24	0.105	0.28	0.12
Oils	Cooking Fats and Salad Oil	0.42	0.28	0.019	0.029	0.44	0.31

* N = 44 composites for each city.

Source: Ryan et al. (1997).

Table 3-39. Example of Method for Estimating Fat Content (percent) of Beef

Item Number	Beef Item Description	Fat Fraction	Beef Intake[a] (g)	Fat Intake from Beef[b] (g)
1	Beef, ground, regular, cooked, broiled, medium	0.2069	5372916272	1111656377
2	Beef, ground, lean, cooked, broiled, medium	0.1846	1804281336	333070335
3	Beef, short loin, top serloin, choice	0.1097	791973251	86879466
4-146	–	–	17855973824	2775999294
SUM	–	–	2.58E+10	4.31E+9
Weighted Average[c]				**0.167**

a Total beef intake for the U.S. population in a day based on survey data weighted to the U.S. population.
b Fat intake from beef calculated as the beef intake multiplied by the fat fraction.
c Calculated as the sum of fat intake from beef (g) divided by the sum of beef intake (g).

Source: Data provided by David Haytowitz, USDA, by personal communication to Linda Phillips, Versar, Inc., January 2001.

Table 3-40. Summary of Coplanar PCBs in a Statistical Sample of Beef Fat in the United States

Description	PCB 77	PCB 118	PCB 105	PCB 126	PCB 156	PCB 157	PCB 169
Number of Samples	63	63	63	63	63	63	63
Limits of Detection, ppt	1.00	30.0	14.0	0.3	4.0	1.0	0.2
Percent Positive	20	100	88	100	100	99	94
Mean, ppt							
ND = ½ DL	1.00	440.5	91.5	4.0	58.7	13.4	0.69
ND = 0.00	0.60	440.5	90.6	4.0	58.7	13.4	0.69
Range, ppt	ND - 7.97	61 - 2295	ND - 438	0.74 - 23.2	4.87 - 426	ND - 91.7	ND - 2.4
TEF_P-WHO_{94}	0.0005	0.0001	0.0001	0.1	0.0005	0.0005	0.01
TEQ_P-WHO_{94} Concentration, ppt (ND = ½ LOD)	5.0×10^{-4}	4.4×10^{-2}	9.2×10^{-3}	4.0×10^{-1}	2.9×10^{-2}	6.7×10^{-3}	6.9×10^{-3}
TEF_P-WHO_{94}	0.0001	0.0001	0.0001	0.1	0.0005	0.0005	0.01
TEQ_P-WHO_{94} Concentration, ppt (ND = ½ LOD)	1×10^{-4}	4.4×10^{-2}	9.2×10^{-3}	4.0×10^{-1}	2.9×10^{-2}	6.7×10^{-3}	6.9×10^{-3}

Source: Winters et al. (1996b).

Table 3-41. Concentration Levels of CDD/CDF Congeners in Back Fat and Ratios of Muscle Fat/Back Fat in Cattle

Congener	Oregon State University		North Dakota State University		Pennsylvania State University		Pennsylvania State University		Pennsylvania State University	
	Back Fat Concentration (ppt lipid)	Ratio Muscle/ Back Fat	Back Fat Concentration (ppt lipid)	Ratio Muscle/ Back Fat	Back Fat Concentration (ppt lipid)	Ratio Muscle/ Back Fat	Back Fat Concentration (ppt lipid)	Ratio Muscle/ Back Fat	Back Fat Concentration (ppt lipid)	Ratio Muscle/ Back Fat
2,3,7,8-TCDD	0.3	1.2	0.3	0.9	0.2	1.2	0.6	1.4	0.9	1.1
1,2,3,7,8-PeCDD	2.3	0.5	1.6	0.6	5.1	0.9	9.9	1.7	31.5	0.6
1,2,3,4,7,8-HxCDD	2.2	0.6	2.4	0.5	6.4	0.9	7.3	2.4	18.9	0.8
1,2,3,6,7,8-HxCDD	7.7	0.8	9.3	0.7	24.6	1.0	36.1	1.8	60.4	0.9
1,2,3,7,8,9-HxCDD	2.3	0.7	2.3	0.3	7.3	0.8	11.6	2.7	25.0	0.8
1,2,3,4,6,7,8-HpCDD	8.0	0.8	24.8	0.7	41.7	0.9	56.7	1.7	65.7	1.1
OCDD	6.3	1.7	33.0	0.8	12.8	1.6	33.7	2.4	19.6	1.5
2,3,7,8-TCDF	0	NA	0	NA	0	NA	0	NA	0	NA
1,2,3,7,8-PeCDF	0	NA	0	NA	0	NA	0	NA	0	NA
2,3,4,7,8-PeCDF	0.6	NA	1.2	0.7	1.4	0.6	2.9	1.0	6.3	0.6
1,2,3,4,7,8-HxCDD	0.8	NA	1.6	0.7	1.7	0.7	2.7	0.5	5.2	0.3
1,2,3,6,7,8-HxCDF	0.7	NA	1.3	0.3	1.7	0.5	6.5	1.7	14.0	0.7
1,2,3,7,8,9-HxCDF	0	NA	0	NA	0	NA	0	NA	0	NA
2,3,4,6,7,8-HxCDF	0.9	NA	1.2	0.2	1.2	0.3	4.3	1.3	16.9	0.4
1,2,3,4,6,7,8-HpCDF	1.3	NA	4.3	0.4	2.8	0.6	10.6	3.4	24.2	1.0
1,2,3,4,7,8,9-HpCDF	0	NA	0	NA	0	NA	0	NA	0.4	NA
OCDF	0	NA	0	NA	0	NA	0.1	NA	0.6	1.0
PCB 77	0.7	12.6	2.0	2.8	1.7	7.3	16.5	16.7	19.5	4.7
PCB 118	859	1.7	1087	1.2	1332	1.8	3551	2.9	3649	2.5
PCB 105	145	2.8	237	1.2	233	2.8	612	5.7	486	5.3
PCB 126	8.4	0.9	11.0	1.3	8.8	1.1	27.8	0.8	18.1	1.2
PCB 156	88.4	0.9	105	1.0	102	1.5	390	1.5	281	1.3
PCB 157	20.7	1.0	26.3	1.0	23.1	1.4	83.4	1.4	69.7	1.1
PCB 169	1.3	1.2	4.7	1.1	1.6	1.1	4.5	0.7	2.7	NA
I-TEQ_{DF}	3.3	0.60	3.8	0.64	8.3	0.86	14.6	1.7	34.8	0.71
TEQ_{DF}-WHO_{98}	4.4	0.58	4.6	0.64	10.8	0.86	19.5	1.7	50.5	0.69
TEQ_{P}-WHO_{94} or TEQ_{P}-WHO_{98}	1.0	1.0	1.3	1.2	1.1	1.3	3.5	1.1	2.4	1.5

NA = Either (or both) intramuscular and back fat samples had nondetect concentration, such that a ratio could not be derived.

Source: Lorber et al. (1997a).

Table 3-42. TEQ_{DFP}-WHO_{98} Summary of Nationally Extrapolated Pork Results on a Lipid Basis Assuming Nondetects (ND) Equal ½ Detection Limit (results are in ppt, or pg/g; ND = 0 results are in parenthesis).

Description	Dioxins and Furans			Coplanar PCBs		
	Mean	Standard Deviation	Min/Max	Mean	Standard Deviation	Min/Max
Overall	1.48 (0.46)	1.47 (1.50)	0.76/22.47 (0/22.76)	0.06 (0.04)	0.08 (0.09)	0.02/1.66 (0/1.66)
Market Hogs	1.44 (0.42)	1.17 (1.34)	0.78/9.30 (0/9.58)	0.06 (0.04)	0.07 (0.08)	0.02/0.40 (0/0.11)
Sows	1.85 (0.94)	1.46 (1.76)	0.80/5.63 (0/5.41)	0.06 (0.04)	0.03 (0.04)	0.02/0.11 (0/0.11)
Boars	3.60 (3.03)	6.31 (6.63)	0.76/22.47 (0/22.76)	0.27 (0.26)	0.48 (0.48)	0.02/1.66 (0/1.66)

Source: Lorber et al. (1997b).

Table 3-43. TEQ_{DFP}-WHO_{98} Summary of Nationally Exptrapolated Results From U.S. Poultry Fat on a Lipid Basis Assuming Nondetects (ND) Equal ½ Detection Limit (Results are in ppt, or pg/g; ND = 0 results are in parenthesis)

Description	Dioxins and Furans		Coplanar PCBs	
	Mean	Max	Mean	Max
Overall	0.77 (0.48)	4.72	0.29 (0.29)	1.68
Young Chickens	0.76 (0.47)	4.08	0.28 (0.28)	1.68
Light Fowl	0.47 (0.16)	0.92	0.27 (0.27)	0.75
Heavy Fowl	1.14 (0.90)	2.60	0.34 (0.34)	1.12
Young Turkeys	1.09 (0.88)	4.72	0.65 (0.65)	1.28

Source: Ferrario, et al. (1997).

Table 3-44. CDD/CDF Concentrations in Eggs and TEQ_{DF}-WHO_{98}s

	Number of Positive Samples	Mean Positive Samples (ppt)	Number of Non-detect Samples	LOD (ppt)	Mean Conc. ND = 1/2 LOD (ppt)	Mean Conc. ND = 0 (ppt)	TEQ ND = 1/2 LOD (ppt)	TEQ ND = 0 (ppt)
2,3,7,8-TCDD	1	0.009	14	0.02	0.0099	0.0006	0.0099	0.0006
1,2,3,7,8-PeCDD	0	--	15	0.04	0.020	0	0.02	0
1,2,3,4,7,8-HxCDD	0	--	15	0.08	0.040	0	0.004	0
1,2,3,6,7,8-HxCDD	0	--	15	0.09	0.045	0	0.0045	0
1,2,3,7,8,9-HxCDD	0	--	15	0.14	0.040	0	0.004	0
1,2,3,4,6,7,8-HpCDD	13	0.31	2	0.2	0.28	0.27	0.0028	0.0027
OCDD	1.4	1.2	1		1.1	1.1	0.00011	0.0011
2,3,7,8-TCDF	2	0.042	13	0.04	0.023	0.0056	0.0023	0.00056
1,2,3,7,8-PeCDF	3	0.043	12	0.05	0.029	0.0086	0.0014	0.00043
2,3,4,7,8-PeCDF	3	0.061	12	0.046	0.031	0.01	0.015	0.0061
1,2,3,4,7,8-HxCDF	1	0.12	14	0.095	0.052	0.008	0.0052	0.0008
1,2,3,6,7,8-HxCDF	1	0.081	14	0.094	0.049	0.0054	0.0049	0.00054
2,3,4,6,7,8-HxCDF	NR	NA	NR	NA	NA	NA	NA	0
1,2,3,7,8,9-HxCDF	0	--	15	0.11	0.055	0	0.0055	0
1,2,3,4,6,7,8-HpCDF	5	0.11	10	0.098	0.069	0.037	0.00069	0.00037
1,2,3,4,7,8,9-HpCDF	0	--	15	0.1	0.050	0	0.0005	0
OCDF	5	0.12	10	0.18	0.10	0.04	0.00001	0.00004
TOTAL							0.081	0.013

Notes: ND = non-detect
NR = not reported
LOD = limit of detection

Source: Hayward and Bolger (2000).

Table 3-45. Weighted Milk Fat Percent

	Whole Milk Intake (g/day)	Low Fat Milk Intake (g/day)	Skim Milk Intake (g/day)	Total Milk Intake (g/day)
Males >20 years	66	92	32	190
Females >20 years	46	74	34	154
Average >20 years	56	83	33	172
Fraction of Total Milk Intake	0.326	0.483	0.192	1
Percent Fat	3.19	1.3	0.7	–
Weighted Percent Fat (fraction of total milk intake * percent fat)	1.04	0.63	0.13	**1.80**

Table 3-46 Average Congener Concentrations of 8 Composite Milk Samples
(pg/g lipid; ND = 0 in parenthesis)

CDDs	Concentration	CDFs	Concentration	PCBs	Concentration
2,3,7,8-TCDD	0.07 (0.07)	2,3,7,8-TCDF	0.08 (0.08)	PCB 77	10.6 (10.6)
1,2,3,7,8-PCDD	0.32 (0.32)	1,2,3,7,8-PCDF	0.05 (0)	PCB 118	685.3 (685.3)
1,2,3,4,7,8-HxCDD	0.39 (0.39)	2,3,4,7,8-PCDF	0.28 (0.28)	PCB 105	170.3 (170.3)
1,2,3,6,7,8-HxCDD	1.87 (1.87)	1,2,3,4,7,8-HxCDF	0.39 (0.39)	PCB 126	3.6 (3.6)
1,2,3,7,8,9-HxCDD	0.55 (0.55)	1,2,3,6,7,8-HxCDF	0.25 (0.25)	PCB 156	60.1 (60.1)
1,2,3,4,6,7,8-HpCDD	5.03 (5.03)	1,2,3,7,8,9-HxCDF	0.05 (0)	PCB 157	13.8 (13.8)
OCDD	4.89 (4.89)	2,3,4,6,7,8-HxCDF	0.28 (0.28)	PCB 169	0.5 (0.5)
		1,2,3,4,6,7,8-HpCDF	0.83 (0.83)	TEQ_{P}-WHO_{98}	0.49 (0.49)
		1,2,3,4,7,8,9-HpCDF	0.05 (0)		
		OCDF	0.05 (0)		
		TEQ_{DF}-WHO_{98}	0.98 (0.97)		

Source: Lorber et al. (1998b).

Table 3-47 Calculation of Fractional Fat Content of Dairy Products Category

Milk or Dairy Product[a]	Mean Whole Weight Dietary Dairy Intake (g/day)[b]	Mean Fat Content (%)	Total Dairy Fat Intake (g/day)	Mean Whole Weight Dietary Intake of Dairy Other Than Milk (g/day)	Percent Dietary Intake of Dairy Other Than Milk (%)	Dairy Product Fat (%)
Whole milk	56	3.16	1.77	--	--	--
Lowfat milk	83	1.33	1.10	--	--	--
Skim milk	33	0.17	0.06	--	--	--
Yogurt	4.5	1.47	0.07	4.5	7.76	0.11
Cheese	14	25.3	3.54	14	24.14	6.11
Milk desserts and other[c]	39.5	8.25(d)	3.26(d)	39.5	68.10	5.62
TOTAL	230		9.80	58	100	11.84(e)

a CSFII food categories taken from USDA (1995).

b USDA (1995).

c Milk desserts = 21 g/day. Because total dairy = 230 g/day and total dairy minus milk desserts and other = 190.5; other is assumed to = 18.5 g/day (i.e., 230 minus 190.5 minus 21 = 18.5).

d No fat content data available for milk desserts and other dairy products. Total dietary fat intake for milk desserts and other calculated as the total dietary fat intake (i.e., 9.8 g/day, based on adult total fat intake of 81.39 g/day [CDC, 1994; as cited in U.S. EPA, 1997]), times the fraction of fat that comes from dairy products (i.e., 0.12, based on NLMB, 1993; as cited in U.S. EPA, 1997), minus the dairy fat intake of the other milk and dairy foods [i.e., (81.39 g/day * 0.12) - (6.54 g/day) = 3.26 g/day]. The mean fat content of milk desserts and other was calculated as the dairy fat intake (3.26 g fat/day) divided by the dietary intake (39.5 g/day).

e The overall fractional fat content of dairy products other than milk (11.84%) is calculated as the sum of the products of the fractions of dairy intake other than milk times the fractional fat contents, on the various non-milk dairy products [i.e., (0.0776 * 0.0147) + (0.2414 * 0.253) + (0.6810 * 0.0825) = 0.1184].

Table 3-48 CDD/CDF Levels in German Food

	Mean I-TEQ_{DF}[a] (pg/g fat)	Number of Samples
Cow's Milk	1.35	168
Cheese	0.98	10
Butter	0.66	5
Beef	1.69	3
Veal	3.22	4
Pork	<0.4	3
Sheep	1.23	2
Chicken	1.41	2
Canned Meat	1.29	2
Lard	0.47	4
Fresh Water Fish	13.25	18
Salt Water Fish	16.82	15
Fish Oil	2.64	4
Cod Liver Oil	13.31	4
Salad Oil	<0.4	4
Margarine	<0.4	6
Infant Formula	0.5	10

[a] I-TEQ_{DF} computed using one-half the detection limit for nondetects.

Sources: Milk data based on Fürst et al. (1991); other data from Fürst et al. (1990).

Table 3-49. CDD/CDF Background Levels in Some European, Canadian, and New Zealand Food

Country	Food	Source	pg I-TEQ$_{DF}$/g fat
Germany	Cow's milk Cow's milk	Background contamination Consumer's milk	1.0 - 2.8 0.8 - 2.6
United Kingdom	Cow's milk	Rural area	1.3
Netherlands	Cow's milk	Background contamination	0.7 - 2.5
New Zealand	Cow's milk	Background contamination	0.18 - 0.22
Germany	Pork Beef Veal Sheep Poultry Canned Meat Lard		0.5 3.5 7.4 2.0 2.3 1.7 0.8
Canada	Beef Pork Poultry		2.9 0.2 2.6

Source: Fürst et al. (1991).

Table 3-50. CDD/CDF Levels in German Food (1993-1996)

Sample	Mean I-TEQ_{DF} (pg/g fat)	Number of Samples
Cow's Milk	0.71	538
Cheese	0.66	99
Butter	0.64	222
Beef	0.71	14
Veal	0.95	11
Lamb, Sheep, Mutton	0.52	13
Poultry	0.62	19
Eggs	2.10	218
Ham	0.39	8
Venison	1.41	6
Sausage	0.28	1
Kidney (sheep)	1.11	1
Horsemeat	3.76	1
Salt-water Fish	14.7	42
Trout	7.44	61
Rhine River Fish	39	19
Artificial Lake Fish	104.1	14
Vegetables growing underground (e.g., potatoes, carrots)	16.9	13
Vegetables growing on the ground (e.g., zucchini, Beetroot, kohlrabi, celery, and onions)	12.2	18
Leak vegetables (e.g., lettuce, sugarloaf, endive, savoy cabbage, leek, white cabbage)	12.9	22
Fruit growing above ground (e.g., apples and tomatoes)	4.3	4

Source: Malisch (1998).

Table 3-51. I-TEQ_{DF} Levels in Dairy Products in France

Type of Sample	Mean I-TEQ_{DF} Total pg/g Fat	Number of Samples
Cow's Milk	1.91	12
Cheese	1.11	20
Butter	1.01	8
Milk Dessert and Cream	1.34	12

Source: Defour et al. (1997).

Table 3-52. I-TEQ$_{DF}$ Concentrations in Food from the Netherlands

Food Category	CDD/CDFs (pg I-TEQ$_{DF}$/g fat)
Beef	1.75
Cow's Liver	5.7
Pork	0.43
Pig's Liver	15.3
Poultry	1.65
Chicken's Liver	3.25
Mutton	1.85
Horse Meat	13.85
Game [a]	16.8
Butter	1.8
Cheese [a]	1.4
Nuts [a]	0.2
Cereals [a]	0.34
Eggs	2.0
Fatty Sea Fish [a]	6.65
Lean Fish [a]	48.65
Eel	28.0
Fresh Water Fish [a]	2.4
Mixed Meat Product [a]	0.67
Dairy Products	1.58
Soy Bean Oil	0.025
Rape-Seed Oil	0.006
Palm Oil	0.030
Sunflower Oil	0.006
Coconut Fat	0.024
Palm Fat	0.010
Fish Oil	2.2
Items with Vegetable Oil [a]	0.02
Items from Food Industry [a]	0.41

[a] A proportional mixture of food items was analyzed.

Source: Theelen et al. (1993).

Table 3-53. I-TEQ_{DF} Concentrations in Food from Spain

Food Category	CDD/CDFs (pg I-TEQ_{DF}/g fat)	CDD/CDFs (pg I-TEQ_{DF}/g wet weight)
Vegetables	--	0.14
Pulses	--	0.19
Cerales	--	0.25
Fruits	--	0.09
White Fish	5.39	0.27
Seafood	10.59	0.42
Tinned Fish	2.57	0.24
Blue Fish	7.90	0.76
Pork and Pork Products	0.90	0.11
Chicken and Chicken Products	1.15	0.11
Beef and Beef Products	1.76	0.13
Lamb	1.76	0.13
Eggs	1.22	0.12
Dairy Products	1.25	0.04
Whole Milk	1.02	0.18
Semi-Skimmed Milk	1.20	0.06
Oil	0.64	--
Margarine	0.49	--

Source: Domingo et al. (1999).

Table 3-54. I-TEQ$_{DF}$ Concentrations in UK Foods in 1988

Food Product	Mean I-TEQ$_{DF}$ (ppt)					
	Norwich		Port Talbot		Stonehaven	
	nd = 0	nd = LOD	nd = 0	nd = LOD	nd = 0	nd = LOD
Fish[a,b]	0.69	0.73	0.63	0.63	0.07	0.07
Carcass Meat[a]	--	--	1.1	1.1	0.18	0.26
Offals (internal organs)[a]	--	--	0.20	0.22	0.62	0.69
Poultry[a]	--	--	0.37	0.37	0.28	0.29
Meat Products[a]	--	--	0.20	0.20	0.17	0.21
Milk Products[a]	--	--	0.08	0.33	0.09	0.09
Butter[b]	1.2	1.2	--	--	--	--
Cheddar Cheese[c]	0.16	0.16	--	--	--	--
Reduced Fat Cheese[c]	0.09	0.12	--	--	--	--
Fats and Oils[a]	--	--	0.84	0.88	0.11	0.41
Eggs[a]	--	--	0.22	0.22	0.16	0.16
Green Vegetables[a]	--	--	0.01	0.02	< 0.01	0.01
Other Vegetables[a]	--	--	0.05	0.12	0.06	0.06
Potatoes[a]	--	--	0.04	0.04	0.02	0.03
Fresh Fruit[a]	--	--	< 0.01	0.04	0.04	0.06

[a] One sample analyzed from Port Talbot, and one sample analyzed from Stonehaven.
[b] Eight samples analyzed.
[c] Two samples analyzed.

Source: MAFF (1992).

Table 3-55. I-TEQ$_{DF}$ Concentrations in Bottled Cow's Milk from the United Kingdom

	Mean (ppt) nd = 0	Range (ppt) nd = 0	Mean (ppt) nd = LOD	Range (ppt) nd = LOD
Winter 1990 (n = 8)	0.08	0.05-0.13	0.09	0.05-0.13
Summer 1990 (n = 7)	0.06	0.04-0.07	0.06	0.05-0.07
Rural 1989 (n = 9)	0.04	0.03-0.06	0.05	0.04-0.06
Urban 1989 (n = 9)	0.19	0.12-0.27	0.20	0.12-0.27

Source: MAFF (1992).

Table 3-56. Concentrations and Concentration Ranges (pg/g fresh weight) of Four Dioxin-Like PCBs in Foods from Finland

		PCB 77	PCB 105	PCB 126	PCB 169
Baltic Herring (n = 6)	Mean Range	97 33 - 136	1700 960 - 2700	17 7.4 - 26	4.5 nd - 12
Rainbow Trout (n = 4)	Mean Range	100 8.0 - 150	1200 410 - 2100	17 5.2 - 35	3.9 nd - 7.4
Other Fish (n = 4)	Mean Range	53 5.6 - 153	400 113 - 1100	11 2.3 - 28	1.9 0.6 - 6.5
Beef (n = 6)	Mean Range	13 0.6 - 38	22 5.3 - 38	3.2 0.3 - 7.3	0.5 nd - 1.0
Pork (n = 3)	Mean Range	13 1.0 - 24	24 11 - 47	1.5 0.5 - 3.7	0.8 nd - 2.2
Poultry (n = 2)	Mean	8.2	68	1.2	nd
Inner Organs (n = 5)	Mean Range	3.2 nd - 7.9	45 8.1 - 111	2.6 0.4 - 6.0	0.3 nd - 0.6
Eggs (n = 2)	Mean	4.1	98	2.9	0.1
Fish Liver Oil (n = 2)	Mean	2700	30000	620	130

Note: nd = not detected.

Source: Himberg (1993).

Table 3-57. I-TEQ$_{DF}$s (ppt wet weight) in Foods From the Former Soviet Union

Site	Food Product	Lipid Content (%)	I-TEQ$_{DF}$ Concentration ppt wet weight [1]
Moscow	Lamb	23.8	0.30
	Swiss Cheese	3.0	0.04
	Sausage	57.0	0.60
	Hot Sausage	9.4	0.15
	Turkey Fat & Meat	29.9	0.30
	Hamburger (cooked)	6.7	0.02
	Beef	24.0	0.13
	Ground Beef (cooked)	8.5	0.24
	Fish (Motba)	2.0	0.70
Irkutsk	Pork Fat	54.8	0.15
	Pork Fat	50.8	0.20
	Pork Meat	9.8	0.05
	Lamb Fat	43.5	0.40
	Soft Cheese	4.9	0.04
	Duck Livers	3.0	0.08
	Cow Cream	15.0	0.80
	Uncooked Beef	3.0	0.13
Novosibirsk	Pork Fat	34.1	0.06
	Cheese	27.6	0.17
	Vanilla Ice Cream	1.0	0.005
	Fish	9.2	0.07
	Smoked Fish	16.3	0.80
	Meatball	4.7	0.02
	Chicken	24.6	0.05
	Mintai Fish (cooked)	5.8	0.14
	Cheese with Butter	36.0	0.40
	Beef Fat	34.0	0.30
Baikalsk	Fat Head Minnow	2.7	1.3
	Pork	72.0	0.9
	Butter	53.0	1.4

[1] One-half the detection limit was used in calculating the I-TEQ$_{DF}$s.

Source: Schecter et al. (1992b).

Table 3-58. Percentage Reduction of Total 2,3,7,8-TCDD Residues in Restructured Carp Fillets from Cooking

Cooking Method	Fillet Diameter	End Temperature °C	TCDD Concentration Reduction	
			control[a]	spiked[b]
Roasted covered	7.5	60	41.4 ±4.0	44.2 ± 3.9
		70	50.5 ± 7.9	47.7 ± 2.1
		80	63.4 ± 4.3	55.0 ± 3.9
Roasted uncovered	7.5	60	34.2 ± 8.7	47.0 ± 4.4
		70	49.2 ± 6.3	51.3 ± 2.4
		80	56.6 ± 5.9	57.5 ± 2.0
Roasted uncovered	10.0	80	65.9 ± 2.6	59.2 ± 2.4
Charbroiled	7.5	60	55.3 ± 6.5	59.3 ± 5.2
		80	62.0 ± 4.3	63.6 ± 3.7
Charbroiled	10.0	80	67.5 ± 7.8	70.6 ±7.7

[a] N = 4
[b] Samples were spiked to approximately 100 ppt 2,3,7,8-TCDD.

Source: Stachiw et al. (1988).

Table 3-59. Effects of Cooking and Trimming on PCB Levels in Lake Ontario Fish

Method	Species	Reduction in Concentration (%)	Reduction in Total Amount (%)
Trimming off fat and skin	Smallmouth Bass	64.3	80.0
Trimming off fat and skin	Brown Trout	43.2	77.8
Deep frying trimmed fillets	Smallmouth Bass	45.9	74.0
Smoking untrimmed fillets	Brown Trout	12.0	26.7
Baking untrimmed fillets	Smallmouth Bass	0	16.4
Broiling trimmed fillets	Brown Trout	0	0

Source: Skea et al. (1979).

Table 3-60. Means and Standard Deviations of PCB Cooking Losses (%) of Stewed and Pressure Cooked Chicken Pieces

Chicken Piece	PCB Cooking Losses (%)	
	Stewed	Pressure Cooked
Breast	31.73 ± 2.36	30.24 ± 1.28
Drumstick	31.21 ± 2.38	32.86 ± 1.14
Thigh Meat	36.82 ± 1.50	38.10 ± 0.63
Thigh Skin	39.31 ± 8.18	46.59 ± 4.69
Abdominal Adipose Tissue	85.94 ± 1.98	88.88 ± 2.17

Source: Zabik (1974).

Table 3-61. Weighted Mean CDD/CDF Profiles for Foods

2,3,7,8-Substituted CDD/CDFs	Beef[a]		Pork[b]		Poultry[c]		Eggs[d]		Milk[e]		Dairy[f]	
	Whole Weight Concentration (ppt)	Fraction of Total 2,3,7,8-Substituted CDD/CDFs	Whole Weight Concentration (ppt)	Fraction of Total 2,3,7,8-Substituted CDD/CDFs	Whole Weight Concentration (ppt)	Fraction of Total 2,3,7,8-Substituted CDD/CDFs	Whole Weight Concentration (ppt)	Fraction of Total 2,3,7,8-Substituted CDD/CDFs	Whole Weight Concentration (ppt)	Fraction of Total 2,3,7,8-Substituted CDD/CDFs	Whole Weight Concentration (ppt)	Fraction of Total 2,3,7,8-Substituted CDD/CDFs
2,3,7,8-TCDD	0.0051	0.0028	0.0019	0.00014	0.014	0.018	0.00060	0.00040	0.0013	0.0046	0.029	0.0035
1,2,3,7,8-PeCDD	0.0068	0.0037	0.0019	0.00014	0.011	0.014	0	0	0.0058	0.021	0.169	0.0202
1,2,3,4,7,8-HxCDD	0.031	0.017	0.019	0.0014	0.0043	0.0057	0	0	0.0070	0.026	0.165	0.0198
1,2,3,6,7,8-HxCDD	0.21	0.11	0.15	0.011	0.031	0.040	0	0	0.034	0.12	0.877	0.1050
1,2,3,7,8,9-HxCDD	0.044	0.024	0.0076	0.00057	0.025	0.033	0	0	0.010	0.036	0.205	0.0246
1,2,3,4,6,7,8-HpCDD	0.75	0.41	1.9	0.14	0.13	0.17	0.27	0.18	0.091	0.33	2.565	0.3072
OCDD	0.55	0.31	10	0.75	0.45	0.59	1.1	0.74	0.088	0.32	2.561	0.3067
2,3,7,8-TCDF	0	0	0.00076	0.000057	0.026	0.034	0.0056	0.0037	0.0014	0.0053	0.055	0.0066
1,2,3,7,8-PeCDF	0	0	0	0	0.0076	0.010	0.0086	0.0057	0	0	0.010	0.0012
2,3,4,7,8-PeCDF	0.010	0.0056	0.027	0.0020	0.012	0.015	0.012	0.0081	0.0050	0.018	0.142	0.0170
1,2,3,4,7,8-HxCDF	0.046	0.025	0.11	0.0086	0.0089	0.012	0.0081	0.0053	0.0070	0.026	0.351	0.0421
1,2,3,6,7,8-HxCDF	0.020	0.011	0.11	0.0083	0.0060	0.0079	0.0054	0.0036	0.0045	0.016	0.174	0.0208
1,2,3,7,8,9-HxCDF	0	0	0	0	0	0	0	0	0	0	0	0
2,3,4,6,7,8-HxCDF	0.017	0.0094	0.030	0.0023	0.0069	0.0090	0	0	0.0050	0.018	0.111	0.0133
1,2,3,4,6,7,8-HpCDF	0.13	0.070	0.64	0.048	0.017	0.022	0.037	0.024	0.015	0.055	0.605	0.0725
1,2,3,4,7,8,9-HpCDF	0	0	0.032	0.0024	0.0034	0.0045	0	0	0	0	0.023	0.0028
OCDF	0	0	0.35	0.026	0.0059	0.0078	0.04	0.027	0	0	0.307	0.0368
TOTAL	1.8	1.0	13	1.0	0.76	1.0	1.51	1.0	0.27	1.0	8.35	1.0

NOTE: Non-detects are assumed to be zero.

[a] Based on data from Winters et al. (1996a).
[b] Based on data from Lorber et al. (1997b).
[c] Based on data from Ferrario et al. (1997).
[d] Based on data from Hayward and Bolger (2000).
[e] Based on data from Lorber et al. (1998b).
[f] Based on data from Lorber et al. (1998b).

Table 3-62. Summary of CDD/CDF Levels in U.S. Food (pg/g fresh weight)

	Mean TEQ_{DF}-WHO_{98} Assuming ND = 0.5 DL	Mean TEQ_{DF}-WHO_{98} Assuming ND = zero	Number of Samples	Reference
Beef	0.18	0.061	63	Winters et al. (1996a)
Pork	0.28	0.080	78	Lorber et al. (1997b)
Poultry	0.068	0.043	78	Ferrario et al. (1997)
Eggs	0.081	0.013	15 composites	Hayward and Bolger (2000)
Dairy Products	0.12	0.12	8 composites	Based on data from Lorber et al. (1998b)
Milk	0.018	0.017	8 composites	Lorber et al. (1998b)
Freshwater Fish and Shellfish	1.0[b]	--[c]	222	Fiedler et al. (1997); Jensen and Bolger (2000); Jensen et al.(2000); U.S. EPA (1992)
Marine Fish and Shellfish	0.26[b]	--[c]	158	Fiedler et al. (1997) Jensen et al. (2000)
Vegetable Fat	NA[a]	0.056	30	Versar (1996b)

[a] High detection limits led to a calculation of the mean with ND = 0.5 DL that was judged to be misleading. See text for more detail.
[b] This concentration is a species-specific ingestion-weighted average value.
[c] Not calculated because of lack of congener-specific data for all species.

ND = Nondetect; DL = Detection Limit
NA = Not available

Table 3-63. Summary of TEQ_P-WHO_{98} Levels in North American Food (pg/g fresh weight)

	Mean TEQ_P-WHO_{98} Assuming ND = 0.5DL	Mean TEQ_P-WHO_{98} Assuming ND = Zero	Number of Samples	Reference
Beef	0.084	0.084	63	Winters et al. (1996b)
Pork	0.012	0.0074	78	Lorber et al. (1997b)
Poultry	0.026	0.026	78	Ferrario et al. (1997)
Eggs	0.1	NR	18 1 composite 5 composites	Schecter et al. (1997) Mes and Weber (1989) Mes et al. (1991)
Dairy Products	0.058	0.058	8 composites	Based on data from Lorber et al. (1998b)
Milk	0.0088	0.0088	8 composites	Lorber et al. (1998b)
Freshwater Fish	1.2	NR	1 composite of 10 samples 1 composite 5 composites	Schecter et al. (1997) Mes and Weber (1989) Mes et al. (1991)
Marine Fish	0.25	NR	1 composite of 13 samples 5 composites	Schecter et al. (1997) Mes et al. (1991)
Vegetable Fat	0.037	NR	5 composites	Mes et al. (1991)

NOTE: Schecter et al. (1997) and Mes and Weber (1989) values based on one-half the limit of detection for nondetects and Mes et al. (1991) data based on positive composite samples only. Five additional composite samples labeled "shellfish" from Mes et al. (1991) were not used in estimating background levels because information on the source of the shellfish (i.e., freshwater or marine) needed to categorize the data were not available. It is therefore assumed that the species included in the freshwater and marine categories are representative of both finfish and shellfish from those sources.

Table 3-64. Summary of North American CDD/CDF and PCB TEQ-WHO_{98} Levels in Environmental Media and Food (whole weight basis)

Media	CDD/CDFs[a]	References	PCBs[a]	References	Mean Total CDD/CDF/PCBs
Urban Soil, ppt	n= 270 9.3 ± 10.2[b] Range = 2 - 21	Birmingham (1990), Nestrick et al. (1986), NIH (1995), Pearson et al. (1990), U.S. EPA (1985, 1996), Rogowski et al. (1999), U.S. EPA Region 8 (2000b)	n = 99 2.3	U.S. EPA Region 8 (2000b)	11.6
Rural Soil, ppt	n = 354 2.7[b] Range = 0.11 - 5.7	BC Environment (1995), Birmingham (1990), MRI (1992), Pearson et al. (1990), Reed et al. (1990), Tewhey Assoc (1997), U.S. EPA (1985, 1996), Rogowski et al. (1999), Rogowski and Yake (1999), U.S. EPA Region 8 (2000b)	n = 62 0.59	U.S. EPA Region 8 (2000b)	3.3
Sediment, ppt	n=11 5.3 ± 5.8[b] Range = <1 - 20	Cleverly et al. (1996)	n = 11 0.53 ± 0.69[b]	Cleverly et al. (1996)	5.8
Urban Air, pg/m^3	n=106 0.12 ± 0.094[b] Range = 0.03 - 0.2	CDEP (1988, 1995), Hunt and Maisel (1990), Hunt et al. (1990), Maisel and Hunt (1990), OEPA (1995), Smith et al. (1989, 1990)	n=53 0.0009[f]	Hoff et al. (1992)	0.12
Rural Air, pg/m^3	n=60 0.013[b] Range = 0.004 - 0.02	CDEP (1995), OEPA (1995) Cleverly et al. (2000)	n=53 0.00071	Cleverly et al. (2000)	0.014
Freshwater Fish and Shellfish, ppt	n=222 1.0[d]	Fiedler et al. (1997), Jensen and Bolger (2000), Jensen et al. (2000), U.S. EPA (1992)	n = 1 composite of 10 samples plus 6 composites 1.2[d,e]	Schecter et al. (1997), Mes and Weber (1989), Mes et al. (1991)	2.2
Marine Fish and Shellfish, ppt	n=158 0.26[d]	Fiedler et al. (1997a), Jensen et al. (2000)	n = 1 composite of 13 samples plus 5 composites 0.25[d,e]	Schecter et al. (1997), Mes et al. (1991)	0.57
Water, ppq	n=236 0.00056 ± 0.00079	Jobb et al. (1990), Meyer et al. (1989)	--[c]	--	0.00056
Milk, ppt	n=8 composites 0.018[e]	Lorber et al. (1998b)	n = 8 composites 0.0088	Lorber et al. (1998b)	0.027
Dairy, ppt	n = 8 composites 0.12[e]	Based on data from Lorber et al. (1998b)	n = 8 composites 0.058	Based on data from Lorber et al. (1998b)	0.18
Eggs, ppt	n=15 composites 0.081[e]	Hayward and Bolger (2000)	n = 18 plus 6 composites 0.10[d,e]	Schecter et al. (1997), Mes and Weber (1989), Mes et al. (1991)	0.13
Beef ppt	n=63 0.18 ± 0.11 Range = 0.11 - 0.95	Winters et al. (1996a)	n = 63 0.084	Winters et al. (1996b)	0.26

Table 3-64. Summary of North American CDD/CDF and PCB TEQ-WHO_{98} Levels in Environmental Media and Food (whole weight basis) (continued)

Media	CDD/CDFs[a]	References	PCBs[a]	References	Mean Total CDD/CDF/PCBs
Pork, ppt	n = 78 0.28 ± 0.28 Range = 0.15 - 1.8	Lorber et al. (1997b)	n = 78 0.012	Lorber et al. (1997b)	0.29
Poultry, ppt	n = 78 0.068 ± 0.070 Range = 0.03 - 0.43	Ferrario et al. (1997)	n = 78 0.026	Ferrario et al. (1997)	0.094
Vegetable Fats, ppt	n = 30 0.056 ± 0.24[g]	Versar (1996b)	n = 5 composites 0.037[e]	Mes et al. (1991)	0.093

[a] Values are the arithmetic mean TEQs, in ppt, and standard deviations. Nondetects were set to one-half the limit of detection, except for soil and CDD/CDFs in vegetable fats for which nondetects were set to zero.

[b] The values for environmental media are means of the data, but lack the spatial representativeness to be considered true national means.

[c] Congener-specific PCB data are limited.

[d] The values for fish lack the statistical significance to be considered true means; the values for the other food groups were derived from statistically-based surveys and can be considered true national means. The CDD/CDF concentrations are species-specific ingestion weighted average values.

[e] Standard deviations could not be calculated due to limitations associated with the data (i.e., composite analyses).

[f] Based on data from Canadian air, as reported by Hoff et al. (1992). Not used in U.S. background exposure estimates in Chapter 4.

[g] TEQ calculated from Versar (1996b) by setting nondetects to zero.

Table 3-65. CDD/CDF Congeners that Contribute the Highest Percentage of TEQ_{DF}-WHO_{98} to the Total TEQ_{DF}-WHO_{98} for All Congeners Combined

Media	North America	Percentage of Total TEQ_{DF}-WHO_{98}
Urban Soil	1,2,3,7.8-PeCDD	22.0
Sediment[a]	1,2,3,4,6,7,8-HpCDD	18.9
Freshwater Fish and Shellfish	--[b]	
Marine Fish and Shellfish	--[b]	
Urban Air	1,2,3,7,8-PeCDD	22.5
Water[c]	OCDD	56.3
Milk[a]	1,2,3,7,8-PeCDD	32.7
Dairy[a]	1,2,3,7,8-PeCDD	32.7
Eggs[a]	1,2,3,7,8-PeCDD	24.6
Beef[a]	1,2,3,7,8-PeCDD	32.8
Pork[a]	1,2,3,7,8-PeCDD	30.5
Poultry[a]	1,2,3,7,8-PeCDD	31.5
Vegetable Fats[a,d]	1,2,3,7,8-PeCDD	44.0

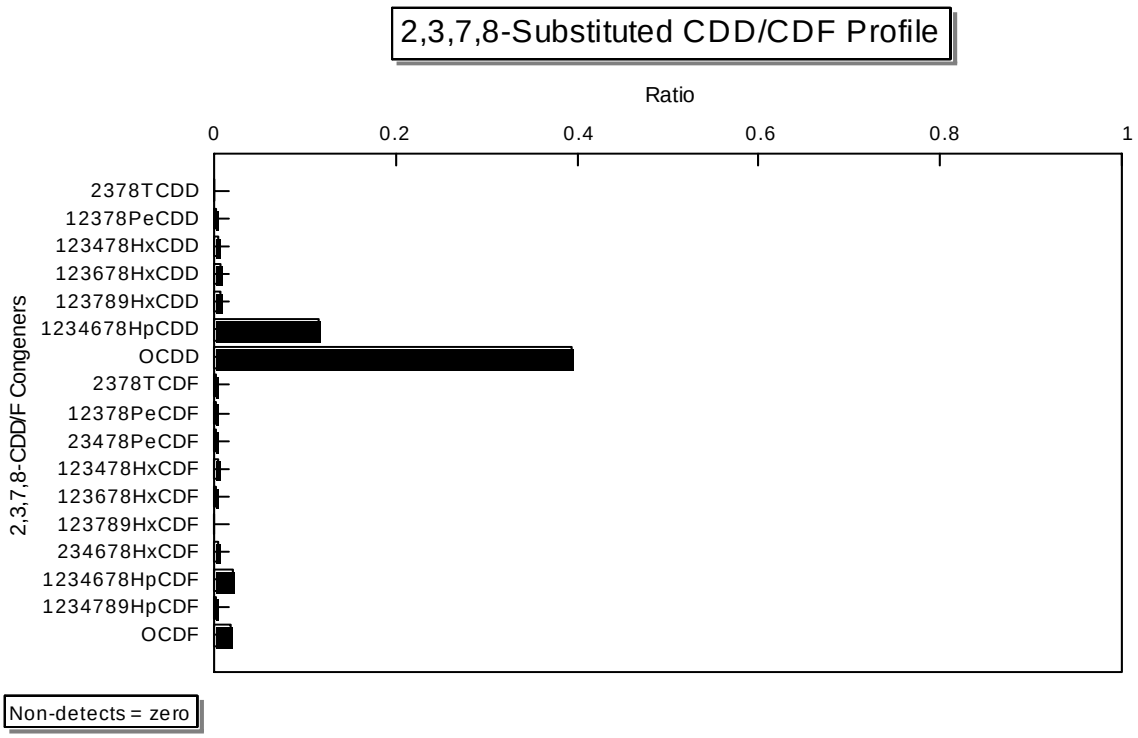
NOTE: Data were not available for all congeners in all media.

[a] Not used in calculation of the standard deviation because adequate congener-specific data were available for all samples allowing for the calculation of means and standard deviations by traditional methods.

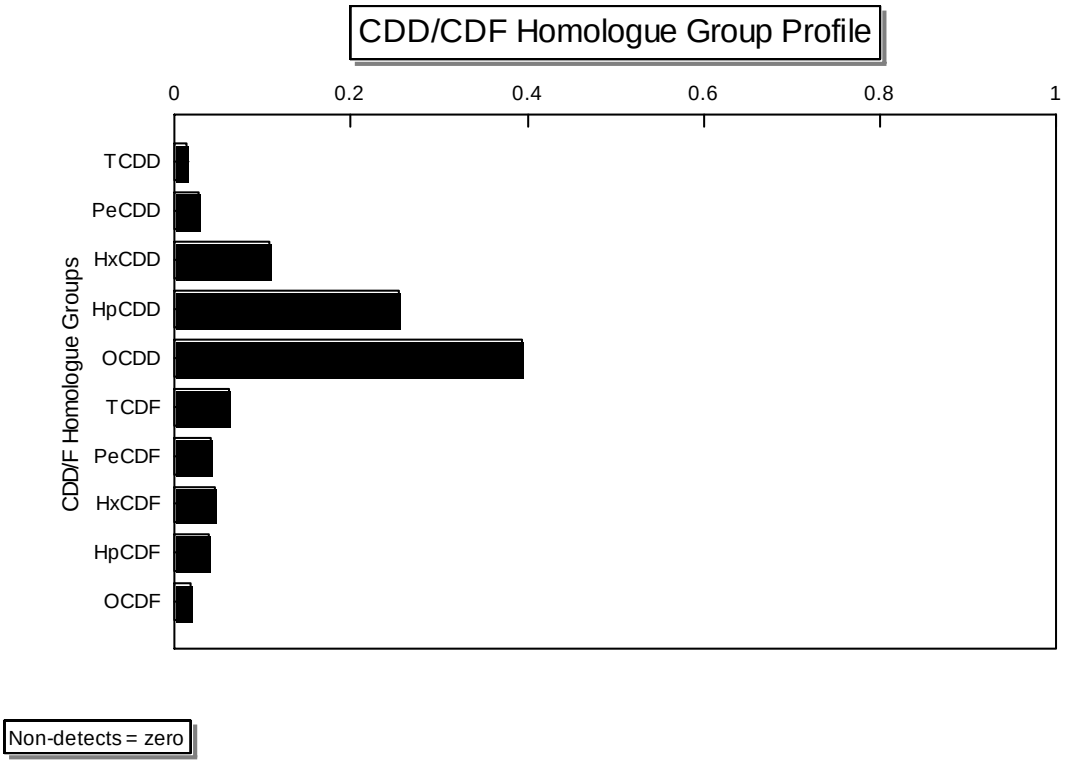
[b] Not calculated due to lack of congener-specific data for all species.

[c] Data available for OCDD and OCDF only.

[d] Due to the large number of nondetects, zero was used to represent nondetects in determining the congener that contributed the most to the total TEQ_{DF}-WHO_{98}.

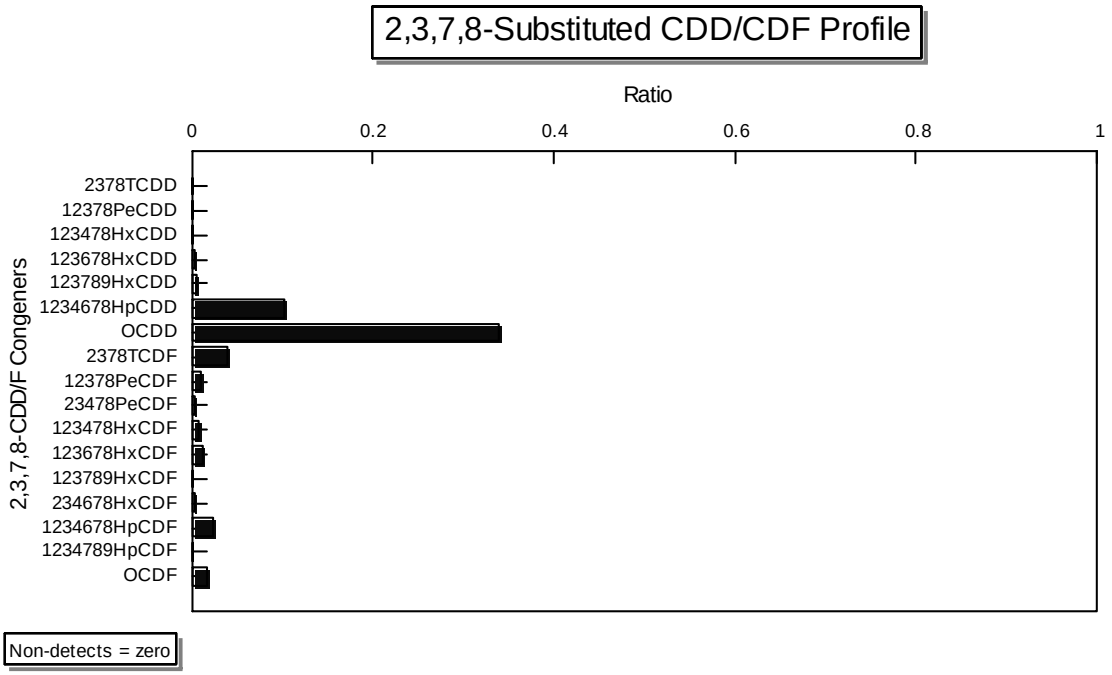


Note: Based on data from OEPA (1995), CDEP (1998), and Cleverly et al. (2000).

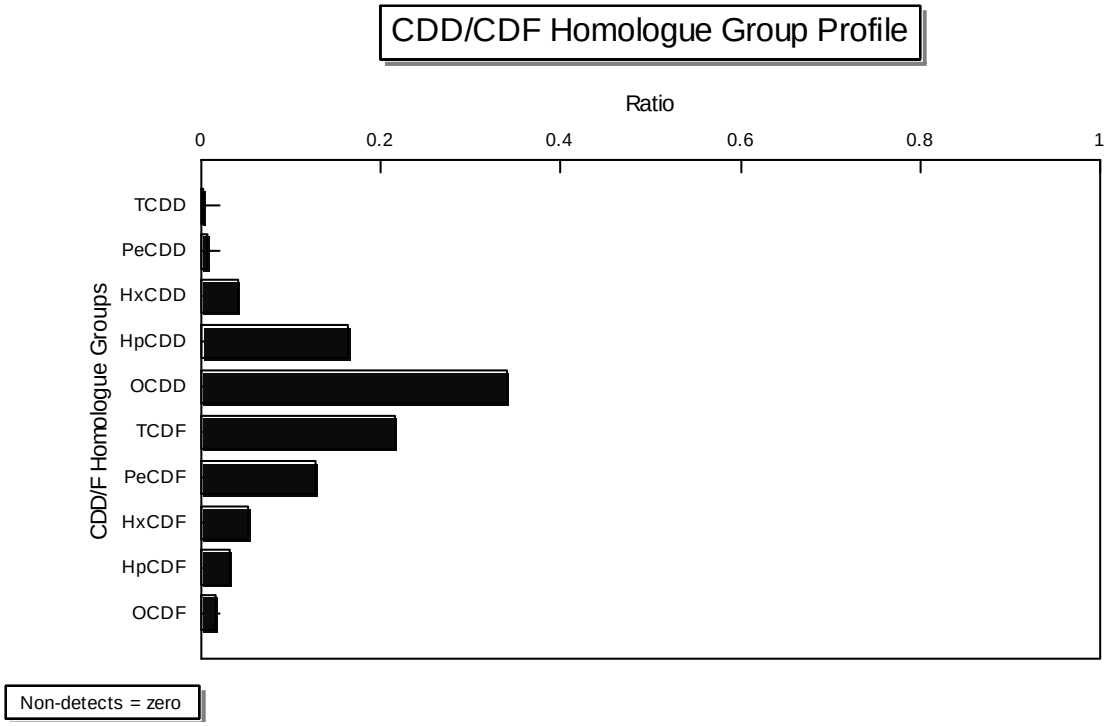


Note: Based on data from OEPA (1995), CDEP (1998), and Cleverly et al. (2000).

Figure 3-1. CDD/CDF Profiles for Rural Background Air

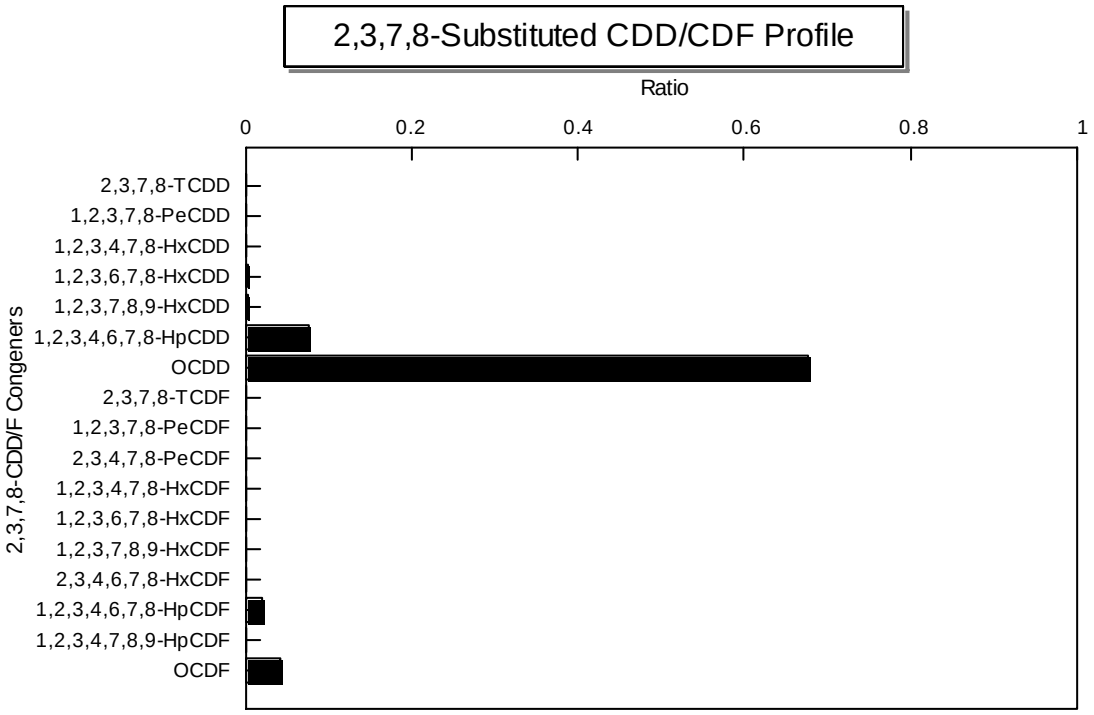


Note:Based on data from CDEP (1988, 1995), Smith et al. (1989), Maisel and Hunt (1990), Hunt et al. (1990, and OEPA (1995).

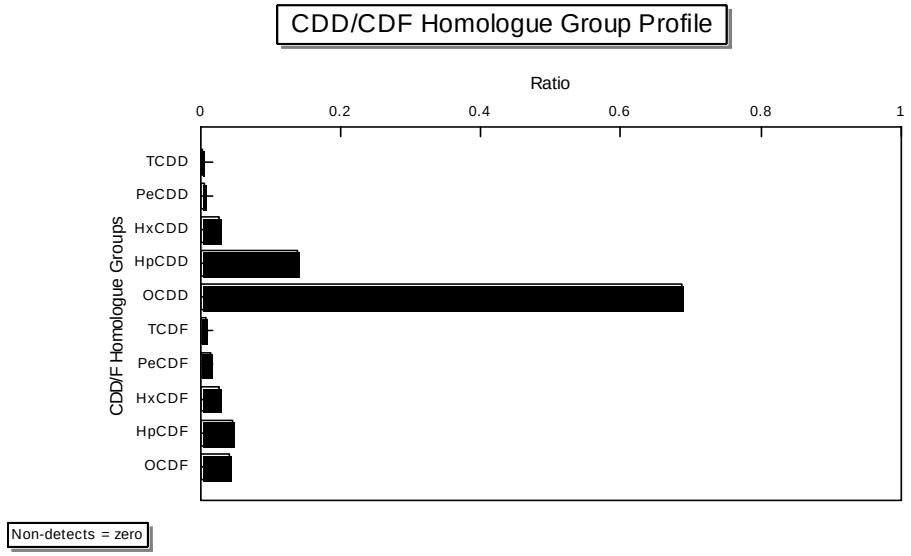


Note:Based on data from CDEP (1988, 1995), Smith et al. (1989), Maisel and Hunt (1990), Hunt et al. (1990, and OEPA (1995).

Figure 3-2. CDD/CDF Profiles for Urban Background Air

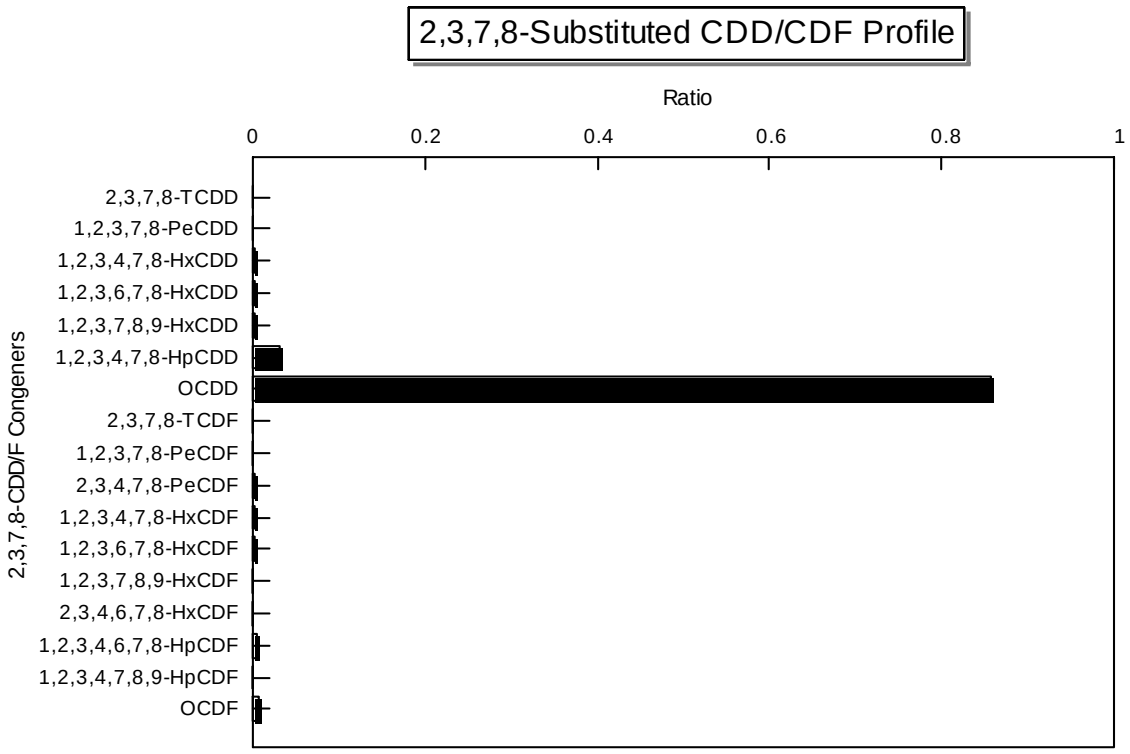


Note: Based on data from Reed et al. (1990), BC Environment (1995), U.S. EPA (1996), MRI (1992), Rogowski et al. (1999), Rogowski and Yake (1999), and Tewhey Associates (1997).

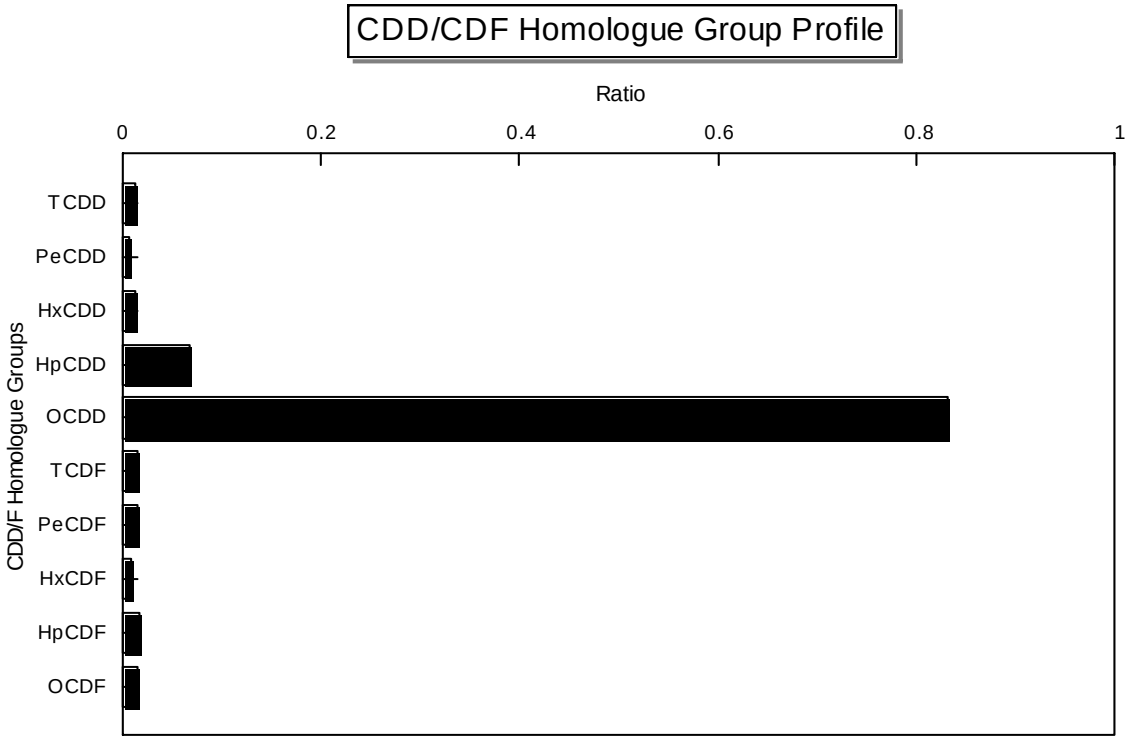


Note: Based on data from Reed et al. (1990), BC Environment (1995), U.S. EPA (1985, 1996), MRI (1992), Tewhey Associates (1997), Birmingham et al. (1990), Rogowski et al (1999), Rogowski and Yake (1999), and Pearson et al. (1990),

Figure 3-3. CDD/CDF Profiles for Rural Soils

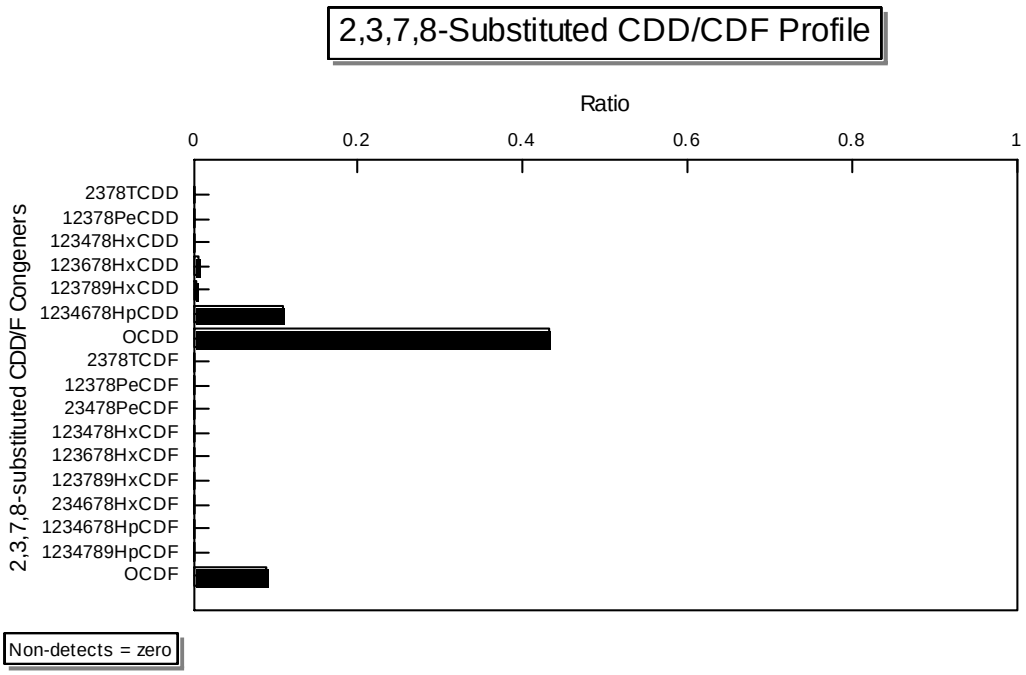


Note: Based on data from Birmingham (1990), Pearsen et al. (1990), NIH (1995), Rogowski et al. (1999) and U.S. EPA 1996).

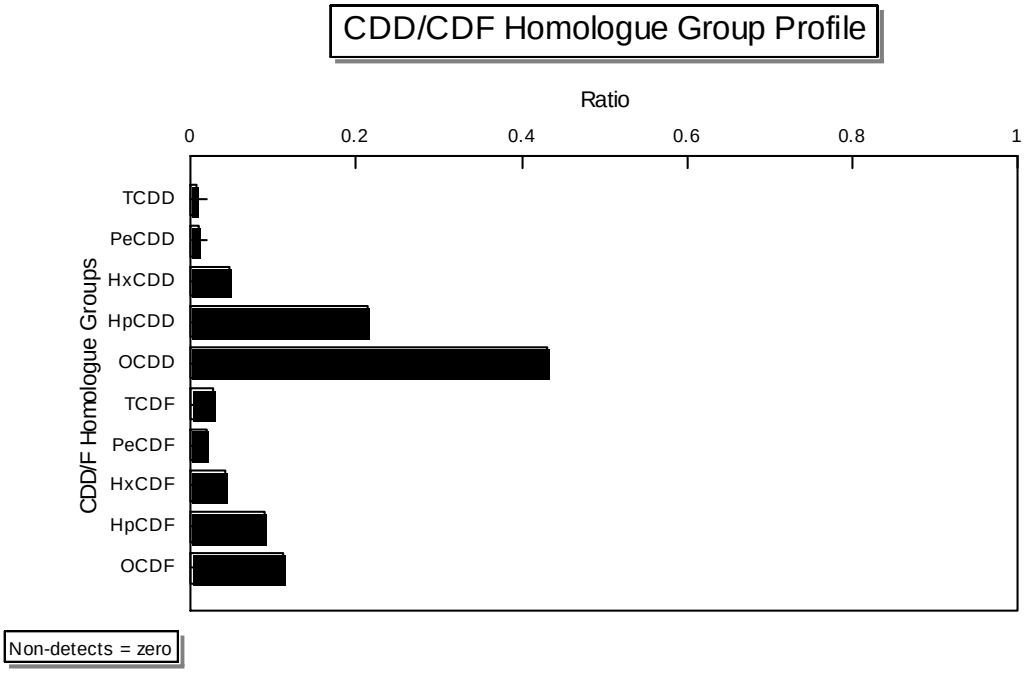


Note: Based on data from Birmingham (1990), Pearsen et al. (1990), NIH (1995), Rogowski et al. (1999) and U.S. EPA 1996).

Figure 3-4. CDD/CDF Profiles for Urban Background Soil

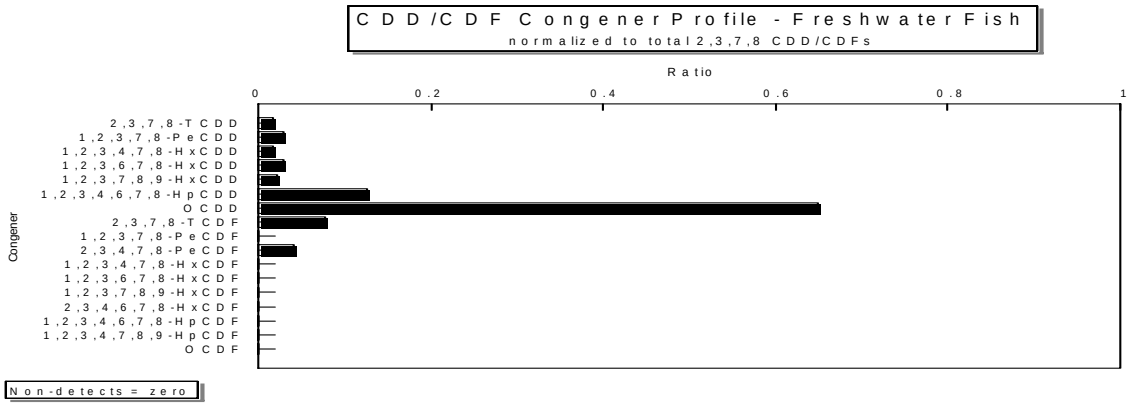


Note: Based on data from Cleverly et al. (1996) and Versar (1996a).

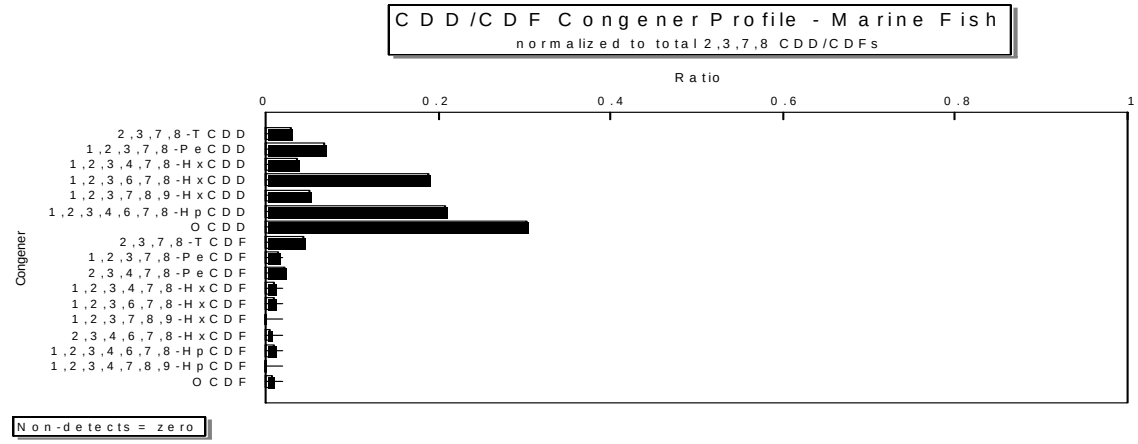


Note: Based on data from Cleverly et al. (1996) and Versar (1996a).

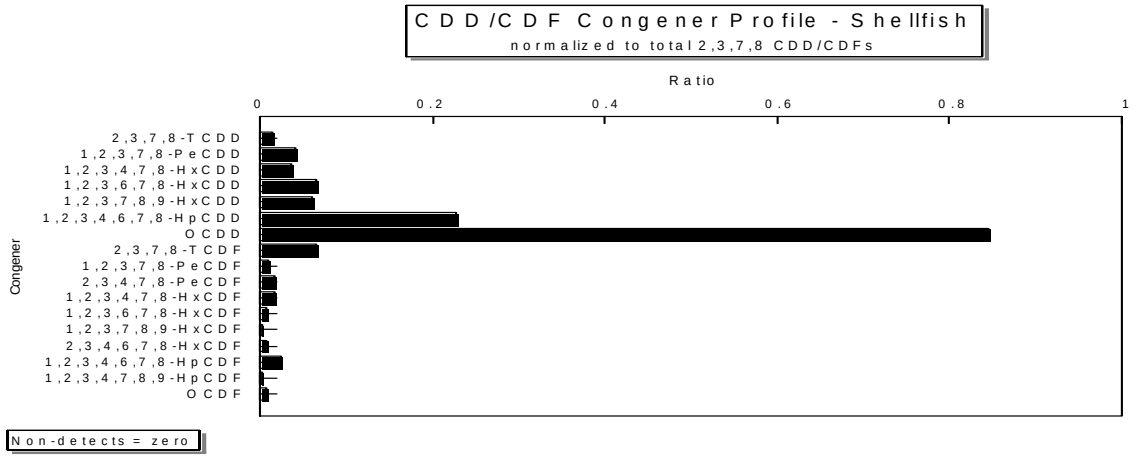
Figure 3-5. CDD/CDF Profiles for Sediment



Note: Based on data from Schecter et al. (1997).

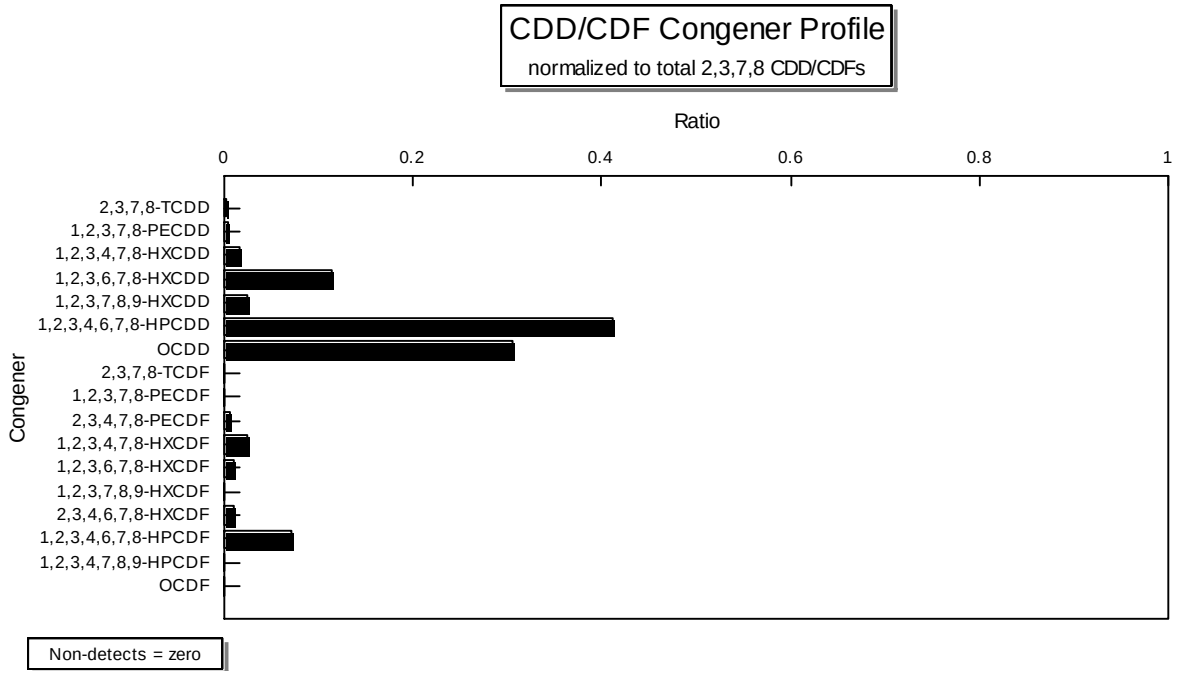


Note: Based on data from Fiedler et al. (1997c).



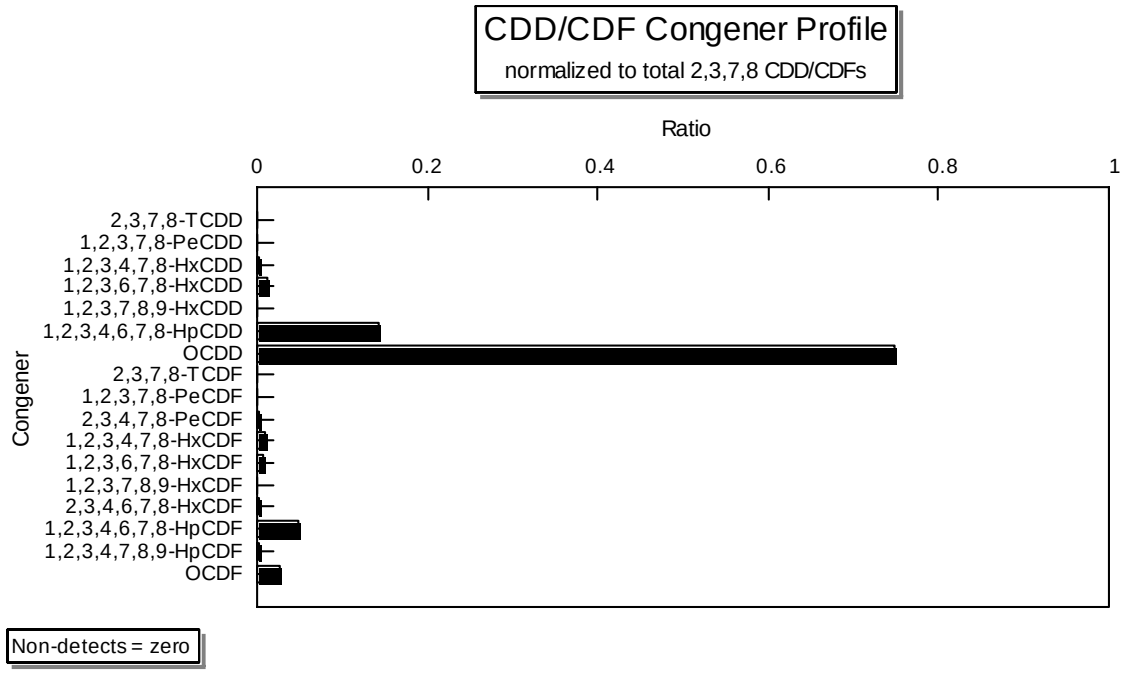
Note: Based on data from Fiedler et. al. (1997c).

Figure 3-6. CDD/CDF Congener Profiles for Fish and Shellfish



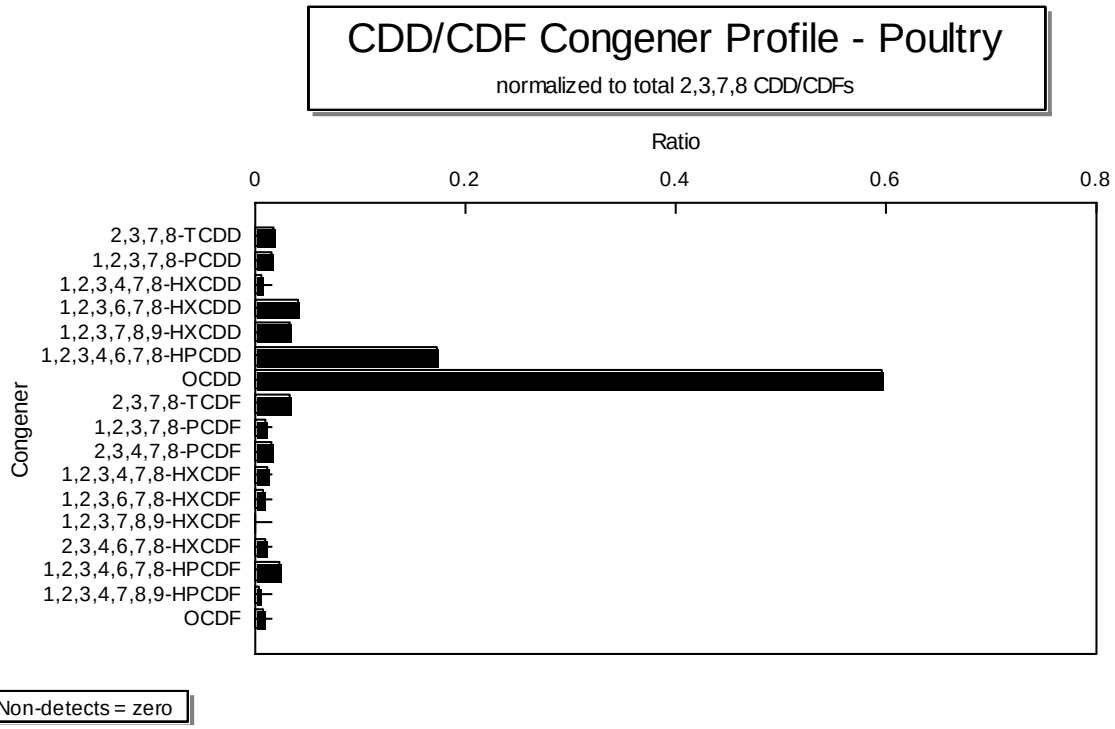
Note: Based on data from Winters et al. (1996a).

Figure 3-7. CDD/CDF Congener Profile for Beef

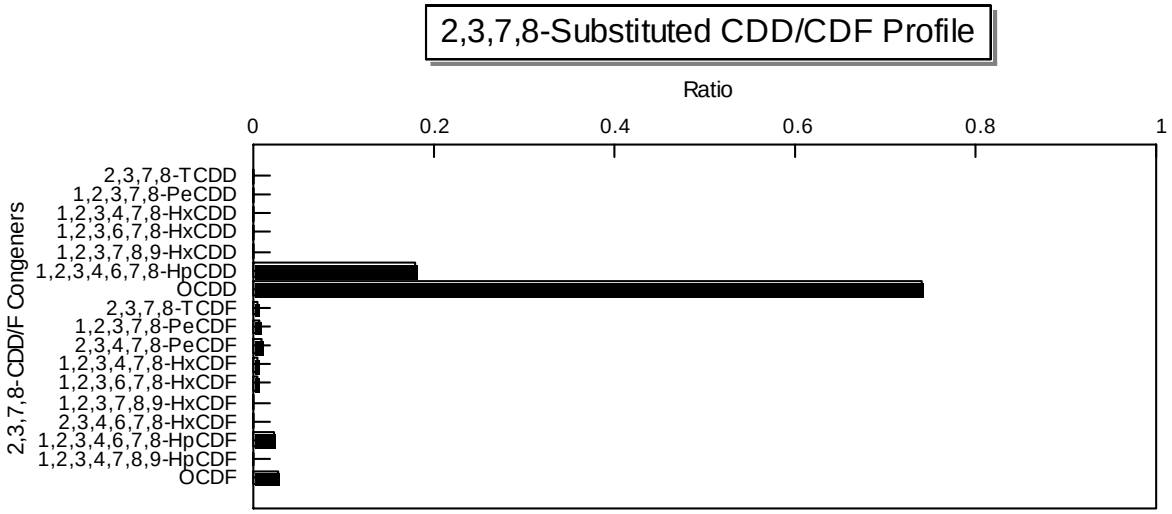


Note: Based on data from Lorber et al. (1997b).

Figure 3-8. CDD/CDF Congener Profile for Pork

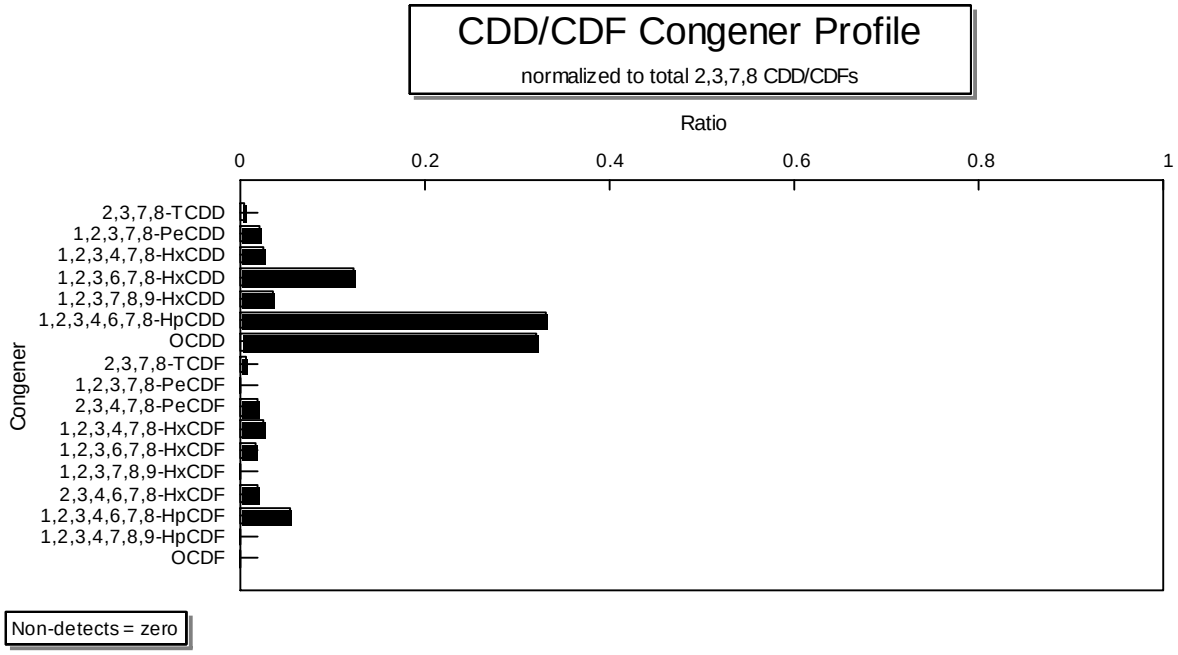


Note: Based on Ferrario et al. (1997).



Note: Based on Fiedler et al. (1997c).

Figure 3-9. CDD/CDF Congener Profiles for Poultry and Eggs



Note: Based on data from Lorber et al. (1998b).

Figure 3-10. CDD/CDF Congener Profiles for Milk and Dairy Products

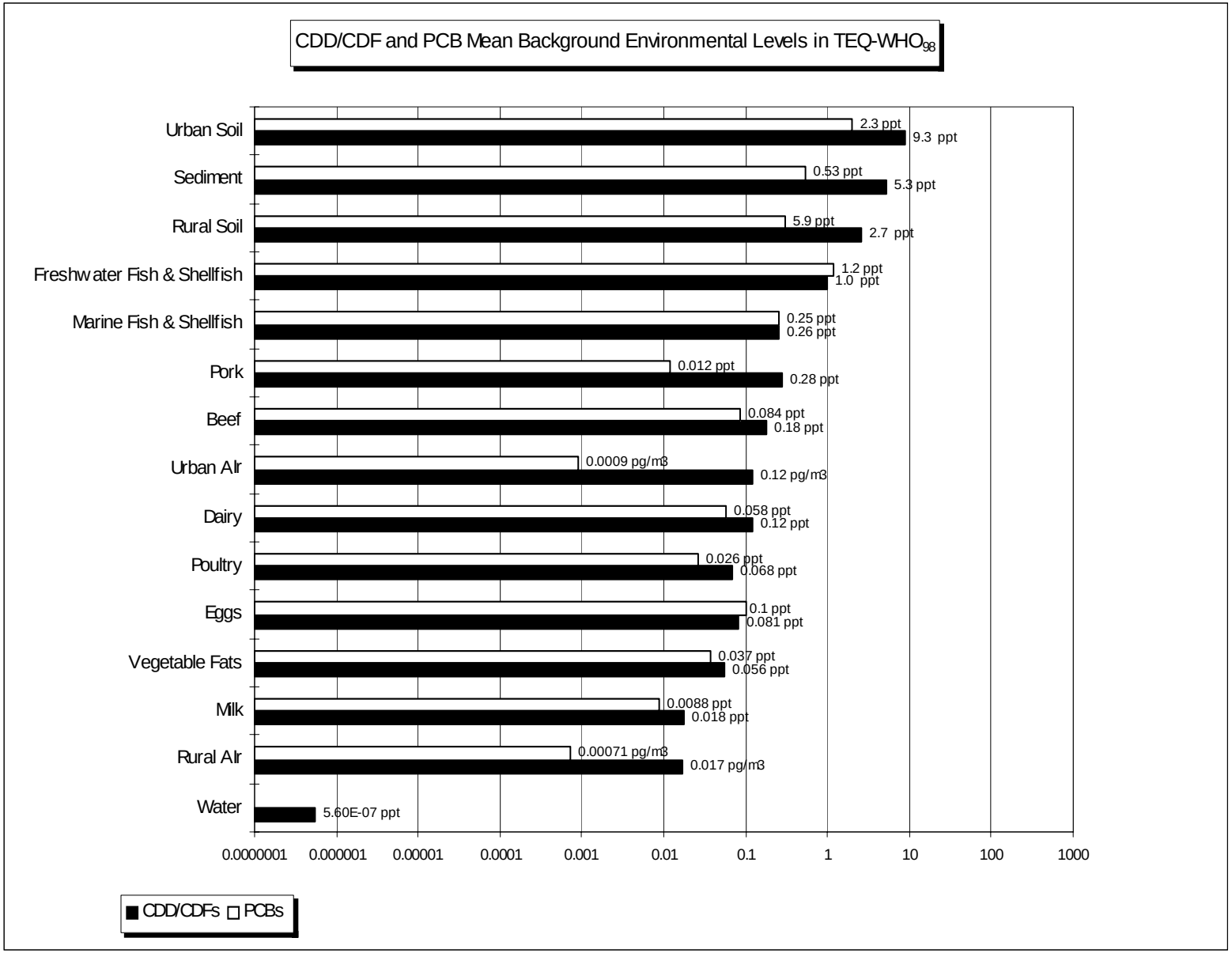


Figure 3-11. CDD/CDF and PCB Mean Background Environmental Levels in TEQ-WHO$_{98}$

4. HUMAN EXPOSURES TO CDD, CDF, AND PCB CONGENERS

4.1. INTRODUCTION

The purpose of this chapter is to assess background exposures to the dioxin-like compounds. Recent assessments of background exposures cited in the scientific literature are summarized, and background exposure estimates based on the data presented in this report are presented. Two methods have been used in this chapter to estimate background daily intake of dioxin-like compounds. One method estimates background exposures based on pharmacokinetic modeling using body burden data. The other derives background exposure estimates from dietary intake and contact with other media containing dioxin-like compounds. These two approaches provide comparable estimates of daily TEQ-WHO_{98} intake of dioxin-like compounds.

The primary focus of this chapter is background exposure among the general population. The general population consist of people who are exposed to background levels of dioxin-like compounds in soil and air. Most of their exposure comes from the commercial food supply and they do not have significant occupational exposure. People outside the general population are those living in areas with elevated soil or air levels, or whose dietary exposure is strongly influenced by food outside the commercial food supply (i.e., nursing infants, sports or subsistence fishermen, etc.).

The term "background," as applied to exposure, can be used to represent different concepts. Two common definitions are (1) the level of exposure that would occur in an area without known point sources of the contaminant of concern or (2) the average level of exposure occurring in an area whether sources are present or not. For the purposes of this document, "background" is defined as suggested in the first definition above. To the extent possible, background exposures estimated in this chapter are based on monitoring data obtained from sites removed from known contaminant sources (i.e., food data representative of the general food supply) and body burden data from nonoccupationally exposed members of the general population. Most of the data are based on studies published in the late 1980s and 1990s, but primarily the 1990s. These data are considered to be the most useful for describing background exposure levels.

Chapter 5 also includes information on potentially elevated exposures. It describes the potential for elevated exposures among subpopulations such as nursing infants, sport

and subsistence fishermen, cigarette smokers, and individuals living in areas that may be affected by localized sources of dioxin-like compounds.

4.2. LEVELS OF DIOXIN-LIKE COMPOUNDS IN HUMAN TISSUE

4.2.1. Adipose Tissue and Blood Studies from the 1980s and Early 1990s

The most extensive U.S. study of CDD/CDF body burdens is the National Human Adipose Tissue Survey (NHATS) (U.S. EPA, 1991a). NHATS was designed to estimate national population average levels of CDD/CDFs. The survey analyzed for CDD/CDFs in 48 human tissue samples that were composited from 865 samples. Each composite contained an average of 18 specimens. These samples were collected during 1987 from autopsied cadavers and surgical patients. The sample compositing prevents use of these data to examine the distribution of CDD/CDF levels in tissue among individuals. Also, not all 48 composites were used for all congeners in the statistical analysis of the data because some components did not meet the data quality objectives of the study. However, the study results allowed conclusions to be made in the following areas:

- National Averages - The national population averages for all TEQ congeners were estimated as listed in Table 4-1. Nondetects were treated as half the detection limit for averaging purposes. As shown in this table, all congeners except some CDFs, had a very low frequency of nondetects. Thus, the overall TEQ estimate is not sensitive to how nondetects were treated in the averaging.

- Age Effects - Tissue concentrations of CDD/CDFs were found to increase with age (Orban et al., 1994) (Table 4-2).

- Geographic Effects - In general, the average CDD/CDF tissue concentrations appeared fairly uniform geographically. Only one TEQ congener was found to have a significant difference among geographic regions of the country. This compound, 2,3,4,7,8-PeCDF, was found at the lowest level in the West (4.49 pg/g) and the highest in the Northeast (13.7 pg/g).

- Race Effects - No significant difference in CDD/CDF tissue concentrations was found on the basis of race (Table 4-2).

- Sex Effects - No significant difference in CDD/CDF tissue concentrations was found between males and females (Table 4-2).

- Temporal Trends - The 1987 survey showed decreases in tissue concentrations relative to the 1982 survey for all congeners. However, it is not known whether these declines were due to improvements in the analytical methods or actual reductions in body burden levels. The percent reductions among individual congeners varied from 9 percent to 96 percent.

Patterson et al. (1994) provided additional information on levels of dioxin-like compounds in human tissue. Human adipose from 28 individuals was collected. The individuals studied were ones who died suddenly in the Atlanta area during 1984 or 1986. Their ages ranged from 19 to 78 years and averaged 49 years. 2,3,7,8-TCDD levels varied with the upper end of the range equaling between three and four times the mean concentration. The tissue data are summarized in Table 4-3. This table shows that the mean PCB levels generally exceeded the mean 2,3,7,8-TCDD level and PCB-126 exceeded the 2,3,7,8-TCDD level by over an order of magnitude. The mean TEQ levels for these dioxin-like PCBs summed to about 14 ppt on a lipid basis (using either TEF_P-WHO_{94}s or TEF_P-WHO_{98}s). A complete CDD/CDF congener analysis was conducted on tissues of four of the individuals, resulting in an average of 26 ppt I-TEQ_{DF} (31 ppt TEQ_{DF}-WHO_{98}) on a lipid basis. These tissue samples were also analyzed for PCBs 77, 126, and 169. The lipid-based TEQ_P-WHO_{94} levels for these dioxin-like PCBs summed to 5.4 ppt. Thus, PCBs 77, 126, and 169 contributed between 15 and 20 percent of the total CDD/CDF and PCB TEQs. Patterson et al. (1994) also studied serum collected by the CDC blood bank in Atlanta during 1982, 1988, and 1989. These samples were pooled from over 200 donors. The average levels for 2,3,7,8-TCDD and PCBs are summarized in Table 4-4 in units of ppt on a whole weight basis. The serum data appear to indicate a decrease in exposure to PCBs from 1982 to 1988/1989. The lipid-based TEQ_P-WHO_{94} for the 1988 sample was 14 ppt based on PCBs 77, 126, 160, 105, 118, and 180. In general, the Patterson et al. (1994) data suggest that the dioxin-like PCBs can contribute significantly to body burdens of dioxin-like compounds. The data suggest that the dioxin-like PCBs can increase the total background body burden to over 40 ppt of total TEQ_{DFP}-WHO_{94}. This conclusion is uncertain because the people studied by Patterson et al. (1994) may not be representative of the overall U.S. population.

Schecter et al. (1993) reported on the comparisons of congener-specific measurements of CDDs, CDFs, and dioxin-like PCBs (77, 105, 118, 126, 156, 169, 170, and 180) in whole blood samples of four individuals with known exposures to that of the

general population. In this comparison, the analytical results of separate 450 mL blood samples collected from 50 Michigan residents, and a pooled blood sample from 5 donors at a blood bank in Missouri were used as the control group. Two of the exposed individuals were pulp and paper plant workers with potential exposure to dioxins, and the other two were Michigan residents who had elevated blood PCB levels from consuming contaminated fish. It was found that the control group and the pulp and paper mill workers who had no known exposures to PCBs had relatively high levels of coplanar, mono-ortho, and di-ortho PCBs in their whole blood. On average, the Michigan and Missouri control samples showed mean I-TEQ_{DF} concentrations of 27 ppt and 24 ppt (TEQ_{DF}-WHO_{98}s were 31 ppt and 26 ppt), respectively. These same samples showed TEQ_{P}-WHO_{94} mean concentrations of 17 ppt for the Michigan controls, and 10 ppt for Missouri controls.

Cole et al. (1995) reported on CDD/CDFs and PCBs in 132 serum samples (pooled to 14) from Ontario Great Lakes anglers and control populations. Based on a preliminary survey, anglers from the communities of Cornwall and Mississauga, Canada, were categorized based on the numbers, species, and locations of fish caught and kept for consumption, and on data reflecting the contaminant levels for the fish in these areas. Individuals categorized as having the highest and lowest potential for having elevated body burdens of CDD/CDFs and PCBs were selected for biological sampling. Individuals who did not consume fish served as controls. Study participants were further categorized by age (i.e., $<$38 years, 38-50 years, and $>$50 years). The results indicated that mean CDD/CDF TEQ levels were similar for both eaters and noneaters of Great Lakes' fish in these communities. I-TEQ_{DF}s ranged from 20.8 to 41.2 ppt for fish eaters and 24.7 to 36.8 ppt for noneaters. In general, mean I-TEQ_{DF}s increased with age (Table 4-5). PCBs 77, 126, and 169 were also evaluated in the serum samples collected from Cornwall residents. TEQ_{P}-WHO_{94}s ranged from 2.6 to 17.3 ppt for fish eaters and noneaters combined. Because no statistical differences were observed between fish eaters and noneaters, the data from this study were assumed to represent background exposures and were included in the background tissue level calculations in this chapter.

Schecter et al. (1989a) provided data on PCB levels in adipose samples from three patients from North America with no known chemical exposure history. The mean TEQ_{P}-WHO_{94} level based on PCBs 118, 105, 156, and 180 was 12.2 ppt on a lipid basis (the

TEQ_P-WHO_{98}, recalculated using TEF_P-WHO_{98}s, was 11.5 ppt on a lipid basis). Williams and LeBel (1991) reported on the mean residue levels of PCBs 126 and 169 in 62 adipose tissue samples collected in Canada during 1984. The mean lipid-based TEQ_P for these samples was estimated to be 28 ppt based on TEF_P-WHO_{94} or TEF_P-WHO_{98}s for PCBs.

Kang et al. (1997) reported on the levels of PCBs 77, 126, and 169 in human serum collected from white male paper mill workers (n = 46), as well as residents (n = 16) of a northeastern U.S. community. PCB 77 was not detected in any samples, but PCBs 126 and 169 were detected in most samples. The mean lipid-based concentrations of the two congeners (i.e., PCB 126 and 169) were 25 ppt and 31 ppt, respectively, for paper mill workers, and 18 ppt and 27 ppt, respectively, for community residents. Using TEF_P-WHO_{94}s for these PCBs (PCB 126 - 0.1, PCB 169 - 0.01), the relative contribution of these PCBs to the total CDD/CDF/PCB TEQ (using I-TEF_{DF}s for CDD/CDFs) for all study participants was approximately 10 percent. Kang et al. (1997) also observed that age, body mass index, and consumption of locally caught fish were significant predictors of coplanar PCB concentrations in human serum.

The levels of dioxin-like compounds found in human tissue/blood appear similar in Europe and North America. Schecter (1991) compared levels of dioxin-like compounds found in blood among people from U.S. (pooled samples from 100 subjects) and Germany (85 subjects). Although mean levels of individual congeners differed by as much as a factor of two between the two populations, the total I-TEQ_{DF} averaged 42 ppt in the German subjects and 41 ppt in the pooled U.S. samples. Using TEF_{DF}-WHO_{98}s, these TEQ_{DF}-WHO_{98} concentrations would be 49 ppt and 50 ppt, respectively. In later papers, Schecter et al. (1992a; 1994a) reported human blood levels for the general population from various countries. These data are presented in Table 4-6. Schecter (1991) reported adipose tissue levels in various countries, as summarized in Table 4-7. The adipose tissue data show more variation between countries, but also involved much fewer samples, reducing confidence in the accuracy of the mean.

Gonzalez et al. (1993) reported that the levels and patterns of CDD/CDFs in the adipose tissue obtained from the general population of Madrid, Spain, were similar to those of other industrialized countries. A total of 17 adipose tissue samples were collected from male and female patients ranging in age from 48 to 89 years. The lipid-based mean I-TEQ_{DF} was 42 ppt (46 ppt using TEF_{DF}-WHO_{98}s) and the mean level of

2,3,7,8-TCDD was 3.28 ppt. CDDs were found to be higher than CDFs in these samples with the higher-chlorinated CDDs accounting for the highest portion of the total CDD/CDFs (Table 4-8). The mean lipid-based I-TEQ_{DF} concentration in the blood of 11 individuals from Madrid, Spain, was 15.7 ppt (Jimenez et al., 1995). The higher-chlorinated CDDs (i.e., HpCDD and OCDD) were the dominant congeners observed in these samples.

Schumacher et al. (1999a and 1999b) conducted two studies to analyze background concentrations of CDD/CDFs in blood and adipose tissue from individuals from Tarragona, Spain. In the first study (Schumacher et al., 1999a), blood plasma samples were collected from 20 nonoccupationally exposed subjects living near an area where a hazardous waste incinerator is being constructed. The reported mean blood lipid CDD/CDF concentration was 27.0 ppt I-TEQ_{DF} with a range of 14.8 to 48.9 ppt. The maximum TEQ_{DF} value observed in this study was approximately 1.7 times the mean. CDD/CDF TEQs were higher in women (e.g., 27.7 ppt) than in men (e.g., 25.2 ppt). The results, however, were not statistically significant. Schumacher et al. (1999b) conducted a second study on adipose tissues of 15 autopsied subjects. The arithmetic mean I-TEQ_{DF} was 30.98 ppt (range of 13.4 to 69.4 ppt). The maximum I-TEQ_{DF} value observed in this study was approximately 2.2 times the mean. Unlike their previous study, I-TEQ_{DF}s were statistically higher ($p < 00.1$) in the fat of women (mean value: 45 ppt) than in men (mean value: 24 ppt). Levels of CDD/CDFs were higher for those people that lived in industrialized areas than the residents who lived in the city, but this difference was not statistically significant.

Beck et al. (1994) reported on levels of CDD/CDFs in adipose tissue from 20 males (mean age-50 years) from Germany. I-TEQ_{DF}s ranged from 18 ppt to 122 ppt with a mean of 56 ppt (using TEF_{DF}-WHO_{98}s, the mean TEQ_{DF} would be 65 ppt), on a fat weight basis. The I-TEQ_{DF} maximum concentration in this study was approximately 2.4 times the mean. Beck et al. (1994) also reported on CDD/CDF levels in various organs of the body. In comparison to adipose tissue, the concentrations of CDD/CDFs in brain and placental tissue were found to be low. Accumulation of CDD/CDFs was not found to occur in the thymus, spleen, and liver, based on whole weight concentrations. Schecter et al. (1994a) also reported on I-TEQ_{DF} levels in organs of two autopsy patients from New York. The highest concentrations of CDD/CDFs were found in adipose tissue (28 ppt I-TEQ_{DF}),

adrenal tissue (14 ppt I-TEQ_{DF}), and liver (12 ppt I-TEQ_{DF}), on a whole weight basis. Lower concentrations were observed in spleen (4.6 ppt I-TEQ_{DF}), muscle (2.4 ppt I-TEQ_{DF}), and kidney (0.8 ppt I-TEQ_{DF}). Schecter et al. (1994b) reported PCB levels for these two autopsy patients. Total PCBs in adipose tissue were 280.7 ppb on a wet weight basis and 344.2 ppb on a lipid weight basis.

Beck et al. (1994) also observed that CDD/CDF tissue levels were dependent on the age of the individual. I-TEQ_{DF} concentrations in infants ranged from 2.1 pg/g to 22 pg/g on a lipid basis. 2,3,7,8-TCDD was found to increase at a rate of 0.12 pg/g fat per year, and I-TEQs increased at a rate of 0.77 pg/g fat per year. Schecter et al. (1995a) measured levels of CDD/CDFs in human fetal tissue (N = 10) at 8 to 14 weeks gestational age and observed an average of 5 pg I-TEQ_{DF}/g on a lipid basis. Stillborn liver (N = 3) concentrations averaged 10 pg I-TEQ_{DF}/g on a lipid basis. These levels are considerably lower than those observed in adult tissues (Schecter et al., 1995a). Päpke et al. (1996) also observed that I-TEQ_{DF} levels in human tissues were age dependent. Whole blood samples collected in 1994 indicated that I-TEQ_{DF} concentrations increased with increasing age. Similar age effects were noted for PCBs 77, 126, and 169 (Päpke et al., 1996).

Wuthe et al. (1995) studied body burdens of CDD/CDFs among children in Germany. Three study groups were evaluated: blood from 11 nonexposed children, age 9 to 15 years; adipose and liver tissue from 20 stillborn or otherwise deceased infants, age 0 to 44 weeks, some of whom had been breast-fed; and pooled blood from 10-year-olds from 3 different regions. The total I-TEQ_{DF} concentration for the first study group (i.e., blood from 11 children between the ages of 9 and 15 years) was 10.7 ppt. Based on the other study groups, the authors made the following conclusions: (1) because CDD/CDFs were found in stillborns, a diaplacental transfer of these compounds occurred; (2) breast feeding has an impact on CDD/CDF concentrations (i.e., the mean I-TEQ_{DF} concentration was 12.7 ppt for breast-fed infants and 3.6 ppt for formula-fed infants); and (3) body burdens of CDD/CDFs are lower among children than adults.

Lanting et al. (1998) examined PCBs in adipose tissue, liver, and brain from nine stillborns at varying gestational ages. Of the four PCB congeners examined, only PCB 118 was dioxin-like. The median levels reported for PCB 118 were 20 ppt for adipose tissue, 17 ppt for the liver, and 6 ppt for the brain. The results of the study indicated that there was a significant relationship (correlation coefficient = 0.98; $p < 0.01$) between adipose

tissue concentrations and liver concentrations. Correlation between the levels of PCB congeners in these tissues and gestational age of the infants were not significant; correlation coefficients varied between 0.22 and 0.47.

Kruezer et al. (1997) reported CDD/CDF concentrations from lipids of adipose tissue and livers from cadavers (3 stillborns and 17 infants aged 0.43 to 44 weeks old who died from sudden infant death syndrome). I-TEQ_{DF} lipid-based concentrations were in the range of 1.55 to 29.63 ppt for adipose tissue (n = 20) and 2.05 to 57.73 ppt (n = 19) for liver. TCDD concentrations in lipids of breast-fed infants were higher compared to nonbreast-fed infants.

Nagayama et al. (1995) studied the effect of birth order on the body burdens of CDD/CDFs and PCBs among 50 healthy Japanese women. The concentrations of these dioxin-like compounds in blood were found to be significantly higher among first-born women than among other women. No relationship was found between the method by which these women were fed (i.e., breast-fed, formula-fed, or mix between breast milk and formula) and the blood concentrations of CDD/CDFs and PCBs.

Human breast tissue has also been analyzed for dioxin-like PCBs (Dahl et al., 1994; Petreas et al., 1998). Dahl et al. (1994) examined breast tissue collected from 16 women seeking hospital care for breast tumors in Sweden. PCB levels were observed to increase with age. Based on PCBs 105, 114, 118, 156, 157, 170, 180, and 189, the mean total TEQ_P-WHO_{98} for these samples was 40 ppt. Petreas et al. (1998) studied human breast adipose tissue collected from women undergoing breast surgery at Stanford University in California to determine CDD/CDF and PCB levels. Of the 17 CDD/CDF congeners, only OCDD, HpCDD, HxCDD, and PeCDF were observed to be above the limit of detection. I-TEQ_{DF} lipid-based concentrations, using one-half LOD for non-detects, ranged from 6 ppt to 78 ppt with a mean of 17.8 ppt (n = 62). Based on only the four detected congeners, the I-TEQ_{DF} concentration ranged from 5 ppt to 42 ppt with a mean of 12.6 ppt (the maximum I-TEQ_{DF} value is 3.3 times higher than the mean). Lipid-based PCB levels ranged from 451 ppb to 3,830 ppb with a mean of 1,120 ppb, based on PCBs 153/132, 180, 74, 138, 182/187, 170, 196/203, 194, 199, 156, 118, 206, 183, 99/113, 177, 28, 105/127, 128/162, 157, and 101 (n = 61). The maximum concentration is 3.4 times the mean. Lipid-based TEQ_P-WHO_{94} levels for coplanar PCBs 77, 126, and 169 ranged from 7 ppt to 110 ppt with a mean of 38 ppt (the maximum TEQ_P-WHO_{94} is 2.9 times higher than

the mean). The most prevalent PCB congeners included PCBs 153/132, 180, 74, 138, 182/187, and 170, which, when summed, contributed over 50 percent of the total PCB measure.

Iida et al. (1999) analyzed blood samples from 50 young (i.e., approximately 20 years of age) Japanese women for dioxin-like compounds. The women were described as "normal subjects" who had not yet had children, and the samples were collected in 1993 and 1994. The range if I-TEQ_{DF}s was 7.3 pt to 28.0 ppt with a mean of 16.4 ppt (the maximum value is 1.7 times higher than the mean). The range of TEQ_{P}-WHO_{94}s (based on PCBs 77, 126, and 169) was 1 ppt to 10 ppt with a mean of 4.9 ppt. The total TEQ_{DFP}-WHO_{94} was 21 ppt and the maximum value was 37 ppt. This maximum value is 1.8 times higher than the mean.

4.2.2. Breast Milk Studies from the 1980s and Early 1990s

Schecter et al. (1989b; 1992b) reported that in a study of 42 U.S. women, the average I-TEQ_{DF} was 16 ppt (20 ppt of TEQ_{DF}-WHO_{98}) (3.3 ppt of 2,3,7,8-TCDD) in the lipid portion of breast milk. Schecter et al. (1989b) also reported a total I-TEQ_{DF} of 27 ppt (TEQ_{DF}-WHO_{98} = 31 ppt) for human milk collected in Germany (n = 185). A much larger study in Germany (n = 526) showed an average of 29 ppt of I-TEQ_{DF} (TEQ_{DF}-WHO_{98} = 34 ppt) in lipid portion of breast milk (Fürst et al., 1994). Bates et al. (1994) analyzed breast milk samples from 38 women in New Zealand and reported mean lipid-based I-TEQ_{DF}s of 16.5 ppt for urban women and 18.1 ppt for rural women (average I-TEQ_{DF} = 17.2 ppt; average TEQ_{DF}-WHO_{98} = 21 ppt). The age of the mother was found to be positively correlated with the concentration of CDD/CDFs in breast milk. Beck et al. (1994) reported a mean I-TEQ_{DF} of 30 ppt (TEQ_{DF}-WHO_{98} = 35 ppt) in the milk fat based on 112 human milk samples from Germany. The congeners that contributed the most to the total I-TEQ_{DF} were 2,3,4,7,8-PeCDF (35 percent), total HxCDD (22 percent), and 1,2,3,7,8-PeCDD (21 percent). Beck et al. (1994) observed that CDD/CDF levels decreased with the number of children and the duration of breast feeding, but increased with the age of the mother. Beck et al. (1994) also compared the adipose tissue levels of breast-fed and bottle-fed infants who had died of sudden infant death syndrome. The breast-fed infants had higher tissue levels (5.4 to 22 pg/g fat; n = 4) than the bottle-fed infants (2.1 to 4.4 pg/g fat; n = 2).

Hirakawa et al. (1995) studied differences in CDD/CDF levels in human milk collected from primipara and multipara Japanese women. Human milk samples were taken from seven primiparas and eight multiparas between the ages of 22 and 40 years and analyzed for CDD/CDFs and dioxin-like PCBs. Total lipid-based TEQ concentrations were 34.6 ppt for the primiparas and 30.7 for multiparas, using I-TEF_{DF}s for CDD/CDFs and TEF_P-WHO_{94} for PCBs. Significant differences were observed between the concentrations of 2,3,7,8-TCDD; 1,2,3,7,8-PeCDD; 1,2,3,6,7,8-HxCDD; 1,2,3,7,8,9-HxCDD; 2,3,4,7,8-PeCDF; and 1,2,3,6,7,8-HxCDF in primipara and multipara women. The concentrations of these congeners varied by a factor ranging from 1.3 to 1.8 for the two study groups (Table 4-9). The mean I-TEQ_{DF} plus three standard deviations indicates that the high-end CDD/CDF concentration is approximately 2 times higher than the mean.

Van Cleuvenbergen et al. (1994) observed lipid-based I-TEQ_{DF} levels in human milk ranging from 27 to 43 ppt with a mean of 34 ppt (TEQ_{DF}-WHO_{98} = 40 ppt), based on samples from 9 women living in Belgium in 1992. The maximum I-TEQ_{DF} concentration observed in this study was approximately 1.3 times higher than the mean. OCDD and 1,2,3,4,6,7,8-HpCDD accounted for the highest proportion of total CDD/CDFs, but 2,3,4,7,8-PeCDF accounted for the largest proportion of the total CDD/CDF I-TEQ_{DF} (i.e., approximately 45 percent (Table 4-10)). Similar I-TEQ_{DF} levels have been observed in other countries. Schecter et al. (1989c) collected human milk samples from southern Japan in 1986. The mean lipid-based total I-TEQ_{DF} for two composites, containing three samples each, was 26 ppt. Based on data from Startin et al. (1989), the mean lipid-based I-TEQ_{DF} for a pool of 80 human milk samples from the United Kingdom was 33 ppt (TEQ_{DF}-WHO_{98} was 39 ppt).

Pluim et al. (1994a) studied the influence of short-term dietary changes in fats and carbohydrate intake on CDD/CDF concentrations in human milk. Two different diets were administered to two groups of lactating women in The Netherlands. Sixteen women had a low-fat/high-carbohydrate/low-dioxin diet, and 18 women had a high-fat/low-carbohydrate/low-dioxin diet for 5 consecutive days. At the end of this dietary regimen, milk samples were collected and analyzed for CDD/CDFs. No significant differences between CDD/CDF levels were observed. The mean I-TEQ_{DF} values for mothers using the low-fat/high-carbohydrate/low-dioxin diet were 30.2 ppt and 30.0 ppt before and after the test period, and the mean I-TEQ_{DF} values for the mothers using the high-fat/low-

carbohydrate/low-dioxin diet were 24.4 ppt and 24.0 ppt before and after the test period. Pluim et al. (1994a) concluded that short-term dietary changes were not an effective means of reducing dioxin concentrations in human milk. In another study, Pluim et al. (1994b) measured the levels of CDD/CDFs in breastmilk as part of a study to evaluate relationships between neonatal CDD/CDF exposure via breastmilk and potential physiological effects. CDD/CDFs were measured in the breastmilk of 35 Dutch mothers when their nursing infants were 11 weeks of age. The mean lipid-based I-TEQ_{DF} level in these breastmilk samples was 28.1 ppt (TEQ_{DF}-WHO_{98} = 33.5 ppt).

In 1994 and 1996, Hooper et al. (1998) monitored levels of CDD/CDFs in breast milk samples collected in Kazakstan, a country of the former Soviet Union. The mean reported CDD/CDF levels ranged from 7.2 to 57 ppt I-TEQ_{DF}. The detection limit for the sampling was 1 ppt, and only levels above the detection limit were reported. Approximately 92 breast milk samples were collected in both of these years. The range and mean values of individual and composite samples were similar by region and ethnicity. In addition, this study found that CDD/CDF levels were significantly higher in breast milk samples collected from rural sites (mean 46 ppt I-TEQ_{DF}, n = 23) than from a nonrural site (mean 11 ppt I-TEQ_{DF}, n = 32). Hooper et al. (1998) did not identify the reason for the higher CDD/CDF concentrations in samples from rural women. Several postulations include the high use of a pesticide (Hexachlorocyclohexane) in Kazakstan, the Kazakstan diet may include more contaminated fish from the Ural River, and consumption of cottonseed oil and kefir (a beverage of fermented cow's milk), which has been shown to have high dioxin levels. Consumption of cottonseed oil and kefir is more common in the rural areas than in urban areas.

Recently, Liem et al. (1996) reported on the results of the second round of a human breast milk study conducted by the World Health Organization (WHO). Human milk samples were collected from women in 19 countries during 1992/93 and analyzed for CDDs, CDFs, and PCBs (i.e., non-ortho 77, 126, 169; mono-ortho 105, 118; markers 28, 52, 101, 138, 153, 180). The results were compared to the results of the first round of sampling that occurred among 11 countries in 1987/88 to evaluate trends in exposure to dioxin-like compounds. Based on the 1992/93 results of pooled human milk samples, lipid-based I-TEQ_{DF} concentrations ranged from 3.8 pg/g for the Librazhd area of Albania to 27.1 pg/g for the Liege area of Belgium (Table 4-11). Overall, significantly lower I-TEQ_{DF}s

and PCBs were observed in Albania, Hungary, and Pakistan (Table 4-11). The highest I-TEQ_{DF} levels were observed in Belgium and The Netherlands (Table 4-11), and the highest TEQ_P-WHO_{94} levels were observed in Canada's Hudson Bay region and in regions of the Czech and Slovak Republics. An analysis of individual samples from The Netherlands and Denmark indicated a high level of variability among individuals (i.e., levels varied by a factor of 3 to 5). Comparison of the 1992/93 data to the 1987/88 data indicated that the levels of CDD/CDFs and marker PCBs in breast milk have declined in some countries with concentrations decreasing up to 50 percent in some areas (Table 4-12). Liem et al. (1996) estimated an overall annual decrease in CDD/CDFs of 7.2 percent over the 5-year time period evaluated.

Vartiainen et al. (1997) reported CDD/CDF and PCB levels in the human milk of 167 women collected in 1987 from an urban area and a rural area in Finland. The average CDD/CDF levels were significantly higher ($p < 0.001$) in the urban area (26.3 pg I-TEQ_{DF}/g fat; $n = 47$) than in the rural area (20.1 pg I-TEQ_{DF}/g fat; $n = 37$) for all primiparae individuals. Similarly, the total PCB concentrations were higher ($p < 0.01$) among urban primiparae (496 ng/g fat; 36.8 pg TEQ_P-WHO_{94}/g; n-47) than among rural primiparae (396 ng/g fat/ 26.3 pg TEQ_P-WHO_{94}/g; $n = 37$). The CDD/CDF and PCB levels in the milk of these women decreased with the increasing number of children breast-fed by them. Vartiainen et al. (1997) estimated that a woman's third child would be exposed to about 70 percent of the CDD/CDF and PCB levels that her first-born child was exposed to, and the eighth to tenth child would be exposed to only about 20 percent of the levels of the first-born. In addition, Vartiainen et al. (1997) observed a possible correlation between average I-TEQ_{DF} levels and total PCB concentrations (correlation coefficient (R) was 0.84 for the urban area and 0.71 for the rural area).

Kiviranta et al. (1999) coordinated a study from 1992-1994, which was designed as a follow-up of the Vartianen et al. (1997) study, measuring CDD/CDF and PCB levels in human milk in Finland. One round of 20 samples focused on urban areas (Helsinki, Finland) and the second round of 64 samples focused on rural areas (Koupio, Finland, and surroundings). Samples were divided into groups based on the number of children the mother has nursed. The groups included women who have had 1, 2, 3, 4, 6, or 13 children. The average CDD/CDF levels reported were 13.6 pg I-TEQ_{DF}/g fat for rural areas and 19.9 pg I-TEQ_{DF}/g fat for urban areas for all primiparae women. The average total

PCB concentrations were 198 pg/g fat from rural areas, and 296 pg/g fat for urban areas. The conclusions of the Kiviranta et al. (1999) study were identical to the Vartianen et al. (1997) study. The differences between the breast milk I-TEQ_{DF}s and PCB concentrations for rural and urban women remain and I-TEQ_{DF}s and PCB concentrations in breast milk also decreased proportionally when women had two or more children. It was also evident that there was a marked decrease in I-TEQ_{DF} and PCB levels when comparing to the values reported in 1992-1994 to those in 1987.

Tuinstra et al. (1994) evaluated the CDD/CDF and dioxin-like PCB content of human milk from The Netherlands. Samples were collected 10 and 42 days after delivery from about 200 mothers. Based on these data, the mean total I-TEQ_{DF} was 31 ppt (TEQ_{DF}-WHO_{98} = 36 ppt) (Tuinstra et al., 1994), and the mean TEQ_P-WHO_{94} for PCBs 77, 126, 169, 105, 118, 156, 170, and 180 was 36 ppt (TEQ_P-WHO_{98} = 31 ppt) (Tuinstra et al., 1994; Koopman-Esseboom et al., 1994).

Similar estimates of the dioxin-like PCB content of human milk have been obtained for North America and Europe. Hong et al. (1992) analyzed human milk samples from upstate New York for PCBs 77, 105, 114, 118, 123, 126, 156, 157, 167, 169, and 189. PCB 118 accounted for the highest proportion of the total PCB concentration. The mean lipid-based TEQ_P-WHO_{94} and TEQ_P-WHO_{98} for these samples was 13 ppt. The total TEQ_P-WHO_{94} for 96 pooled human milk samples from Canada was also 13 ppt (TEQ_P-WHO_{98} = 10 ppt) (Dewailly et al., 1994). She et al. (1995) analyzed 12 human milk samples for PCBs 77, 118, 105, 126, 156, 169, 170, and 180. The total TEQ_P-WHO_{94} for these samples was 16 ppt (TEQ_P-WHO_{98} = 14 ppt).

For European countries, the lipid-based TEQ_P-WHO_{94} levels were 22 ppt (TEQ_P-WHO_{98} = 18 ppt), based on 1990/91 data for PCBs 118, 156, 170, and 180 from 68 German women (Georgii et al., 1995) and 32 ppt (TEQ_P-WHO_{98} = 30 ppt), based on data for PCBs 77, 126,169, 105, 118, 114, 156, 170, and 180 from 28 Norwegian mothers (Johansen et al., 1994). Noren et al. (1990) and Noren and Lunden (1991) analyzed human milk samples from Sweden in 1989 (n = 2) and in every 4 years between 1972 and 1988/89, respectively. Total TEQ_P-WHO_{94}s based on Noren et al. (1990) were 29 ppt (TEQ_P-WHO_{98} = 27 ppt) (PCBs 118, 105, 156, 180, 77, 126, and 169). Noren and Lunden (1991) observed that the concentrations of PCBs in human milk declined between 1972 and 1984/85, but that the 1988/89 samples had similar concentrations as the

1984/85 samples. Based on the 1988/89 sampling period, the total TEQ_P-WHO_{94} was 19 ppt (TEQ_P-WHO_{98} = 18 ppt) based on PCBs 105, 156, 180, 77, 1216, and 169 (n = >100).

Van der Velde et al. (1994) compared the levels of PCBs 77, 126, and 169 in cow's milk and human milk from The Netherlands. The concentrations of these compounds were found to be higher in human milk than in cow's milk collected from a background location (Table 4-13). Based on these data, the total TEQ_P-WHO_{94} and TEQ_P-WHO_{98} for human milk was 9.4 ppt for these three dioxin-like PCBs.

Abraham et al. (1998) measured CDD/CDF and coplanar PCBs in blood of four mothers before and after delivery and during lactation. Abraham et al. (1998) also examined their breast milk and their infants blood for concentrations of CDD/CDF and coplanar PCBs. CDD/CDF and coplanar PCBs were also quantified in the cord blood, meconium, and transit stool. Table 4-14 presents a summary of the TEQ_{DF}s of mothers' milk and blood, and infants' blood. For two of the mothers (mother 1 and mother 2), the data were associated with their second delivery, and data were also available for their first-born infants at the age of 11 to 12 months. Mother 3 was the only subject that did not fully breastfeed her infant for at least 17 weeks. The results of this study suggest that CDD/CDF and coplanar PCB TEQs in the blood of the second infants were only about half as much as in the first born children (at the same age). This is likely a result of reductions in CDD/CDF concentrations in breast milk as a result of previous lactation. In addition, the infant that was not fully breast-fed had a lower l-TEQ_{DF} concentration in the blood than the fully breast-fed infants. Lipid-based CDD/CDF concentrations in the infants' tissues appeared to increase during the 11 months after birth, based on the comparison of infants' blood CDD/CDF concentrations at 11 months and CDD/CDF concentrations in cord blood concentrations.

Schecter et al. (1998) analyzed blood and milk from a mother that nursed twin babies over a 38-month period. In this study, a woman gave birth to twins on December 15, 1992. Blood and milk samples were taken each month starting in February 1993 and ending in September 1995. Overall, CDD levels in milk decreased from 309 ppt to 173 ppt, CDF levels dropped from 21 ppt to 9 ppt, and total coplanar PCB levels decreased from 151 to 21 ppt during that time period. Schecter et al. (1998) estimated that the mother reduced her dioxin body burden from 310 to 96 ng TEQ_{DFP}-WHO_{98}, or

approximately 69 percent during that time period. Overall, the CDD/CDF/PCB concentrations in the maternal whole blood dropped from 698 ppt to 262 ppt in lipids during that time period. The twins' consumption of CDD/CDF and coplanar PCBs from breast feeding was estimated to be approximately 115 ng TEQ_{DFP}-WHO_{98} per twin.

The levels of dioxin-like compounds in human breast milk can be predicted on the basis of the estimated dioxin intake by the mother. Such procedures have been developed by Smith (1987) and Sullivan et al. (1991). The approach by Smith assumes that the concentration in breast milk fat is the same as in maternal fat and can be calculated as:

$$C_{milk\ fat} = \frac{m\ h\ f_1}{0.693\ f_2} \qquad \text{(Eqn. 4-1)}$$

where:

$C_{milk\ fat}$ = Concentration in maternal milk (pg/kg of milk fat);
m = Average maternal intake of dioxin (pg/kg of body weight/day);
h = Half-life of dioxin in adults (days);
f_1 = Proportion of ingested dioxin that is stored in fat; and
f_2 = Proportion of mother's weight that is fat (kg maternal fat/kg total body weight).

This steady-state model assumes that the contaminant levels in maternal fat remain constant. Though not described here, Smith (1987) also presents more complex approaches that account for changes in maternal fat levels during breast feeding. The model developed by Sullivan et al. (1991) is a variation of the models proposed by Smith (1987). The Sullivan model considers changes in maternal fat levels and predicts chemical concentrations in milk fat as a function of time after breast feeding begins. The model proposed by Smith assumes that infant fat concentration at birth is zero; whereas, Sullivan assumes that the infant fat concentration at birth is equal to the mother's fat concentration.

Flesch-Janys et al. (1996) estimated the half-life of 2,3,7,8-TCDD in humans to be approximately 7 years. For the purpose of this preliminary analysis, it is assumed that a 7-year half-life applies to all of the dioxin-like compounds. Smith (1987) suggests values of 0.9 for f_1 and 0.3 for f_2. Using these assumptions and a background exposure level of

1 to 3 pg of TEQ_{DFP}-WHO_{98}/kg-d (derived from diet analysis, see Section 4.4.2 and previous assessments of background exposure), the concentration of dioxin-like compounds in breast milk fat is predicted to be about 10 to 30 ppt of TEQ, which is slightly lower than the measured values.

Uncertainty is introduced into this estimate by the assumption that the assumed half-life rate and partitioning factors apply to all the dioxin related compounds. Although these properties are likely to be similar among the various congeners, some variation is expected. It is unknown whether the net effect of these uncertainties would lead to over or under estimates of dose. However, the simple model appears to provide reasonable predictions of background levels found in breast milk and was judged adequate for purposes of a preliminary analysis. For detailed assessments, readers should consider using the more complex models and developing chemical-specific property estimates.

Travis et al. (1988) presented an alternative approach to estimating breast milk contaminant levels. They proposed a biotransfer approach:

$$C_m = B_m I \qquad \text{(Eqn. 4-2)}$$

where:

C_m = Contaminant concentration in breast milk fat (mg/kg);
B_m = Biotransfer factor for breast milk fat (d/kg); and
I = Maternal intake of contaminant (mg/d).

Travis et al. (1988) also argued that the biotransfer factor is primarily a function of the octanol-water partition coefficient (K_{ow}) and developed the following geometric mean regression:

$$B_m = 6.2 * 10^{-4} K_{ow} \qquad \text{(Eqn. 4-3)}$$

This regression was derived from data on six lipophilic compounds (log K_{ow} range: 5.16 to 6.5), but did not include any dioxins or furans. Assuming a log K_{ow} of 6.6 for 2,3,7,8-TCDD, a B_m of 3,700 d/kg is predicted. Combining this value with a maternal intake of 6

pg/d, a breast milk concentration on a fat basis of 22 ppt is predicted. This prediction is about 7 times higher than what has been measured for TCDD in breast milk in the United States. Thus, this approach appears to overpredict TCDD levels while the approach suggested by Smith (1987) appears to underpredict total TEQ levels.

4.2.3. The Blood Studies of the CDC Collaboration (1995-1997)

The Centers for Disease Control (CDC) has compiled data on blood concentrations of dioxins, furans, and coplanar PCBs from individuals in the United States with no known exposures to dioxins (CDC, 2000). These data come from site-specific studies (with permission from principle investigators in those studies), and CDC has provided the laboratory analyses of all the blood samples. All the samples were collected between 1995 and 1997. There are a total of 316 individuals included in their compilation from six locations: 1) Manchester, Missouri (n = 61), 2) Times Beach, Missouri (n = 67), 3) Jacksonville, Arkansas (n = 57), 4) Oregon (n = 9), 5) Wisconsin (n = 93), and 6) North Carolina (n = 29). CDC is preparing manuscripts for peer literature publication of statistical summaries and interpretations of this data. They have provided EPA with an overall statistical summary of the congener-specific and overall TEQ results from this compilation (Patterson, 2000), and those results will be described shortly. EPA judges these data to be the best representation of current background concentrations of dioxin-like compounds in the blood of US citizens, for these reasons: 1) all individuals were evaluated by the CDC analysis group as appropriately representing US background conditions and EPA concurs with this evaluation - that is, all individuals were judged to be exposed only through background exposures, including inhalation of background ambient air (i.e., not impacted by nearby high dioxin stack emitters), consumption of animal food products not known or expected to be contaminated, no occupational exposures, and so on, 2) the blood was analyzed using a consistent, high resolution, mass spectrometry state-of-the-art protocol (Patterson and Turner, 1997) which included 4 dioxin-like coplanar PCBs, 3) the data represent a wide range of adult ages, from 20 to over 70 years of age, and 4) the sampling was of relatively recent origin - 1995 to 1997, more recent than other studies reviewed in this chapter. Prior to describing this overall profile, information on four of the six study sites have been made available to EPA, and these will be described first.

With the assistance of the Agency for Toxic Substances and Disease Registry, the Missouri Department of Health (MDOH, 1999) conducted an exposure study to evaluate the potential impact of incinerating contaminated soil from Times Beach. Approximately 265,000 tons of soil and other materials containing 2,3,7,8-TCDD from 27 eastern Missouri sites were burned at the Times Beach Superfund site during the period March 17, 1996 through June 20, 1997. MDOH (1999) undertook a study to evaluate the impact of emissions from this incineration. Their approach was to take blood samples from a target and a comparison population before, during, and after the incineration, and evaluate the differences in blood levels of dioxin-like compounds between the populations and over time. MDOH (1999) selected a target population based on air dispersion and deposition modeling. This population resided within a 4-kilometer radius of the incinerator. A comparison population from Manchester was located about 16 kilometers from the incinerator. From a list of over 650 individuals from both populations, totals of 76 and 74 individuals were selected from the target and comparison groups, respectively, for blood sampling. These selections considered demography, whether or not a woman was pregnant or breast feeding (neither was selected), and other critical factors. Blood samples were taken from all participants in September 1995, July 1996, and June 1997, and questionnaires were administered each time. Mean concentrations of each of 15 dioxin and furan congeners, and 4 coplanar PCB congeners were determined assuming non-detects were equal to one-half the detection limit. These detection limits, on a lipid basis, were: 0.8 ppt for the tetra- and penta-CDD congeners and the tetra- through octa-CDF congeners, 1.2 ppt for the hexa- through hepta-CDD congeners, 3.8 ppt for the coplanar PCB congeners, and 15.4 ppt for OCDD. Concentrations for two hexa-CDD congeners, 1,2,3,4,7,8-HxCDD and 1,2,3,6,7,8-HxCDD, and one hexa-CDF congener, 1,2,3,7,8,9-HxCDF, were not reported, and concentrations of one hepta-CDD congener which is not assigned a TEF value, 1,2,3,4,6,7,9-HpCDD, was reported. The mean concentrations for each congener for each testing period and study group, is shown in Table 4-15. Further details on this study can be found in MDOH (1999).

The CDC compilation included only the data from 1997. For that year, 67 of the 76 individuals from Times Beach had available measurements for their compilation, and 61 of the 74 individuals from the comparison site, Manchester, had available measurements.

MDOH (1999) concluded that there was no statistically significant differences between the target and comparison groups for all the analytes measured except for PCB 126, which was slightly higher in the comparison group. MDOH (1999) concluded that the values measured were some of the lowest values ever recorded on a human population. As seen in Table 4-15, the TEQ_{DFP}-WHO_{98} for the target group was 11.7 ppt while for the comparison group it was 12.6 ppt (averaged over all sampling dates). However, the actual TEQ concentrations would be higher than these since this study did not report on measurements for the three congeners noted earlier. Other data suggest that the hexa-CDD congeners not reported on in this study, mainly 1,2,3,6,7,8-HxCDD, comprise in the range of one-fourth to one-third of the total body burden of TEQ. MDOH (1999) also observed that there appeared to be a decrease in concentrations from pre- to post-incineration for most analytes. Of all factors examined through questionnaires, only two appeared to be important for dioxin body burdens: smoking and age. Combining both populations, the average TEQ for participants living in homes with cigarette smokers as 12.8 ppt (I-TEQ_{DF} + TEQ_{P}-WHO_{94}), compared to 9.4 ppt (I-TEQ_{DF} + TEQ_{P}-WHO_{94}) in homes that do not have smokers. No age-specific results were presented in MDOH (1999), but a Pearson correlation of 0.525 for average TEQ concentration (statistical significance <0.001, two-tailed) was found for age. The average age of participants in both populations was about 43 years.

The Arkansas Department of Health (ADH) and the Agency for Toxic Substances and Disease Registry (ATSDR) cooperated on the design and implementation of a study to evaluate the exposure of individuals to dioxin-like compounds and other contaminants manufactured and then disposed of through incineration at the Vertac/Hercules Superfund Site (abbreviated the Vertac Site) in Jacksonville, Arkansas (ADH, 1995). The site had been used from the 1950s to manufacture herbicides such as 2,4,-D, 2,4,5-T, and 2,4,5-TP. It had changed hands several times until being abandoned by Vertac in 1987. Incineration occurred between 1992 and 1994. One component of the study was to sample and then analyze blood from three target groups of individuals: 1) residents living near the Site for more than 15 years as of 1991 - 72 individuals recruited, 2) residents living between 1 and 5 years as of 1991 - 36 recruited, and 3) residents living in a comparison area - 72 recruited; 71 participated. The comparison area chosen was in Mabelvale, Arkansas, a demographically similar community approximately 25 miles south

of Jacksonville. Study participants ranged in age from 18 to 65 years old. The average age of the comparison group at the first sampling in 1991 was 40 years. Blood samples were taken in March, 1991, and participants also filled out an extensive questionnaire at that time. Subsets of individuals from all three populations were sampled once again in 1994 and 1995 after the incineration had been completed.

The CDC compilation used only the data from 1995 in their compilation. This data set included individuals who lived both in Jacksonville and in Mabelville - most of the individuals followed into 1995 lived in Jacksonville. The number of individuals sampled in 1995 included in the CDC compilation is 57.

The 1991 and 1994 sampling were described in a draft report released by the Arkansas Department of Health for public comment in 1995 (ADH, 1995). This report has never been finalized. However, the blood data has been available and even used by one researcher citing results from the Mabelville population sampled in 1991 as a comparison group to his own study of dioxin-like compounds in the blood of a Great Lakes sport-fishing population (Anderson et al., 1998). Individual results that are summarized here have been provided to EPA via personal communication (Cranmer, 1996). The data supplied for each dioxin-like congener was either: identified as a quantified concentration (in serum, on a lipid basis), identified as "not detected" (ND), or identified as "not reported"(NR). Detection limits were not specified. Therefore, for purposes of the calculation of means, non-detects were assumed equal to zero. Measurements identified as NR were not included in the calculation of means.

Table 4-16 summarizes the results from the comparison population only. This table shows the results for the entire set of 71 individuals sampled in 1991. It also shows the results for subsets of these individuals that were sampled in 1994 and 1995. For comparison, the 1991 means for these same subsets are also provided. Unlike the target population of the Times Beach study described earlier, there appeared to be measurable impacts on the blood levels of dioxin-like compounds in the target populations at Vertac, as evidenced by the 1991 sampling. However, these impacts have not been tied directly to activities at Vertac. For example, in groups 1 (15 years residence near the site) and 2 (between 1 and 5 years residence), the mean lipid-based concentrations of 2,3,7,8-TCDD were 8.5 and 4.2 ppt, while the mean for the background population was 2.5 ppt. The high means for groups 1 and 2 were driven by a small number of very high concentrations

(the three high concentrations from group 1 were 29.7, 84.9, and 94.8 ppt). However, if these high values are excluded, the overall concentrations from these groups are still higher than for the comparison group. The average TEQ_{DFP}-WHO_{98} from the comparison population in 1991 was 25.2 ppt. The select group of 18 individuals who were targeted for resampling in 1994 were individuals whose lipid-based concentration of 2,3,7,8-TCDD ranged from 2 to 5 ppt. Table 4-16 suggests that the average blood TEQ_{DFP}-WHO_{98} level for this group decreased between 1991 and 1994, from 26.8 to 22.6 ppt. However, when evaluating the average CDD/CDF/PCB concentration of the 14 individuals resampled in 1995 (a further subset of the 18 who provided samples in 1994), there appears to be little evidence of a decline in TEQ_{DFP}-WHO_{98}. The TEQ_{DFP}-WHO_{98} concentrations were 25.0 ppt in 1991 and 24.0 ppt in 1995 for this group. As with other studies, ADH (1995) also reported on an important age effect - the levels of dioxins and furans increased with age.

Grassman et al. (1999) developed a method to evaluate inter-individual variation in dioxin responsiveness among humans. Specifically, they developed a system that measures dioxin-responsive biomarkers in peripheral blood lymphocytes challenged *in vitro* with 10 nM TCDD during cell culture. Grassman et al. (1999) evaluated the capabilities of this method by obtaining blood samples from 3 populations widely variable in the magnitude and duration of their exposure to dioxin. One was a group of plant workers in a German chemical manufacturing plant, one was comprised of men, women, and children living in the vicinity of Seveso, Italy, during the accidental release of 2,3,7,8-TCDD in 1976, and the third was comprised of adult North Carolina volunteers, with no known occupational or unusual exposures to dioxin. This third group is comprised of 29 individuals, with ages ranging from 21 to 52 years, mean of 34.5 years, and it is the results from their analyses that are considered here as a U.S. background population. Grassman et al. (1999) reported that their average lipid-based TEQ_{DFP}-WHO_{94} was 14.2 ppt. Results of the study comparing the three study groups are reported in Grassman et al. (1999).

The North Carolina participants were sampled in 1996. EPA was provided the congener specific data for the 29 individuals of this study (Masten, 2000). Average congener concentrations from this group are provided in Table 4-17. Interferences were found in the analysis for 1,2,3,6,7,8-HxCDD, so this congener was not reported for any of the individuals, and TEQs were calculated without this congener. Other body burden data

suggests that this congener could comprise in the range of one-fourth to one-third of the body burden of TEQ_{DFP}, so the overall TEQ for this population is underestimated. A small number of additional measurements from other congeners were not reported, and these were not considered in the generation of mean congener values. The mean values were calculated by assuming that non-detects were equal to one-half the detection limit. With this procedure, the lipid-based TEQ_{DFP}-WHO_{98} was calculated to be 15.0 ppt. Assuming that non-detects are equal to zero would not change these results by much; the lipid-based TEQ_{DFP}-WHO_{98} in this case was calculated as 13.0 ppt.

The CDC compilation includes these same data from the 29 North Carolina individuals. The congener profile for the overall compilation done by CDC is shown in Table 4-18. These averages were derived assuming non-detects were equal to ½ the detection limit. These average congener concentrations were derived only using data from the overall set where these congeners were reported. As noted in the above discussions, there were some studies where congeners were not reported, such as 1,2,3,6,7,8-HxCDD. Therefore, the number of observations that went into calculating overall averages for each congener was less than or equal to the total number of individuals (n = 316) in the study. These congener profiles were not used to generate TEQ concentrations for the overall data base. Instead, Patterson (2000) supplied statistical results for the TEQ_{DFP}-WHO_{98} concentrations that were generated using substitution methods for each individual included who had "not reported" (NR) for some of the congeners. Each time a congener was NR in an individual's congener profile, the average concentration from other individuals in the same study set was substituted for the individual who had the missing data. When that congener was missing from an entire study set, then the average for that congener from all other data sets where it was reported was substituted for all individuals in the data set with the missing congener. With these substitution techniques, every individual included in the overall data base had a complete set of congener results including quantified concentrations, non-detects with known detection limits, and substituted values. Then, each individual's TEQ_{DFP}-WHO_{98} lipid-based concentration was derived (assuming non-detects equal ½ detection limit), and from these TEQs, means and percentiles were generated. By this discussion, it should be clear that one cannot derive the TEQ concentrations in Table 4-18 from the congener profiles in Table 4-18, although they will be close.

As seen in Table 4-18, the average lipid-based TEQ_{DFP}-WHO_{98} concentration was 22.1 ppt. It was found that the substituting ND = ½ LOD did not influence the TEQ results. At ND = 0, the average TEQ concentration was only 1 ppt lower at 21.1 ppt TEQ_{DFP}-$WHO_{98.}$ However, this TEQ_{DFP}-WHO_{98} concentration included only 4 of the 12 coplanar PCB congeners. The overall compilation of literature data on coplanar PCB concentrations in human tissues, other than this CDC compilation, shown later in this chapter in Table 4-21, includes data on 11 of the dioxin-like coplanar PCBs. That data suggests a weighted mean TEQ_P-WHO_{98} concentration in blood of 15.6 ppt TEQ_P-WHO_{98}, of which these four congeners comprise 5.9 ppt. Therefore, the congeners missing from the CDC data base account for 62% [(15.6-5.9)/15.6 * 100%] of the total PCB TEQ estimated in the early 1990's for blood. From the congener profile in Table 4-18, it is calculated that the 4 PCB congeners add about 2.0 ppt TEQ to the overall mean concentration of 22.1 ppt. Assuming that the missing congeners from the CDC study data contribute the same proportion to the total PCB TEQ as in earlier data, they would increase the estimate of current PCB blood concentrations by another 3.3 ppt TEQ_P-WHO_{98} lipid for a total PCB TEQ of 5.3 pg/g lipid and a total TEQ_{DFP}-WHO_{98} of 25.4 ppt lipid. This will be the TEQ lipid concentration assumed to represent current background conditions in the United States.

4.2.4. Additional Recent Tissue Studies

Petreas, et al. (2000) reported on the analysis of breast adipose tissue samples for the seventeen dioxin-like CDD/F congeners. Samples were taken in 1998 from women in San Francisco area hospitals undergoing breast surgery for suspected breast cancer. l-TEQ_{DF} concentrations were reported for 45 of these women who were found to be cancer-free. The range of l-TEQ_{DF} concentrations found in this study population was 10 to 60 ppt lipid-basis, with a median concentration of 19 ppt. This was calculated assuming non-detects were equal to ½ the detection limit. When assuming non-detects were equal to zero, this dropped slightly to 16 ppt l-TEQ_{DF}. When recalculating TEQs using the WHO_{98} TEF scheme, Petreas et al. (2000) found the concentrations to increase by 2-3 ppt. These concentrations compare well to the mean concentration of WHO_{98}-TEQ_{DF} of approximately 21.6 ppt lipid-basis found in the 316 samples of the CDC compilation (Patterson, 2000) reported on earlier. These results were compared to a set of 17 adipose

samples from other women patients undergoing surgeries for other reasons 10 years earlier in 1988. From 17 samples, the range was similar at 13 to 63 I-TEQ_{DF}, but the median was higher at 27.3 pg/g I-TEQ_{DF} lipid-basis. Other analyses by Petreas demonstrate the apparent downward trend in body burdens in these adipose tissues.

4.2.5. Summary of Human Tissue Levels

Tables 4-19 and 4-20 present summaries of the TEQ_{DF} concentrations in human tissues from North America, and Europe and Japan, respectively, as reported in the literature. In general, these data represent studies conducted in the late 1980s and early 1990s. These data on human adipose tissue, blood, and breast milk indicate that mean tissue concentrations of CDD/CDFs ranged from 20 to 50 ppt TEQ_{DF}-WHO_{98} on a lipid basis, with a midpoint of 35 ppt TEQ_{DF}-WHO_{98} during that time period. The mean TEQ_{DF}-WHO_{98} from the U.S. studies was 32.7 ppt, and the mean from the European and Japanese studies was 41.0 ppt. The assumption is made here that levels in all three tissues are similar (on a lipid basis) and that levels in all of these tissues can be considered representative of overall body burden. Van den Berg et al. (1994) reported that (on a lipid basis) the serum-to-blood tissue ratio for 2,3,7,8-TCDD is approximately one and this ratio increases with higher chlorinated CDD/CDFs. Van den Berg et al. (1994) also compared lipid-based concentrations for all CDD/CDF congeners reported in human milk, blood, and adipose, and concluded that the levels are strikingly similar across tissues.

It should be noted that all available human tissue studies have uncertainties that prevented a precise, statistically-based estimate of the national mean. Except for NHATS, the number of people in the available studies of CDD/CDFs in human tissues is relatively small, and participants are not selected in a statistically based manner. Other biases may have also been present in NHATS, as well as in other studies. Thus, it is uncertain how representative these data were of the general population.

Tables 4-21 and 4-22 present summaries of PCB TEQ concentrations in human tissues from North America and Europe, respectively, based on data from the 1980s and early 1990s. The average tissue level of dioxin-like PCBs for the general U.S. population was probably within the range of 10 to 30 ppt TEQ_{P}-WHO_{98} on a lipid basis, with a midpoint of about 20 ppt. The mean TEQ_{P}-WHO_{98} from these U.S. studies was 16.7 ppt. The mean from the European studies was 31.9 ppt. This indicates that on a TEQ_{P}-WHO_{98},

PCB levels were between one-half and two-thirds that of CDD/CDFs. Inclusion of dioxin-like PCBs raised the estimate of U.S. human tissue levels to approximately 30 to 70 ppt TEQ_{DFP}-WHO_{98} (midpoint = 55 ppt) for the late 1980s and early 1990s.

As discussed above, the representativeness of these PCB studies for the general population is unknown. The toxic equivalency factors for PCBs are not as well established as the CDD/CDFs and increase uncertainty in these estimates. Uncertainty is also increased by the high background levels of PCBs found in many laboratories, which can create analytical difficulties. In addition, not all studies presented data for the same set of PCB congeners. Therefore, studies were combined to calculate a total TEQ_P-WHO_{98} based on all PCB congeners for which TEF_P-WHO_{98}s have been established. Total TEQ_P-WHO_{98}s were calculated by summing weighted mean TEQ_P-WHO_{98} concentrations (based on one or more studies) for each toxic PCB congener.

The CDC data base includes 316 individuals from 6 sites in the time frame of 1995-1997. These data form the basis of the estimates of current background tissue levels in the United States. The mean TEQ tissue level from the study data alone is 22.1 ppt TEQ_{DFP}-WHO_{98}. Because this concentration does not include important dioxin-like PCB congeners, this average has been increased to 25.4 ppt TEQ_P-WHO_{98} using information from earlier studies of dioxin-like PCBs in blood. This concentration will be used to represent current background conditions in the United States. This use includes an overall conclusion for body burdens of dioxin-like compounds in this chapter, as well as an assumption for mother's milk concentration in an evaluation of the impacts of nursing on infants in Chapter 5.

It is important to note that the 95th percentile concentration from this study data base is 38.8 ppt TEQ_P-WHO_{98}, which is nearly twice the mean of 22.1 ppt TEQ_P-WHO_{98} from this study. Later in this chapter, variation in background dose is investigated using data on dietary consumption of fats. Using statistical surveys on food consumption, it was found that the 95th percentile of fat consumption was about twice the mean (and the 99th percentile is about 3 times the mean). Knowing that dioxins are transmitted primarily through consumption of dietary fat, this result from the CDC blood compilation is consistent with the dietary result; the 95th percentile consumption of dietary fat appears to lead to the 95th percentile in body burden of dioxin-like compounds.

A portion of the CDC blood data were plotted as a function of age. This plot is shown in Figure 4-1. This figure was generated as part of a site-specific study conducted by the Agency for Toxic Substances and Disease Registry at Mossville, Louisiana (ATSDR, 1999). The data shown in Figure 4-1 encompass the control population that was to be compared against measurements in Mossville. This comparison population is a subset of the full CDC (2000) population. Figure 4-1 shows that blood levels generally increase with age, and also that the variability in blood levels increase with age. An age trend such as this one has been observed in other studies, such as the NHATS tissue data described earlier (U.S. EPA, 1991a).

4.2.6. Body Burden Profiles

The profiles for CDD/CDF concentrations in human adipose tissue, blood, and human milk are presented in Figure 4-2 and Table 4-23 based on the literature studies from the 1980s and early 1990s. These profiles were generated by calculating the ratio of the mean concentrations of the 2,3,7,8-substituted congeners to total concentration of 2,3,7,8-substituted CDD/CDFs when nondetects were set to one-half the detection limit. In addition, it should be noted that some studies (i.e., adipose tissue - Schecter, 1991 and U.S. EPA, 1991a; blood - Schecter et al., 1994a and Cole et al., 1995) reported total 2,3,7,8-substituted HxCDD/F and HpCDD/F concentrations instead of reporting concentrations for the individual HxCDD/F and HpCDD/F congeners. Thus, in order to provide a complete profile based on all 17 of the 2,3,7,8-substituted congeners, the concentrations of total HxCDDs, HxCDFs, HpCDDs, and HpCDFs from these studies were apportioned among the individual HxCDD/F and HpCDD/F congeners based on the ratios of individual congeners to total HxCDD/Fs and HpCDD/Fs reported in studies providing data for the individual 2,3,7,8-substituted HxCDD/F and HpCDD/F congeners (i.e., adipose tissue - Patterson et al., 1994; blood - Schecter et al., 1993). The profiles generated for these three body tissues appear to be similar. In general, higher-chlorinated CDDs dominate with OCDD accounting for over 65 percent of the total 2,3,7,8-substituted CDD/CDFs. CDFs account for a relatively small portion of the total 2,3,7,8-substituted CDD/CDFs.

The profile of 2,3,7,8-CDD/CDF congeners in human blood from the more recent (i.e., 1995-1997) CDC blood data set was also generated. This profile is shown in Figure

4-3 and is based on the data in Table 4-18. The profile is similar to that generated from earlier human tissue data (Figure 4-2).

4.3. INTAKE ESTIMATES BASED ON TISSUE LEVELS AND PHARMACOKINETIC MODELING

4.3.1. Steady State Approach

Examination of human tissue data provides a way to estimate exposures of humans to CDD/CDFs. Average daily intake of CDD/CDFs may be estimated using human tissue data and pharmocokinetic modeling as follows:

$$D = \left[\left(\frac{\ln 2}{t_{1/2}}\right) V * CF_1 (C) CF_2\right] / (A) \qquad \text{(Eqn. 4-4)}$$

where:

D	=	Daily intake of CDD/CDF (pg/day);
$T_{1/2}$	=	Half-life of CDD/CDF (years);
V	=	Volume of body fat (kg);
C	=	Concentration of CDD/CDF in tissue (pg/g)
CF_1	=	Conversion factor (1,000 g/kg);
CF_2	=	Conversion factor (year/365 days); and
A	=	Fraction of dose that is absorbed.

The level of 2,3,7,8-TCDD found in human adipose tissue averages about 5.5 ppt in the United States based on data from a variety of studies from the 1980s and mid 1990s, and 2.1 pt based on the CDC data set. These values may be used to estimate the associated exposure levels using a simple pharmacokinetic model that back calculates the dose needed to achieve the observed tissue levels under the assumption of steady-state exposure/dose, as given above. (See Equation 4-4.) This model requires an estimate of the fraction of the dose that is absorbed, the elimination rate constant, and body fat volume.

A complete summary of the literature on gastrointestinal, dermal, transpulmonary, and parenteral absorption is provided in Part II - Health Assessment of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds, Chapter 1 - Disposition and Pharmacokinetics. The summaries there pertaining to oral absorption justify the selection of 0.8 as an absorption fraction for dioxin TEQs in simple exercises conducted in this section on pharmacokinetic modeling. Most of the gastrointestinal absorption research has been conducted on 2,3,7,8-TCDD and laboratory animals. Results suggest that 2,3,7,8-TCDD is absorbed at a rate greater than 50% in oil or in diet, with several studies reporting average absorption at 70% or more: Rose, et al. (1976) found an average of 84% in rats where the vehicle was a mixture of acetone and corn oil; Piper, et al. (1973) found an average of 70% on rats with the same vehicle; Diliberto et al. (1996) reported 88% in rats in a vehicle of vegetable oil, ethanol, and water; and Olson, et al (1980) reported 70% in hamsters in a vehicle of olive oil. Similar and even higher absorption was found for 2,3,7,8-TCDF, 1,2,3,7,8-PCDD, 2,3,4,7,8-PCDF, and 3,3',4,4'-TCB. Lower absorption at 2 to 15% was found for OCDD (Birnbaum and Couture, 1988), but since background TEQ doses are dominated by the lower chlorinated congeners, the low absorption of OCDD may be less critical. In limited studies and evaluations of oral absorption on humans, it is concluded that the more soluble congeners, such as 2,3,7,8-TCDF are almost completely absorbed, whereas the extremely insoluble OCDD is poorly absorbed. In one experiment, Poiger and Schlatter (1986) found that >87% of the oral dose of TCDD in corn oil in a 42 year-old man was absorbed from the gastrointestinal tract. Like some of the experiments on rats, the amount absorbed in some cases was dose dependent, with lower absorptions at higher doses. Again, low absorption at high doses is less critical for the current exercises, which focus on low background dose of TEQs.

Flesch-Janys et al. (1996) estimated the half-life of 2,3,7,8-TCDD (and other CDD/CDFs) based on blood levels of a group of occupationally exposed individuals. The median half-life for 2,3,7,8-TCDD (n=48) was estimated to be 7.2 years. Half-lives for other CDD/CDF congeners ranged from 3.0 to 19.6 years. Van der Molen et al. (1998) estimated the elimination rate constant of 2,3,7,8-TCDD using data on the TCDD blood lipid levels of Vietnam veterans who had been involved in the spraying of Agent Orange. The Van der Molen et al. (1998) model predicted half-lives ranging from 5.5 years in

young adults to 11 years in elderly men. The model accounted for age-dependent body composition, and age- and time-dependent background intake.

Ryan et al. (1997) reported the elimination rate constant of 2,3,7,8-TCDD by back calculating from the levels in 1992 and 1996 blood samples collected from six of the 2,4,5-trichlorophenoxyacetic (2,4,5-T) workers in Russia. The elimination rate constants of four of the six samples ranged from 6.9 to 17 years (6.9, 9.7, 9.7, and 17, respectively), while those of two of the six samples were incalculable. Ryan et al. (1997) stated that these four values were in the range reported by other investigators. However, no supporting references were provided. Due to the large variability of values, the small sample sizes (one single value for each sample), and a potential inconsistency in sample analysis (samples were analyzed by two different laboratories at two different times), there is uncertainty in these values. Therefore, these values require further consideration.

Based on available data, the elimination rate constant (i.e., half-life) for 2,3,7,8-TCDD was assumed to be about 7.1 years, and the fat volume was assumed to be 17.5 kg (i.e., 70 kg body weight * 0.25 fat) which yielded a background TCDD dose of about 32 pg/day using the TCDD tissue estimate from the 1980s to mid 1990s (5.5 ppt), and 12 pg/day (0.18 pg/kg/day) using the TCDD tissue concentration from the CDC data set (2.1 ppt). These estimates agree well with the background exposure estimates (to 2,3,7,8-TCDD only) of 35 pg/day by Travis and Hattemer-Frey (1991) and 25 pg/day by Fürst et al. (1991), but are somewhat higher than the current background exposure estimate of 5.6 pg/day from this assessment (see Section 4.4.2), as derived using typical media levels and contact rates. Using the current CDD/CDF TEQ body burden data presented in Table 4-18 and the pharmacokinetic model presented in Equation 4-4, the average daily intake of total CDD/CDFs is estimated to be 126 pg TEQ_{DF}-WHO_{98}/day. This estimate assumes a half-life of TEQ_{DF}-WHO_{98}s in the body of 7.1 years, a fat volume of 17.5 kg, a concentration in the body fat of 21.6 ppt (i.e., the approximate mean TEQ concentration for CDD/CDFs only, as calculated from the data in Table 4-18), and steady-state conditions. This value is also three times higher than the current background exposure estimate of 41 pg TEQ_{DF}-WHO_{98}/day from this assessment, as derived using typical media levels and contact rates. If PCBs are included in this exercise (i.e., using the current TEQ_{DFP}-WHO_{98} background tissue concentration of 25.4 ppt) the estimated TEQ_{DFP}-WHO_{98} dose would be 146 pg/day. This estimate is approximately 2.2 times higher than

the direct estimate from the dietary data of 65 pg TEQ_{DFP}-WHO_{98}/day. Because this model was originally developed for use with 2,3,7,8-TCDD, the effect of using it to model CDD/CDFs introduces uncertainty into these estimated values.

An important uncertainty in the modeling exercise described above was the assumption that the half-life estimate for 2,3,7,8-TCDD (7.1 yr) would apply to TEQ_{DF}-WHO_{98}s. Thus, the same pharmacokinetic model was applied to average human tissue levels for each congener, using half-lives that are specific to each congener, and then summing the estimated intakes for each congener. This approach yielded an estimated intake of 87 pg TEQ_{DF}-WHO_{98}/day (Table 4-24). This value is approximately 2 times higher that the current background estimate of 41 pg TEQ_{DF}-WHO_{98}/day.

Another, perhaps more important, uncertainty in using this approach to estimate current dose is that the dose is assumed to be constant over time. If, in fact, the dose which has resulted in current average body burden were constant over the past several decades, than use of this steady-state PK model would provide quite reasonable estimates of current dose. The only uncertainty in this case (beside the simplistic nature of it being a one-compartment PK model) is the use of 7.1 years as the half-life (as described above). If the dose regime instead was characterized by very low doses in the middle of the twentieth century only to rise significantly in the latter part of the century, than this model would, by definition, provide an underestimate of current dose. If, on the other hand, doses were very much higher in the mid-portions of the twentieth century only to drop towards the end of the century, than this steady state model would, by definition again, provide an overestimate of the current dose. The steady-state model only provides an average dose over time that could account for a given body burden - it obviously doesn't address the possibility of changes in dose over time. As will be described in the next section, there is a very large amount of evidence suggesting that doses were higher in the mid-decades of the twentieth century, and may be significantly higher, as compared to the latter decades. The tissue levels representing the "current average body burdens" included a significant number of individuals living in this middle decades of the twentieth century. This being the case, it is concluded that the steady state approach will overestimate current dose.

4.3.2. Non-Steady State Approach

Chapter 6 describes evidence supporting temporal trends in CDD/CDF/PCB concentrations in environmental media, foods, and associated doses. It appears that the levels of dioxin-like compounds have increased in the environment starting from the 1930s through the 1960s, and loadings began to decline perhaps starting in the 1970s to the present. Recent evidence collected on animal food products in the United States (Winters, et al., 1998), combined with body burden data, provide evidence that human exposures to dioxins may have followed the same trends. (See Chapter 6.)

Pinsky and Lorber (1998) used a non-steady state approach to reconstruct the pattern of past exposure and estimate current exposure to 2,3,7,8-TCDD, using a simple pharmacokinetic model that included a time-varying TCDD dose. A first order, one-compartment PK model was used to compute an individual's body lipids TCDD concentration through time. Key inputs for that model include: (1) a time-varying dose of TCDD (expressed in units of pg/kg-day), (2) a fraction of dose absorbed into the body lipid compartment (assumed to be constant), (3) the volume of the body lipid compartment (assumed to be time varying), and (4) a rate of TCDD loss from the lipid compartment (modeled as a function of the percent of body fat). In order to calculate the rate of TCDD loss, a model of how body lipid volumes vary over time, in addition to a model of how overall body weight varied over time, was required.

In this modeling exercise, all inputs were fixed, except the time-varying dose of TCDD. Using Bayesian statistical approaches, the non-steady state dose was "calibrated" to best-fit a set of data on TCDD concentration in body lipids from the 1970s to the 1990s. The results of this exercise indicated that the dose appears to have increased from the 1940s through the 1960s, and began to drop through the 1970s, with a baseline level being reached by the 1980s. The results suggest that TCDD exposures may have been 20 times higher during the 1960s than the 1980s. Over a 10-year peak period in the 1960s and early 1970s, daily exposures could have been as high as 1.5 to 2.0 pg/kg-day, possibly dropping as low as 0.10 pg/kg-day (7 pg/day) and less into the 1980s. This estimate of current dose of 7 pg 2,3,7,8-TCDD/day is quite similar to the estimate of 6.1 pg 2,3,7,8-TCDD/day made using typical media levels and contact rates. In another test, Pinsky and Lorber (1998) used the same modeling structure to test the steady state assumption by forcing the dose to be constant over time. In that test, Pinsky

and Lorber (1998) solved for a 'best-fit' dose of 0.35 pg/kg-day. This is higher than the 1980s calibrated 'current dose' of 0.10 pg/kg-day, derived by allowing the dose to vary over time. As described in the previous section, if much higher doses of dioxin occurred in the middle part of the twentieth century, than a steady state model will provide an overestimate of current dose; in other words, this Pinsky and Lorber (1998) result is to be expected. In addition, the steady-dose 'best-fit' solution provided a significantly poorer fit to the data as compared to the non-steady dose solution, providing even more evidence that doses have not been steady during the twentieth century. (See Chapter 6 for a complete description of this modeling approach.)

4.4. INTAKE ESTIMATES BASED ON EXPOSURE MODELING

4.4.1. Previous Assessments of Background Exposures

Several researchers have published quantitative assessments of human exposures to CDDs and CDFs. Some of the more recent assessments are discussed below (Travis and Hattemer-Frey, 1991; Fürst et al.,1990; Fürst et al., 1991; Henry et al., 1992; Theelen, 1991; Schuhmacher et al., 1997; Gilman and Newhook, 1991; Schrey et al., 1995; MAFF, 1995; and Jacobs and Mobbs, 1997; Himberg, 1993; and Liem et al. 2000a, 2000b). It is generally concluded by these researchers that dietary intake is the primary pathway of human exposure to CDDs and CDFs. Over 90 percent of human exposure occur through the diet, with foods from animal origins being the predominant sources.

Travis and Hattemer-Frey (1991) estimated that the average daily intake of 2,3,7,8-TCDD by the general population of the United States is 34.8 pg/day. Ingestion exposures were estimated by multiplying the concentration of 2,3,7,8-TCDD in beef, milk, produce, fish, eggs, and water (estimated using the Fugacity Food Chain model) times the average U.S. adult consumption values for these products reported by Yang and Nelson (1986). The calculations assume that 100 percent of the 2,3,7,8-TCDD ingested are absorbed through the gut. Intake via inhalation was estimated by multiplying the concentration in air times the amount of air inhaled per day (20 m^3) assuming that 100 percent of inhaled 2,3,7,8-TCDD are absorbed through the lung. The results of their assessment, summarized in Table 4-25, indicate that foods from animal origins comprise

95 percent of the estimated total daily exposure. These foods include milk and dairy products, beef, fish, and eggs. Exposure resulting from consumption of vegetables and other produce was estimated to account for 3.4 percent of the total intake. Exposure from ingestion of water, ingestion of soil, and inhalation of air together accounted for about 1 percent of the total daily intake.

Fürst et al. (1990) estimated human exposure to CDD/CDFs based on the analysis of 107 food samples collected in the Federal Republic of Germany. The average daily I-TEQ_{DF} intake was estimated to be 85 pg/person/day or 1.2 pg/kg body weight/day. Fürst et al. (1990) concluded that foods of animal origin contribute significantly to the human body burden of CDD/CDFs. In a subsequent study, Fürst et al. (1991) assessed human exposure to CDDs and CDFs from foods using data from more than 300 randomly selected food samples and food consumption data reflective of consumption habits of the German population. These authors estimated that the German population's average daily intake of CDDs and CDFs from food is 158 pg I-TEQ_{DF} per person of which 25 pg is 2,3,7,8-TCDD. Dairy products, meat and meat products (primarily beef), and fish and fish products each contribute about 32 to 36 percent of the daily intake of I-TEQ_{DF}. Based on the levels of CDD/CDFs observed in human samples, the average daily intake via food was estimated to be in the range of 1 to 3 pg I-TEQ_{DF}/kg body weight.

Henry et al. (1992) of the U.S. Food and Drug Administration estimated the average exposure to the U.S. population from 2,3,7,8-TCDD through the food supply using the following assumptions: (1) all dairy products have background lipid 2,3,7,8-TCDD levels equivalent to those found in milk and half-and-half, i.e., about 55 ppq (whole dairy food levels were estimated using percent fat in each food); (2) levels averaging 35 ppq in beef tissue are present in all meat products; (3) ocean fish with tissue levels equal to half of the detection limit (about 0.5 ppt) are the sole fish source in the diet; (4) average food consumption figures (total-sample-basis) available from nationally representative data bases were used for frequency of eating (Market Research Corporation of America's (MRCA) Menu Census VI (1977-78)) and for serving sizes (U.S. Department of Agriculture's 1977-78 National Food Consumption Survey). The concentration assumptions used in the Henry et al. (1992) study were based on previously published data. For example, most of the food data were based on La Fleur et al. (1990), and the fish data were based on U.S. EPA (1992). These studies are described in Sections 3.7.2

and 3.6.1, respectively. FDA's estimates of 2,3,7,8-TCDD intake were derived by multiplying the food dioxin levels by the average amounts of food consumed per day. The results of the FDA assessment, summarized in Table 4-26, indicate an average daily exposure of 15.9 pg/day of 2,3,7,8-TCDD of which 4 percent are due to dairy and milk products, 41 percent are due to meats, and 54 percent are due to ocean fish.

Theelen (1991), of The Netherlands National Institute of Public Health and Environmental Protection, estimated the average daily intake of 2,3,7,8-TCDD and total I-TEQ_{DF} by residents of The Netherlands for various possible routes of exposure. The results, summarized in Table 4-27, indicate an average intake of 20 pg/day of 2,3,7,8-TCDD and 115 pg/day of total I-TEQ_{DF} from food and 0.08 pg/day (2,3,7,8-TCDD) and 3.2 pg/day (I-TEQ_{DF}) from combined direct air and soil exposure. Milk and dairy products make up about one-third of the total daily exposure. Animal fat in meat, poultry, and fish (i.e., fish oil) also contribute about one-third. Fish consumption represents 18.5 percent of total daily exposure. In a later study, Theelen et al. (1993) reported a median daily intake for adults of 1 pg I-TEQ_{DF}/kg body weight, and a 95th percentile rate of 2 pg I-TEQ_{DF}/kg body weight. These values were based on CDD/CDF residue levels in food products and food consumption survey data.

Becher et al. (1998) estimated dietary intake of CDD/CDFs and dioxin-like PCBs in the Norwegian population. Average food consumption data obtained from the 1992-1994 Norwegian consumer survey of 4,033 households was analyzed in conjunction with measured CDD/CDF and dioxin-like PCB concentrations in basic foodstuffs to determine dietary intake. Becher et al. (1998) investigated pooled samples from 20 to 25 seafood samples and 10 to 15 samples of other foodstuffs. Average CDD/CDF dietary intake ranged from 71 to 85 pg I-TEQ_{DF}/day and average PCB dietary intake ranged from 86 to 106 pg TEQ_{P}-WHO_{94}/day. Fish and fish products constituted the largest contribution to the dietary intake of CDD/CDFs and PCBs. PCBs contributed more to the total dioxin related toxicity (i.e.,TEQ_{DFP}-WHO_{98}) than CDD/CDFs in the following food groups: milk, meat, eggs, and cod liver oil; while CDD/CDFs were the higher contributor in the fats food group.

Buckland et al. (1998) estimated dietary intake of CDD/CDFs and PCBs in the population of New Zealand. The estimate was based on 19 food group composites from 51 individual food samples purchased from retail outlets in four major cities and one

provincial center. Estimated dietary intake was calculated based on two typical diets, an average exposure diet of an adult male and a high-end exposure diet of an adolescent male. Total dietary levels of all CDD/CDF congeners ranged from 14.5 to 30.6 pg I-TEQ_{DF}/day (whole weight). Total dietary PCB levels ranged from 12.2 to 22.7 pg TEQ_P-WHO_{94} (whole weight). Total PCB concentration was based on levels of the following PCBs: 28, 31, 52, 77, 101, 99, 123, 118, 114, 105, 126, 153, 138, 167, 156, 157, 169, 187, 183, 180, 170, 189, 202, 194, and 206. These calculations were made by setting concentrations less than the LOD at one-half the LOD. Vegetable fats/oils, cereals, cooked potatoes and hot chips, and processed meats constituted the largest contribution to I-TEQ_{DF}s in the adolescent diet. Butter, processed meats, and milk constituted the largest contribution of TEQ_P-WHO_{94}s to the adolescent diet. The authors noted that while it is difficult to compare these total dietary TEQ results to countries with different dietary patterns, the results appear to indicate that estimated dietary intake of CDD/CDFs and PCBs is lower in New Zealand than in other countries that have conducted similar studies (e.g., USA, UK, Spain, The Netherlands, Federal Republic of Germany, and Norway).

Schuhmacher et al. (1997) and Domingo et al. (1999) estimated dietary intake of CDD/CDFs based on the analysis of 35 food samples from local supermarkets in Catalonia, Spain. Most of the results are in agreement with the recent data reported elsewhere; however, the levels in whole milk, vegetables, lentils and beans, and cereals are higher than those reported in previous studies. The average intake per adult was estimated as 210 pg I-TEQ_{DF}/day. The contributions from vegetables and cereals were relatively high (8.13 percent and 23.09 percent, respectively, of total intake) compared to previous studies where the vegetable and cereal contributions are almost negligible. The high contributions may be explained by high consumption of these foods in the Mediterranean diet. Schuhmacher et al. (1997) stated that since the Mediterranean diet is typical throughout most Spanish regions, the results reported could be a representative of the dietary intake of CDD/CDFs in Spain.

Gilman and Newhook (1991), of the Canadian Department of National Health and Welfare and the Ontario Ministry of the Environment, respectively, estimated an average lifetime daily intake of 140 to 290 pg of I-TEQ_{DF} for the typical Canadian. Their results, summarized in Table 4-28, indicate that between 94 and 96 percent of the estimated

intake are from food sources. No breakdown of intake by food type was provided in the report.

Schrey et al. (1995) estimated dietary intake of CDD/CDFs using the duplicate method. A total of 14 food samples that were duplicates of the food eaten by seven German men and seven German women (age 24-64 years) were collected and analyzed for CDD/CDFs. The 3-day sampling period included both weekdays and weekends. All samples contained detectable levels of 2,3,7,8-substituted CDD/CDFs, but OCDD had the highest concentrations. Daily intake was estimated to range from 3.3 to 14 pg/day (0.026 to 0.26 pg/kg-day) for 2,3,7,8-TCDD and 23 to 96 pg/day (0.18 to 1.7 pg/kg-day) for I-TEQ_{DF}s. These values are slightly lower than those observed in earlier German studies conducted by Beck et al. (1991), even though the dietary intake of fat was similar.

Recently, the United Kingdom's Ministry of Agriculture, Fisheries, and Food (MAFF, 1995) analyzed Total Diet Study samples collected during 1982 and 1992 for CDD/CDFs to analyze trends in dioxin intake over recent years. Samples of 11 food groups collected from 24 locations in the United Kingdom were analyzed. The average intake of dioxins from each food group was calculated by multiplying the CDD/CDF residue concentration in the food group by the average daily intake of the food based on data from the United Kingdom's National Food Survey. Average daily intake of I-TEQ_{DF}s was estimated to be 240 pg/day in 1982 and 69 pg/day in 1992 (Table 4-29). These values represent upper bound exposures because I-TEQ_{DF}s were calculated by setting nondetects to the limit of detection. Based on these results, the authors concluded that the relative contributions of the various food groups to total dioxin intake in the United Kingdom have changed over the years. In the most recent study, the proportion of total exposure attributable to cereal products increased, while exposures from fats, oils, and milk products decreased.

Jacobs and Mobbs (1997) conducted a reassessment of human dietary exposure to CDD/CDFs in the UK. Based on the data of the UK Total Diet Survey (TDS) in 1992, the levels of CDD/CDFs in 11 fat-containing food groups were recalculated. Instead of using the food consumption data from the UK's National Food Survey as in the MAFF study, Jacobs and Mobbs (1997) obtained individual dietary intake data from three other surveys that included adults, children (aged 1.5 to 4.5 years), and infants (aged 6 to 12 months) in the UK. Combining the dietary intake data with the data of CDD/CDF levels in foods, Jacobs and Mobbs (1997) reported an adult daily dietary intake of CDD/CDF as 175.5 pg

I-TEQ_{DF}/day (2.93 pg TEQ/kg/day), a value that is more than twice that estimated by MAFF (1995). The levels for young children ranged from 54.19 pg I-TEQ_{DF}/kg/day at 6 months of age, to 0.25 pg TEQ_{DF}/kg/day at 4.5 years of age. It should be noted that for infants (under 1 year of age), breast milk is the largest contributing source. Estimation of the cumulative dietary I-TEQ_{DF} intake indicated that the levels peak sharply between age 0 and 1 year at about 80 pg I-TEQ_{DF}/kg/day, decrease until 10 years of age, and then rise to about 15 pg TEQDF/kg/day at 22 years of age.

Dioxin-like PCBs can also contribute to TEQ exposures. Himberg (1993) evaluated exposures to dioxin-like PCBs 77, 15, 126, and 169 in Finnish foods. Based on fish, beef, pork, poultry, and inner organs, total TEQ_P-WHO_{94} intake was estimated to be 118 pg/day, calculated using TEQ_P-WHO_{94} concentrations in foods and consumption data from Finland's 1990 household survey. PCB congeners 105 and 126 contributed the most to total TEQ_P-WHO_{94} intake. Intake of PCBs in fish products accounted for the greatest proportion (i.e., approximately 70 percent) of the total TEQ_P-WHO_{94} intake from these foods.

Currado and Harrad (1997) measured air concentrations of PCBs from 9 different indoor environments, including two laboratories, two offices, and five residential houses in the United Kingdom (UK). The results indicated that the total PCB levels found in indoor air (1.4 to 19.1 ng/m^3, mean = 7.1 ng/m^3) were between 2 and 19 times higher than the levels in outdoor air (0.77 to 0.87 ng/m^3, mean = 0.82 ng/m^3). Currado and Harrad (1997) also calculated the daily human intake of PCBs via inhalation. The estimate ranged from 36.9 to 176.5 ng/person/day (mean = 103.5 ng/person/day), and represented between 10 and 33 percent of overall exposure to PCBs for a typical UK individual with a 340 ng/day dietary intake of PCBs (estimated by the UK Ministry for Agriculture, Fisheries and Food (MAFF) in 1992). Currado and Harrad (1997) suggested that, compared to the dietary intake of 340 ng/person/day of PCBs, inhalation of indoor air might be a significant pathway for PCB exposure. It should be noted that the study did not focus on dioxin-like PCBs; only concentrations of four dioxin-like PCB congeners were reported for indoor and outdoor areas.

Liem et al. (2000a) reported on a European cooperative study coordinated by the National Institute of Public Health and the Environment in the Netherlands, and the Swedish National Food Administration. Ten countries, including Belgium, Denmark,

Finland, France, Germany, Italy, The Netherlands, Norway, Sweden, and the United Kingdom, delivered available data on the occurrence of PCDDs, PCDFs, and dioxin-like PCBs in food products and human milk. When available, these countries also delivered data on the consumption of these foods and other data on the dietary exposures of the general populations of these countries. Consumption data were combined with concentration data to arrive at exposure doses in pg TEQ_{DFP}-WHO_{94}. Concentrations and doses expressed in terms of the more recent WHO 1998 TEF scheme are generally higher than these earlier TEF schemes, by about 5-10%, in American food and environmental media. Some countries also provided consumption data representative of the 95th, or 97.5, percentile of the population. These consumption data were combined with mean concentration data from the countries to evaluate higher end exposures of the general population. Liem et al. (2000) concluded that data were reasonably available for dioxins and furans, but limited for the dioxin-like PCBs.

Based on the short summary of this effort in Liem et al. (2000a), it appears that trends in European CDD/F food concentrations and exposures are consistent with those from the United States, although dioxin-like PCB concentrations may be somewhat higher in Europe. National average concentrations of CDD/Fs in eggs, fats and oils, meat products, and milk products are generally less than 1 up to 2-3 pg/g fat, I-TEQ_{DF} basis. Concentrations in fruits, vegetables and cereals were found to be generally close to the limits of detection. Some of the data suggested reductions in concentrations over time, but the available information was insufficient to draw general conclusions. Limited data on dioxin-like PCBs suggest average TEQ_P-WHO_{94} that are between 1 and 2 times higher than I-TEQ_{DF} concentrations in all food products, more so in fish. PCB TEQ concentrations in fish were between 0.25 and 10-20 pg/g fat WHO_{94}-TEQ_P. In contrast, in the United States, TEQ concentrations of dioxin-like PCBs are roughly comparable, if not lower, than TEQ concentrations of CDD/Fs in foods of terrestrial origin Some data on dioxin-like PCBs in fish suggest higher concentrations than CDD/Fs, particularly from a recent study of several fish species from the Great Lakes (Kolic et al., 2000a).

Given the limitations of the available data, Liem et al. (2000a) reported that for eight countries and for the period after 1995, the average adult dietary intakes of CDD/Fs ranged between 29 and 97 pg I-TEQ/day. This compares well to the estimate of 45 pg TEQ_{DF}-WHO_{98}/day developed in this assessment. The upper percentiles estimates of

dietary exposures, where 95 and 97.5% of consumption rates were combined with average concentrations, was 2-3 times the mean intake. This analysis was only available from data on consumption supplied by the Netherlands and the United Kingdom. This also compares well to evaluations done in this assessment based on dietary fat (and total diet) intake, which suggest that the TEQ intakes at the 95th (2 standard deviations above the mean) and 99th (3 standard deviations above the mean) percentiles would be 2 and 3 times the mean intakes, respectively.

Their limited data on dioxin-like PCBs suggest perhaps more of an impact than developed in this assessment. Their average daily intake estimates ranged between 48 and 110 pg TEQ_P-WHO_{94}, compared to the 25 pg TEQ_P-WHO_{94}/day calculated for the US in this evaluation. For countries where data were available for both CDD/Fs and PCBs, the dioxin-like PCBs contributed between a roughly equal amount (Finland, Netherlands, Sweden, United Kingdom) to approximately 4 times (Norway) the TEQ contributions of the CDD/Fs.

Other findings of interest include:

1) Based on concentrations in foods taken in the 1970s and 1980s, calculated doses were much higher, ranging from 127 to 314 pg I-TEQ/day.

2) Similar to findings in this assessment, the highest dietary contributions were made by milk and dairy products (between 16 and 39% of total TEQ intakes), meat and meat products (6-32%), and fish and fish products (2-63%).

3) The intake to breast-fed children was estimated to be between 1 and 2 orders of magnitude higher than adults, on a body weight basis. This is similar to the finding in this assessment that the average infant dose of a year's worth of breast-feeding would be about 77 pg TEQ_{DFP}-WHO_{98}/kg-day.

According to Liem et al. (2000b), "Countries that started to implement measures to reduce dioxin emissions in the late 1980s, such as The Netherlands, United Kingdom, and Germany, clearly show decreasing PCDD/PCDF and PCB levels in food and consequently a

significantly lower dietary intake of these compounds by almost a factor of 2 with the past 7 years".

As reported in Section 3.7.1, CDD/CDFs can migrate from bleached paper packaging and paper food-contact articles to foods. Some investigators have included this pathway in estimates of background exposure. U.S. EPA (1990) estimated that I-TEQ_{DF} intake due to leaching from paper products into food from paper packaging was in the range of 5.5 to 12.7 pg/d. Henry et al. (1992) estimated that daily intake of 2,3,7,8-TCDD due to migration from paper to food could amount to 12 pg/d, almost as much as the daily intake from unaffected food of 16 pg/d. (See Table 4-26.) As shown in Table 4-27, Theelen (1991) estimated that out of a total of about 120 pg of I-TEQ_{DF}/d, 9 pg of I-TEQ_{DF}/d could be due to migration from paper. These estimates are based on levels in paper before recent changes in industry practices that are expected to substantially reduce dioxin levels in paper. As discussed in Section 3.7.1, these reductions are expected to have significantly lowered the CDD/CDF levels currently found in food due to any leaching of dioxin-like compounds from paper.

Horstmann and McLachlan (1994) measured CDD/CDF levels in human skin using an adhesive tape stripping method. Skin samples of the stratum corneum were collected from the backs of eight volunteers of varying age and sex. Two additional layers of increasing depth were collected from five people. All showed a decrease in CDD/CDF levels with depth. The concentration in the first layer ranged from 1,000 to 7,800 pg/g on a total CDD/CDF basis. The second layer was an average of 43 percent lower, and the third layer was an average of 33 percent lower. OCDD was the dominant congener in all three layers. Also, non-2,3,7,8 substituted congeners were identified, congeners which are not normally present in human tissue. In addition, samples of the epidermis and subcutis were analyzed. These analyses indicated that levels of the non-2,3,7,8 substituted congeners were much higher in the stratum corneum than in the epidermis, and none were identified in the subcutis. The authors argue that because these congeners could not be transported from inside the body to the stratum corneum, the CDD/CDF in the stratum corneum must originate from external sources. Horstmann and McLachlan (1994) hypothesized that textiles could be the source of skin contamination. Thirty-five new textiles, primarily cotton products, were analyzed and found to have a total CDD/CDF

level that was generally less than 50 ng/kg; however, several colored T-shirts had high levels, with concentration up to 290,000 pg/g. The homolog patterns in the textiles were similar to the patterns found in the skin. Experiments were then conducted measuring the CDD/CDF levels in human skin before and after wearing T-shirts. Significant increases in CDD/CDF levels in the skin occurred after wearing the highly contaminated shirts for 1-2 weeks, and significant decreases in CDD/CDF levels in the skin occurred after wearing the uncontaminated shirts for 1-2 weeks. This work strongly suggests that dermal exposure to textiles may be contributing to background exposures to CDD/CDFs. Horstmann and McLachlan (1994) comment that although the levels of most CDD/CDF congeners in humans can be explained on the basis of diet, the origins of OCDD in humans is less clear. Because OCDD was found to be the dominant congener in textiles and skin, they speculate that the human body burden of this congener may result from dermal absorption. Horstman and McLachlan (1994) further discuss that human scale (stratum corneum) contributes to house dust and could lead to exposure via inhalation.

Klasmeier et al. (1999) further studied the transfer of CDD/CDFs from textiles to human skin. Spatial variability, variability among individuals, and the percent transfer from different cotton textiles was examined. Spatial variability in transfer to the skin was measured by placing 7 and 10 cm^2 patches of contaminated and uncontaminated (for background determination) textiles on the upper back of human volunteers for 8 hours. The four samples collected from the outermost layers of the skin of the back of 12 volunteers contained similar concentrations of all detected congeners. The results indicated that the skin surface properties determining the transfer of CDD/CDFs from cotton textiles to the stratum corneum of the human back did not vary. An additional volunteer wore a similarly contaminated cotton t-shirt for 72 hours. The mean percent transfer for the 72 hour exposure was 1.6 to 2.5 times higher than for the 8-hour exposure.

Matsueda et al. (1995) measured CDD/CDFs and PCBs in skin lipids from the faces of eight Japanese men between the ages of 21 and 73 years. Skin lipids were collected in the morning before washing the face, using facial wipes containing 70 percent alcohol. The I-TEQ_{DF} concentrations in the samples ranged from 8.8 ppt to 22.3 ppt with a mean of 15.3 ppt. I-TEQ_{P}-WHO_{94} concentrations ranged from 7.3 ppt to 22.5 ppt. Matsueda et

al. (1995) also collected serum samples from these same subjects. Blood I-TEQ_{DF}s ranged from 13.5 ppt to 36.5 ppt, and TEQ_{P}-WHO_{94} ranged from 7.1 ppt to 22.7 ppt.

4.4.2. Updated Assessment of Background Exposures on the Basis of Media Levels and Contact Rates

Background exposures to CDD/CDFs and dioxin-like PCBs in North America were estimated using: (1) the arithmetic mean TEQ_{DFP}-WHO_{98} levels in environmental media and food from Table 3-61; (2) the standard contact rates for ingestion of soil, water, and food, and inhalation of ambient air; and (3) the appropriate unit conversion factors. The general equation used to estimate background exposures is as follows:

$$\text{Intake (pg WHO98-TEQ/kg-day)} = \frac{\text{Daily Contact Rate x Concentration x Unit Conversion Factors}}{\text{Body Weight}} \qquad \text{(Eqn. 4-5)}$$

where:

Contact Rate = inhalation or ingestion rate (m^3/day, mg/day, L/day, or g/day); and

Concentration = residue level in media of concern (pg/m^3, ppt, or ppq).

These background exposure estimates represent administered doses and not absorbed doses.

The estimated exposures and assumptions made for adults concerning ingestion or contact rates are presented in Table 4-30 for CDD/CDFs and Table 4-31 for PCBs. Standard intake rates representative of the adult general population were used. The background exposure estimates reported here do not account for individuals with higher consumption rates of a specific food group (e.g., subsistence fishermen, cigarette smokers, and individuals with exposures from localized impacts--these are discussed in Chapter 5). The estimates are assumed to represent typical (i.e., "central tendency") U.S. background exposures, and do not account for these types of variations in the population as a result of differences in intake rates of the various food groups. Average contact rates for ingestion of soil, water, beef, pork, poultry, other meats, and eggs, and inhalation were derived from the revised Exposure Factors Handbook (U.S. EPA, 1997). The intake

rate for other meats represents total meat intake minus the intake rates for beef, pork, and poultry. Other meats could include lamb, game, etc. It should be noted that the concentration of dioxin-like compounds in other meats was assumed to be similar to that observed in beef, pork, and poultry, because data were not available for these other meats. Thus, the TEQ_{DFP}-WHO_{98} for other meats was estimated as the average of TEQ_{DFP}-WHO_{98} concentrations for beef, pork, and poultry. Mean fish ingestion rates were derived from U.S. EPA (2000). Contact rates for milk, dairy, and vegetable fats were derived from USDA (1995). The contact rate for dermal contact with soil was calculated as the skin surface area that contacts the soil (cm^2/day) x the soil adherence rate (mg/cm^2) x the dermal absorption fraction for CDD/CDFs (0.03) (U.S. EPA, 1999). The age-specific surface areas and adherence factors were based on data and estimation methods recommended in U.S. EPA (1997) and U.S. EPA (1999) for adult and child residents. The soil ingestion rates used here are those recommended by U.S. EPA (1997). Soil ingestion occurs commonly among children during activities such as mouthing of toys and other objects, nonsanitary eating habits, and inadvertent hand-to-mouth transfers. In addition to normal soil ingestion activities, some individuals exhibit behavior known as pica which involves intentional soil ingestion. Soil ingestion rates associated with pica are probably much higher. Some limited data suggest rates as high as 5 to 10 g/day for deliberate soil ingestion rates for pica children. The current Exposure Factors Handbook (U.S. EPA, 1997) suggests a central tendency value for non-pica children of 100 mg/day. To a lesser extent, soil ingestion also occurs among adults from activities such as hand-to-mouth transfer when eating sandwiches or smoking, and other inadvertent ingestion of soil, such as that in household dust. Data on soil ingestion are even more scarce for adults. Based on limited data, a central tendency value of 50 mg/day is suggested by U.S. EPA (1997), which is used here.

It should be noted that the contact rates used in this assessment for some food products (e.g., meats) are lower than those used in an earlier 1994 draft (U.S. EPA, 1994) of this document. The values in the earlier draft were based on the average of food disappearance rates and intake rates. The intake rates were 1-day diary data derived from the 1987/1988 USDA National Food Consumption Survey (NFCS) (USDA, 1995). This type of survey is considered to be the best indicator of food consumption patterns, and statistical designs used by USDA optimized the ability to correctly account for factors

such as seasonality, geography, age of recipients, and other factors. The intake data derived from the 1987/1988 USDA NFCS in the 1994 draft used assumptions to allocate meat mixtures among the various meat groups. These assumptions were required because the meat consumption rates available at the time did not account for meats consumed as mixtures. These assumptions over-estimated intake for the various individual meat groups because it was assumed that intake rates for the NFCS meat mixture category included intake of foods made up of mixed meat items only. For example, it was assumed that meat mixtures were made up of 40 percent beef, 17 percent pork, 32 percent poultry, and 11 percent fish. However, meat mixtures actually included food items that had dietary components (i.e., grains, vegetables, etc.) other than meats. Therefore, the individual meats accounted for a much smaller fraction of the mixtures than assumed in 1994. "Disappearance rates" are derived as the total amount of food that disappears (i.e., is used) from the U.S. commercial food supply divided by the number of people in the U.S., corrected for removal of bone and fat, food that goes into pet foods, and food that is imported (USDA, 1993). These rates are expected to overestimate average daily intakes because they do not account for uneaten portions, spoilage, or waste. In 1994, EPA used the USDA's report on Food Consumption, Prices, and Expenditures between 1970 and 1992 (USDA, 1993) to derive disappearance rates for each food type.

The intake data used in this current assessment are derived from a newer set of USDA intake data. EPA recently conducted a statistical analysis of the USDA food data from the 1989-1991 Continuing Survey of Food Intake among Individuals (CSFII) for inclusion in the Exposure Factors Handbook (U.S. EPA, 1997). The USDA CSFII is a 3-day survey that provides national data on the amount of food eaten by individuals over the survey period. During 1989 through 1991, over 15,000 individuals participated in the CSFII (USDA, 1995). Using a stratified sampling technique, individuals of all ages living in selected households in the 48 coterminous states and Washington, D.C., were surveyed. Individuals provided 3 consecutive days of data, including a personal interview on the first day followed by 2-day dietary records. The survey uses a statistical sampling technique designed to ensure that all seasons, geographic regions of the U.S., and demographic and sociodemographic groups are represented (USDA, 1995). EPA's analysis of the CSFII data tabulated intake rates for the major food groups, as well as individual food items. The

analysis allocated intake of meat mixtures among the various meat groups and other applicable food groups according to the percentages provided by USDA (1995), as described in U.S. EPA (1997). For example, according to USDA (1995), meat mixtures contained 20 percent beef, 2 percent pork, and 8 percent poultry. Intake of other food groups (i.e., grains, vegetables, etc.) accounted for the balance of meat mixture intake. These meat mixture fractions are considerably lower than those assumed for the 1994 draft.

As an example of the difference in the 1994 and the current food consumption rates, the 1994 pork consumption rate, 47 g/day, was derived as the average of the disappearance rate of 62 g/day and the intake rate of 32 g/day. (The intake rate of 32 g/day was estimated as the intake rate for pork of 14 g/day plus an assumed 17 percent of meat mixtures.) The resulting value, 47 g/day, is higher than the intake rate used in this current draft, 0.22 g/kg-day, or approximately 15 g/day assuming a 70 kg adult. Other differences are also significant: 77 g/day beef (1994) versus 50 g/day (currently), 68 g/day poultry (1994) versus 35 g/day, and 67/251 dairy/milk g/day (1994) vs. 55/175 g/day (currently). Also, contact rates for some of the other media are lower (e.g., soil), based on the revised Exposure Factors Handbook (U.S. EPA, 1997).

Another reason that current estimates of exposure are lower than in the 1994 document is that the estimated TEQ_{DF}-WHO_{98} concentrations for several food items (i.e., beef, pork, poultry, milk, and dairy) are also lower in this assessment than in the earlier (1994) draft. Estimates in the earlier draft were based on limited data sets for these foods, whereas the current assessment uses data from the more recent statistically-based national analyses of several food categories, as described in Chapter 3. Some of the older studies had nondetectable congener concentrations and higher detection limits than the newer studies, resulting in higher TEQ concentrations. For example, the beef concentration assumed in the 1994 assessment was 0.48 pg I-TEQ/g whole weight basis, while the current estimate is 0.18 pg TEQ_{DF}-WHO_{98}/g whole; poultry was 0.19 pg I-TEQ/g, while here it is 0.068 pg TEQ_{DF}-WHO_{98}/g. Table 4-32 compares the contact rates, TEQ concentrations, and background exposure estimates from the 1994 draft and this assessment. It should be noted that the previous draft estimated I-TEQ_{DF}s, while TEQ_{DF}-WHO_{98}s are used in the current assessment.

Background exposure levels are also presented for Germany, based on data from Fürst et al. (1990; 1991). The current total background TEQ_{DF}-WHO_{98} exposure shown in Table 4-33 is approximately 43 pg/day for North America. Based on Fürst et al. (1990; 1991), the estimated total CDD/CDF I-TEQ background exposure from food consumption for Germany is 79 pg/day (Table 4-33). However, it should be noted that the estimated background level for the United States and Germany are based on limited data, and exposure to all food groups was not considered. Also, the addition of TEQs for multiple pathways presumes that individuals are exposed by all pathways, and assumes that the fraction absorbed into the body is the same for all ingestion and inhalation pathways (i.e., 100 percent absorption in the gut and lungs is assumed). The dermal absorption pathway assumes that 3 percent of the CDD/CDFs in soil that adheres to the skin surface is dermally absorbed. The following sections present observations about CDD/CDF exposures in North America, comparisons between exposure estimates from this and previous studies, and comparisons between North American and European exposures to CDD/CDFs.

Based on the data presented in this report, the adult general population total background TEQ_{DF}-WHO_{98} exposure for North America was estimated to be 0.61 pg/kg-day (or 43 pg/day assuming a 70 kg adult), for all media combined. Exposure to 2,3,7,8-TCDD accounts for approximately 13 percent (5.5 pg/day) of the total TEQ exposure. Estimated exposures based on total TEQ_{DF}-WHO_{98} from the various exposure pathways are presented in Figure 4-4. The highest exposures were estimated to occur via ingestion of CDD/CDFs in fish and shellfish (0.12 pg/kg-day) and beef (0.13 pg/kg-day), which accounted for about 20 and 21 percent of the total TEQ_{DF}-WHO_{98} exposure, respectively. The ingestion of foods accounted for approximately 95 percent of the total TEQ_{DF}-WHO_{98} exposure. Exposure to CDD/CDFs via ingestion of water appears to be very low. Exposure via inhalation, soil ingestion, and dermal contact with soil are 0.023 pg/kg-day, 0.0063 pg/kg-day, and 0.0015 pg/kg-day, respectively. These exposures account for approximately 5.0 percent of the total CDD/CDF TEQ exposure in North America.

Adult general population TEQ_{P}-WHO_{98} exposure for North America was estimated to be 0.33 pg/kg-day (or approximately 23 pg/day, assuming a 70 kg adult), for all foods combined. This estimate is based on data on dioxin-like PCBs for food items and soil; PCB congener data were not available for urban air or water. For CDD/CDFs, these

environmental media accounted for about 3.8 percent of the overall TEQ_{DF}-WHO_{98} exposure. Assuming that these media account for a similar percentage of dioxin-like PCB exposure, total PCB exposure would be approximately 0.34 pg/kg-day (i.e., 0.33 pg/kg-day x 1.038). Thus, TEQ_{P}-WHO_{98} exposures from PCBs are approximately three quarters the TEQ_{DF}-WHO_{98} exposures from CDD/CDFs.

4.4.3. Assessment of Background Exposures Among Children

Exposures among other age groups of the U.S. population were also estimated using the same media TEQ-WHO_{98} concentrations that were used to estimate adult exposures. However, age-specific contact rates and body weights were used. These values were derived from data presented in U.S. EPA (1997) and USDA (1995). Background exposures were estimated for three age groups (i.e., 1-5 years, 6-11 years, and 12-19 years). Table 4-34 compares the contact rates and estimated CDD/CDF exposures for these age groups to adult contact rates and exposures. Table 4-35 makes similar comparisons for TEQ_{P}-WHO_{98}s. As shown in these tables, the dose per unit body weight (pg/kg/day) decreases with increasing age, but the daily dose (pg/day) increases with age. On a pg/kg-day basis, adult TEQ_{DF}-WHO_{98} doses were 3.6 times lower than those of 1 to 5 year old children and 2.1 times lower than those of 6 to 11 year old children. Likewise, for PCBs, TEQ_{P}-WHO_{98} adult doses were 3.3 times lower for 1 to 5 year old children and 1.8 times lower for 6 to 11 year olds. Table 4-36 presents the percentage contribution of each environmental media and food group to total TEQ dose for each age group. Figure 4-5 depicts these percentages for CDD/CDFs, grouped as meat/fish/eggs, dairy, and other, for the four age groups.

Milk and dairy products accounted for approximately 56 percent of the total TEQ_{DF}-WHO_{98} and TEQ_{P}-WHO_{98} exposures in 1 to 5 year old children, but only approximately 22 percent in adults. In contrast, meat and fish intake accounted for a much smaller portion of total exposure in 1 to 5 year olds, and a higher portion in adults.

Patandin et al. (1999) observed similar results using data for adults and children in The Netherlands. Data on CDD/CDF and PCB residues in foods were combined with food consumption data for various age groups to model dietary intake of dioxin-like compounds in the following age groups: 1 to 5 years, 6 to 10 years, 10 to 15 years, 16 to 20 years, and 20 to 25 years. The doses, on a body weight basis, were higher than those

estimated for the United Sates population, but the ratio of adult to child doses were similar to those described above. For example, Patandin et al. (1999) estimated a daily TEQ_{DFP}-WHO_{94} dose of 6.5 pg/kg-day for male children, age 1 to 5 years; 3.9 pg/kg-day for male children, age 6 to 10 years; and 2.4 pg/kg-day for adults, age 20 to 25 years. The adult value is 2.7 and 1.6 times lower than the values for 1 to 5 year old males and 6 to 10 years old males, respectively. Patandin et al. (1999) also reported on the contributions of various food group to total dietary intake of CDD/CDF/PCBs for various age groups. The results are consistent with those described above for the U.S. population.

4.4.4. Variability in Intake Estimates

The background adult daily intake values presented in Tables 4-30 and 4-31 are representative of mean exposures among the adult general population because they are based on mean TEQ_{DF}-WHO_{98} and TEQ_{P}-WHO_{98} concentrations and mean contact rates. They do not account for individuals with higher contact rates for foods or environmental media, or individuals who may be exposed to higher concentrations of dioxin-like compounds such as those affected by localized contamination.

Exposures to dioxin-like compounds were estimated as the product of media concentrations of CDD/CDF/PCBs times contact rates for these media with food ingestion accounting for the vast majority of the dose. Assuming that, over the long-term, all individuals in the general population are exposed to the mean TEQ_{DFP}-WHO_{98} media concentrations, variability among this population can be assessed by evaluating variations in contact rates. The assumption that long-term media concentrations to which the general population are exposed are represented by mean values is reasonable if temporarily elevated concentrations are offset by lower concentrations during other time periods, and if no regional trends are assumed (e.g., foods with varying CDD/CDF/PCB concentrations are equally distributed in the market place). Also, because food intake accounts for such a large percentage of the total dose, variations in long-term average food contact rates (i.e., ingestion rates) are likely to have the greatest impact on long-term average dose.

Some sense of the variability in general population exposures to TEQ_{DFP}-WHO_{98} can be gained by evaluating either the variability in fat intake among the general population (i.e., because fatty foods account for a high percentage of total exposure), or by

evaluating the variability of specific dietary components (i.e., food groups of the total diet). Published data on the variability in fat intake among the general population are somewhat limited. However, Cresanta et al. (1988), Nicklas et al. (1993), and Frank et al. (1986) analyzed dietary fat intake data as part of the Bogalusa heart study. The Bogalusa study "is an epidemiologic investigation of cardiovascular risk-factor variables and environmental determinants in a population that began 20 years ago" (Nicklas et al., 1995). Among other things, the study collected fat intake data for children, adolescents, and young adults. According to Nicklas (1995), "the diets of children in the Bogalusa study are similar to those reported in national studies of children." Thus, these data are useful in evaluating the variability in fat intake among the general population for the purposes of evaluating variability in exposure for dioxin-like compounds among this group. Based on data for 6 month old to 17 year old individuals during 1973 to 1982, maximum total fat intakes are 2.5 to 5 times higher than mean fat intakes. Maximum animal fat intakes for this group are 3 to 7.6 times mean animal fat intakes (Frank et al., 1986). Based on the mean total fat intake plus three standard deviations for 10-year old children during 1992 to 1994 and young adults (i.e., 19 to 28 years) during 1988 to 1990, upper-range fat intake is between two to three times that of mean intake (Nicklas et al., 1993; Nicklas et al., 1995). (Three standard deviations around the mean should represent approximately 99 percent of the population.) These data are presented in Table 4-37. Based on the assumption that variability in intake is the key contributing factor to variability in exposure to dioxin-like compounds, and that the fat intake data from these studies is representative of the general population of the United States, upper-range exposures to dioxin-like compounds would be expected to be two to three times higher than the mean background exposures estimated in this chapter.

Block (1992) and Norris (1997) estimated dietary fat intake among the adult general population using data from National Health Interview Surveys (NHIS) conducted by the National Center for Health Statistics (NCHS). Block (1992) used data for 20,143 men and women, ages 18 to 80+ years, from the survey. The mean and standard deviation fat intakes from this analysis are presented in Table 4-38. Assuming that the mean value plus three standard deviations represents the upper end of the range of fat intake, maximum fat intake is approximately two to three times higher than the mean. Norris (1997) used data for 10,827 men and women from the 1992 NHIS. The mean fat intake

was 64.4 g/day and the standard deviation was estimated to be 41.6 g/day. Using the same assumption as stated above (mean plus three standard deviations), the upper end of the range of fat intake wold be 189.2 g/day. This value is 2.9 times higher than the mean. Thus, these data from a nationally representative sample of adults are consistent with the data for children and young adults from the Bogulusa study. This variability is also supported by the ranges of tissue CDD/CDF/PCB levels, as described in Section 4.2. These data show that maximum tissue levels of dioxin-like compounds are typically two to three times the mean values.

Another way to assess variability in CDD/CDF/PCB background doses among the general U.S. population is to evaluate variability in total dietary intake and the contribution of specific dietary components to total dietary intake. Recently, EPA conducted an analysis of USDA's 1994-1996 CSFII data set to estimate total dietary intake as well as the contribution of the major food groups (i.e., total dairy, total fish, total meats, total fats, eggs, etc.) to the total diet. Intake data from this analysis were used in conjunction with average CDD/CDF/PCB concentrations in foods to evaluate variability in background dose of dioxin-like compounds.

The procedure used to evaluate variability in CDD/CDF/PCB doses from total dietary intakes derived from the CSFII was developed as follows. First, estimates of "total dietary intake" for individuals in the CSFII were determined as the sum of all food intakes reported by the individuals included in the survey. For purposes of this exercise, specific food items reported by each individual in the CSFII were grouped into classes, including total dairy, total meats, total fish, total vegetables, total eggs, and total fats. Once these total dietary intakes were compiled, CSFII survey adult individuals were ranked from lowest to highest based on total dietary intake, and intake rates at specific percentiles, such as the 50th or 90th percentile were examined. From these percentiles, subsets were defined including a "central" group of adults, which were those in the 45-55th percentile of total intake, and an upper percentile group of adults, which were defined as those above the 90^{th} percentile of total intake. For the purposes of evaluating variability in CDD/CDF/PCB doses that extend above the average doses reported in this chapter, intake rates for the upper percentile group of adults was of interest. To calculate upper percentile doses of CDD/CDF/PCBs, point estimates of the intake rates for each of the major food groups were calculated as the mean intake rate for the individuals within the upper percentile of

total food intake (i.e., above the 90th percentile). As noted above, these intake rates represented intakes for major food groups only (e.g., total meats) and not specific food items (e.g., beef, pork, poultry). Therefore, to complete this exercise, it was necessary to convert the intake rates of the major food groups to intake rates for the categories of individual foods for which CDD/CDF/PCB concentration data were available. To do so, it was assumed that the proportions of individual foods (e.g., beef, pork, poultry, and other meats) making up a food group (e.g., total meats) were the same for the upper percentile groups as for the average background individual assessed in Tables 4-30 and 4-31. Finally, average concentrations of CDD/CDF/PCBs in the various individual food items (as shown in Tables 4-30 and 4-31) were combined with the upper percentile intakes rates for individual food items to arrive at the doses to an upper percentile adult. The results for this exercise for the "upper percentile" intake rates are shown in Tables 4-39 and 4-40, which also include the average non-food exposures associated with soil, water, and air. As shown in Table 4-39 the estimated TEQ_{DF}-WHO_{98} dose among adults in the "upper percentile" of total food intake is 1.1 pg/kg/day or 77 pg day. This dose is 1.8 times higher than the mean TEQ_{DF}-WHO_{98} dose estimated in Table 4-30. The estimated TEQ_{P}-WHO_{98} dose for "upper percentile" adults is 0.65 pg/kg-day or 45 pg/day (Table 4-40). This dose is 1.9 times higher the mean dose estimated in Table 4-31.

The variability in current dose of about 2 to 3 times above the mean is similar to the range of tissue CDD/CDF/PCB levels, as described in Section 4.2. These data show that maximum tissue levels of dioxin-like compounds are typically two to three times the mean values. However, it was also discussed that important factors such as the age of the individual and their past history of exposure also contributed to variability in tissue levels, perhaps more so than their current dose. Therefore, this variability in tissue data, while similar to the variability in intakes based on the dietary data discussed here, should not be considered as important supportive evidence to a finding that elevated intakes of dioxin-like compounds range up to 3 times higher than the average dose. Also of note is that the 1994 Dioxin Reassessment documents developed an estimate of variability of intake of between 3 and 7 times the mean intake rates. This variability estimate was based on statistical extrapolations from a relatively small study measuring CDD/CDFs in blood. The new variability estimates presented here are considered more strongly

supported because they are based on larger studies, do not involve extrapolations, and more directly reflect consumption.

4.4.5. Comparison of Previous North American Studies to This Study

Previous studies of CDD/CDF exposures in North America were presented in Section 4.4.1 of this report. These studies reported CDD/CDF exposures based on the most toxic congener, 2,3,7,8-TCDD, and not on the total TEQ_{DF} value for all congeners combined. For the purposes of comparison, mean background levels of 2,3,7,8-TCDD in North America from this assessment were used to calculate exposure via various pathways. Background exposures were calculated using background environmental levels of 2,3,7,8-TCDD, standard contact rates, and appropriate unit conversion factors, as described previously. Total 2,3,7,8-TCDD exposure among adults for all pathways combined was 5.5 pg/day for the current assessment compared to 15.9 and 34.8 pg/day for the two previous studies of 2,3,7,8-TCDD exposure in North America (Henry et al., 1992; and Travis and Hattemer-Frey, 1991). Figure 4-6 depicts the comparisons of the percent contribution of various exposure pathways to total exposure to 2,3,7,8-TCDD for the current assessment and for previous North American studies. Figure 4-6 indicates that exposure via ingestion of meats accounted for a large portion of the exposure in all three studies. However, fish accounted for a higher percentage, and dairy products accounted for a lower percentage of the total 2,3,7,8-TCDD exposure in the Henry et al. (1992) study and in the current assessment than in the Travis and Hattemer-Frey (1991) study. These differences reflect differences in assumptions for food ingestion rates as well as in TCDD levels. All three studies indicate that beef, dairy products, and fish comprise over 93 percent of the total exposure. Because of the data base weaknesses noted earlier, it is not known if these differences can be considered significant.

European CDD/CDF exposure studies may also be compared to the exposures estimated in U.S. reports and in the current assessment. Comparisons may be made based on the 2,3,7,8-TCDD congener or on total TEQ_{DF} exposures (Table 4-41). Adult general population exposures to 2,3,7,8-TCDD in North America range from 5.5 pg/day to 34.8 pg/day based on the current assessment and two other U.S. studies. These values are comparable to the 2,3,7,8-TCDD exposures reported in Germany and The Netherlands by Fürst et al. (1991) and Theelen (1991). Fürst et al. (1991) reported an estimated

2,3,7,8-TCDD exposure of 25 pg/day based on ingestion of dairy products, meat, and fish; Theelen (1991) reported an estimate of 20 pg/day based on dairy, meat, poultry, and fish intake. Total TEQ_{DF} background exposure estimates for North America range from approximately 43 pg TEQ_{DF}-WHO_{98}/day for the current assessment to 140 to 290 pg I-TEQ_{DF}/day based on Gilman and Newhook's (1991) Canadian study. For Europe, total I-TEQ_{DF} exposure estimates range from 79 pg/day based on Fürst et al. (1990) to 158 pg/day based on Fürst et al. (1991).

4.4.6. Relative Contribution of Exposure Pathways to Total Intake

Figure 4-7 depicts the contributions of various exposure pathways to total background TEQ exposures for North America, Germany, the United Kingdom, and The Netherlands based on data from the current assessment (Fürst et al., 1990; MAFF, 1995; and Theelen, 1991). For all three geographic regions, over 90 percent of the exposures were attributed to ingestion of CDD/CDFs in foods. For the United States and Germany, intake of meat, fish, and eggs account for over 60 percent of the daily exposure, while milk and dairy consumption account for less than 30 percent, and soil ingestion, inhalation, etc. account for less than 7 percent of the total exposure. For The Netherlands and the United Kingdom, the meat/fish/eggs group accounts for somewhat less of the total intake, while milk/dairy and the "other" category account for more of the exposure. In particular, approximately 30 percent of the total exposure came from breads and cereals in the United Kingdom. These food groups were not evaluated in the United States estimates.

Based on the data presented in Figure 4-7, it is reasonable to expect that the CDD/CDF body burden in vegetarians would be lower than the body burden in nonvegetarians because vegetarians avoid the consumption of meat and fish and their derivative products. Welge et al. (1993) tested this hypothesis by comparing the CDD/CDF levels in the blood of 24 German vegetarians with the blood levels of 24 nonvegetarians, matched for age, sex, body weight, and height. With the exception of two individuals, all vegetarians had practiced a diet without meat and fish for at least 3 years. The CDD/CDF levels in the vegetarian group ranged from 14.64 to 52.85 pg I-TEQ_{DF}/g (lipid basis) with a mean of 32.60 pg I-TEQ_{DF}/g. In the nonvegetarian group, the CDD/CDF levels ranged from 14.26 to 97.98 pg I-TEQ_{DF}/g (lipid basis) with a mean of

34.32 pg I-TEQ_{DF}/g. There was no significant difference (α = 0.05) between the vegetarian and nonvegetarian group in the mean levels of any of the 2,3,7,8-substituted congeners, in the total CDD levels, in the total CDF levels, in the total CDD/CDF levels, or in the total I-TEQ_{DF} levels (each on a lipid and on a whole weight basis). Welge et al. (1993) suggested several reasons why no differences were found. First, all tested vegetarians had at one time been nonvegetarians. The higher levels of exposure during this nonvegetarian period coupled with the long biological half-life of CDD/CDFs may be responsible for the apparent similarity in body burdens using blood as the measure of body burden. Second, the vegetarians may have a higher level of consumption of dairy products than the nonvegetarians and thus have a similar CDD/CDF exposure even without consumption of fish and meat.

Schecter and Papke (1998) collected blood samples from two individuals (one male and one female) who had been vegans for over 20 years and analyzed them for CDD/CDFs and coplanar PCBs. These individuals were strict vegetarians, consuming no milk, cheese, eggs, or other animal products. Total CDD/CDF and PCB concentrations, as well as I-TEQ_{DF} and TEQ_{P}-WHO_{94} concentrations among these vegans were compared to the levels in two pooled samples from 100 men and 100 women from the general population. Total concentrations of CDD/CDF/PCBs were 244 ppt and 330 ppt for male and female vegans, respectively. These values were considerably lower than those observed in pooled samples from the general population; 643 ppt and 906 ppt for male and female subjects, respectively. Likewise, the TEQ_{DFP}-WHO_{94} concentrations were lower among the vegans (4.4 ppt and 8.7 ppt for males and females, respectively) than the general population (24.2 ppt and 29.3 ppt for males and females, respectively). Both the total concentrations and TEQ levels of CDD/CDFs and PCBs were higher in the samples collected from those taken from males.

4.4.7. Geographical Contributions to Dietary Exposure

As indicated in the previous sections, dietary intake appears to be the primary pathway of human exposure to dioxin-like compounds. Over 90 percent of the background dose is obtained through the diet, with foods of animal origin being the predominant sources. Aside from some episodes of localized contamination that may result in elevated exposures among individuals who consume foods from contaminated

areas (see Chapter 5), the general population of the United States is assumed to consume foods, over the long-term, that contain average background concentrations of dioxin-like compounds, resulting in background exposures that are similar across all regions of the United States. Except for some of the more perishable foods (i.e., milk and eggs) most foods are widely distributed in commerce. Thus, the general population of the United States may consume foods from a wide variety of geographic locations. In addition, the concentrations of foods grown in the various geographic regions may not vary widely. The national studies of beef, pork, and poultry, conducted jointly by EPA and USDA (Winters et al., 1996a; Winters et al., 1996b; Lorber et al. 1997; Ferrario et al., 1997), indicated that there was little variation in the concentrations of dioxin-like concentrations, based on geographic location. The milk study (Lorber et al., 1998) suggested the possibility of a geographic trend, with CDD/CDF concentrations being somewhat higher in the southeastern United States than in the southwestern United States.

Based on the distribution of foods in commerce, and the similarities of concentrations in many foods, variations in dietary exposure on the basis of geography would not be likely to be significant and the general population would be expected, over the long term, to be exposed to similar concentrations of dioxin-like concentrations in foods. However, the total amount of dioxin-like compounds entering the food supply may vary geographically because of the predominance of certain types of food production in certain regions of the country. For example, food such as pork is produced primarily in the northern midwest and some areas on the southeastern part of the United States; whereas poultry is produced primarily in the southeast.

The purpose of this section is to present the results of a study of the geographic variability of dioxin production as indicated by variability in production of animal fats. EPA conducted an analysis to determine the geographic origin (within the 48 contiguous United States) of several food groups that are likely to contain dioxin-like compounds (e.g., meats and dairy products). Cattle, chicken, and hog producer sales figures from the 1997 Census of Agriculture (USDA, 1997), enumerated by county, were converted to an equivalent dioxin TEQ using data in Putnam and Allshouse (1999). The 1997 food disappearance data for beef, pork, and chicken in this reference were used to convert the USDA production data, expressed in units of individual animals sold, to grams of animal fat entering the food chain. Food disappearance is the total supply at the start of the

year, plus imports, minus exports and shipments to U.S. territories, minus stock at the end of the year. It therefore includes all food eaten in the home, wasted by spoilage in the home, lost in preparation, or left uneaten on the plate. The food disappearance data were expressed as a boneless weight assuming a standard conversion factor for each animal type (Putnam and Allshouse, 1999). This total weight was converted to dioxin TEQs using CDD/CDF/PCB concentration values from the EPA meat/milk surveys and WHO_{98} TEFs. The total dioxin value was then divided by the total number of animals to yield ng TEQ per animal. This value was multiplied by the county-level USDA data to yield ng TEQ per year for every county.

Production figures for dairy products are not included in the Census of Agriculture, but the number of dairy cows is provided for each county. State-level data on milk fat production were apportioned among each state's counties on the basis of the number of dairy cows in each county. This approach assumes that all milk cows in a given state are equally productive. In a similar way, where only state-level egg production data are available, county values were calculated by apportioning the state-level data among the counties on the basis of the number of layers and pullets in each county. Examples of the county-level production data are shown in Figures 4-8 and 4-9 for pork and dairy products, respectively. Similar maps were produced for the other products (i.e., beef, poultry, and eggs) and for the total TEQ_{DF}-WHO_{98} over all five products. It should be noted that the geographic variability in this analysis is based on variability in food production only, and not in the concentration of dioxin-like compounds in the foods. Thus, it does not indicate that the concentrations of dioxin-like compounds are higher in some regions than in others. Instead it indicates that the production of dioxin-containing foods is higher in some regions than in others. The relative contributions of the five food products included in this study compare favorably with EPA's current estimates of total TEQ_{DF}-WHO_{98} dose based on 1989-91 CSFII food intake data (Figure 4-10).

This analysis may be useful, in conjunction with source analyses, in identifying important food production areas where dioxin-like compounds are also being released. To that end, major contributors to the total dioxin TEQ for the 48 contiguous states were identified. The 3,048 counties in the database were sorted in descending order and divided into four groups, with each group encompassing 25 percent of the 48-state total. The resulting map (Figure 4-11) shows that the top 65 counties account for 25 percent of

the total TEQ. The second, third, and fourth quartiles encompass 212, 498, and 2,303 counties, respectively. Assuming that the dominant pathway resulting in dioxin exposure for domestic meat and dairy animals is air deposition onto feed crops, it necessarily follows that the dioxin sources that dominate general population exposure have to be those sources that dominate ambient air concentrations in the areas flagged by this analysis. Future work is aimed at identifying these dioxin sources.

4.4.8. Contribution of CDD/CDF Congeners to Background Dose and Body Tissue Concentration

The purpose of this section is to evaluate the contribution of individual congeners to background dose and tissue concentrations. This section also evaluates whether the congeners that are the primary contributors to dietary dose are consistent with those that dominate the body burden. Section 4.4.2 derived a background dose of approximately 1 pg TEQ_{DF}-WHO_{98}/kg-day, which included doses of 0.61 pg TEQ_{DF}-WHO_{98}/kg-day for CDD/Fs and 0.33 pg TEQ_{DF}-WHO_{98}/kg-day for coplanar PCBs. These doses were calculated assuming average exposure media concentrations and contact rates for several pathways. Food consumption made up most of this total dose, with the food consumption pathways of beef, pork, chicken, fresh fish, marine fish, dairy, and milk totaling 0.90 pg TEQ_{DFP}-WHO_{98}/kg-day. This exercise will focus on these pathways alone. Section 4.2 examined body tissue concentrations of the dioxin-like congeners. The average TEQ_{DF}-WHO_{98} lipid concentration in blood was calculated at 21.6 pg TEQ_{DF}-WHO_{98}/g. For dioxin-like PCBs, the average lipid concentration in blood was 2.0 TEQ_{P}-WHO_{98}/g. These data were based on the CDC blood data, as described previously, and represent recent body burdens. It should be noted, however, that PCB data were only available for four congeners (i.e., PCBs 77, 81, 126, and 169). The exercise in this section determines the percentage TEQ_{DFP}-WHO_{98} contribution of each toxic CDD, CDF, and dioxin-like PCB congener to the daily total background dose of TEQ_{DFP}-WHO_{98} s. It also determines the percentage TEQ_{DFP}-WHO_{98} contribution of each toxic congener to the body tissue TEQ_{DFP}-WHO_{98} concentrations. The exercise concludes with a comparison of the two sets of percentages.

The following general rules were applied in developing the information for this exercise:

1) *The food surveys used to calculate average concentrations for background dose calculation of TEQ-WHO_{98}s were also used to calculate TEQ-WHO_{98} congener profiles, when possible.*

For all food groups except two, the same data used in calculating background doses were used in this analysis. The total TEQ_{DF}-WHO_{98} for these data are summarized in Table 3-59 and the total TEQ_{P}-WHO_{98} are summarized in Table 3-60. For freshwater and marine fish, it was not possible to derive a CDD/CDF congener profile using the same data as that used to calculate a background dose because the individual congener concentrations were not provided in the core reference. Thus, data from Schecter et al. (1995b) were used. These data represent a sampling of 10 freshwater fish from supermarkets. For marine fish, data from Fiedler et al. (1997) were used.

2) *Average concentration profiles for food were calculated assuming non-detects are equal to one-half detection, which was the same procedure for calculating body tissue concentration profiles.*

This was the assumption used to calculate the background dose. However, it should be noted that this could be problematic for some data, specifically when the detection limits were high. The determination of the food concentration profiles in Chapter 3 was accomplished assuming nondetects were equal to zero for this reason.

3) *When more than one survey was used to determine the average representative concentration profile in food or body tissue concentration, all samples were pooled and assumed equally weighted for dioxins. However, for coplanar PCBs, the data in the literature studies were developed by compositing methods that did not allow for the calculation of weighted averages. Because of this, one concentration per study was derived for each congener, and then the average concentration was assumed to be the average over the number of studies.*

Since many of the studies reporting CDD/CDF concentrations, particularly the food studies, were grab sample studies, it seems most reasonable to simply treat all samples equally. Also, mean food concentrations, for purposes of background dose derivation of the CDD/CDFs, were calculated giving all samples equal weight. Therefore, the determination of the representative profiles was made consistent with the dose

calculation. The background dose calculation for the dioxin-like PCBs was done slightly differently. In these cases, two of the principal studies, Mes and Weber (1989) and Mes et al. (1991) composited several samples. In one study, nondetected congeners on composite samples were set to one-half the detection limits for calculating mean congener concentrations. However, in the other study, mean congener concentrations were based on positive composites only. Thus, there was no simple method for calculating a weighted mean for these studies.

4) *For the dioxin-like PCBs, not all the studies evaluated the same coplanar congeners. This occurred in both the food data and the tissue data. Therefore, this analysis is incomplete with regard to estimating the full dose of dioxin-like PCBs as well as the percentage of dose/body tissue* TEQ_P-WHO_{98} *that can be attributed to each congener. This appears to be an issue for two of the dioxin-like PCBs. However, inclusion of the full information of these two congeners will unlikely change the important qualitative finding in the dioxin-like PCB analysis - that PCB 126 dominates both tissue and body burden concentration.*

There are 11 dioxin-like PCBs with some dioxin-like toxicity, based on the TEQ_P-WHO_{98} scheme (Younes, 1998). Using the TEF_P-WHO_{98} scheme, 13 PCB congeners were considered to have dioxin-like toxicity. The CDC data set included data for only four of the dioxin-like PCBs for human tissues (i.e., PCBs 77, 81, 126, and 169). There were no reported concentrations in food for two of the congeners, PCBs 123 and 167. PCB 114 had some impact on total tissue concentrations and was included in some of the food survey data. However, this congener was not included in the USDA/EPA national studies on pork, beef, poultry, and milk. Other food studies also measured PCB 189, which was not included in the USDA/EPA studies, but contributed an insignificant amount to coplanar TEQ_P-WHO_{98} concentration, so its exclusion in the USDA/EPA studies was not critical. The net effect for exclusion of PCB 114 in these food groups is that the contribution of PCB 126 to TEQ_P-WHO_{98} was overestimated while the contribution from PCB 114 was underestimated. Likewise for human tissues, the contribution of PCB 126 to TEQ_P-WHO_{98} is likely overestimated.

Further details on the procedures used in the forward dose calculations and the body tissue concentrations are presented below.

4.4.8.1. *Background Dose*

Approximately 90 percent of the background daily TEQ_{DFP}-WHO_{98} dose is derived from the following foods: freshwater fish, marine fish, milk, dairy, beef, pork, and poultry. For CDDs/CDFs/PCBs, the total daily dose from these pathways is estimated to be 58 pg TEQ_{DFP}-WHO_{98}/day. The remaining dose comes from: soil ingestion, marine shellfish ingestion, inhalation, water ingestion, egg ingestion, and vegetable fat ingestion. For ease of calculation, this exercise focuses on the higher contributing food groups rather than on all routes of exposure. Further, when calculating the percentage of the total TEQ_{DFP}-WHO_{98} dose which can be attributed to each congener, it is assumed that the 58 pg TEQ_{DFP}-WHO_{98}/d represents 100 percent of the daily dose. For ease of understanding, the CDD/CDF and PCBs are tabulated separately in the tables and figures. The TEQ_{DF}-WHO_{98} dose from CDDs/CDFs is 38 pg/day and the dose for coplanar PCBs is 20 pg TEQ_{P}-WHO_{98}/day. The congener contributions from the dietary intake calculation is characterized in terms of the percentage each congener contributes to the TEQ_{DFP}-WHO_{98}. This will be compared to the congener contributions to body burdens, which are also compiled on an individual percentage basis.

The procedure for doing the dietary intake calculations is described in the following four steps:

1. **Determine the representative congener concentrations in the food product.** These were determined as the average concentrations of the individual congeners from available survey data, given the rules stated above. Based on the way in which the data were reported in the literature, the basis for food concentrations was either on a lipid basis or on a whole weight basis. Most of the CDD/CDF food data were reported on a lipid basis, while most of the coplanar PCB data were reported in the literature on a whole food basis. Although the basis for the food concentrations is important for calculating a dose because the concentration data must be consistent with the intake data (i.e., if concentrations are reported on a whole weight basis, whole weight intake rates must be used), it was not important for calculating the fractional contribution of each congener to the total TEQ since the same values would be calculated using either lipid-based or whole weight concentrations. Therefore, lipid-based CDD/CDF concentrations were used for all foods, and whole weight PCB concentrations were used for all foods.

2. **Determine the toxic equivalent concentrations in the food product.** These were easily determined as the product of the average congener concentration and the appropriate TEF.

3. **Determine the TEQ-WHO_{98} congener profiles as the fractional contribution of each congener to total TEQ-WHO_{98} concentration.** This was determined as the ratio of the toxic equivalent concentration of each congener to the total TEQ-WHO_{98}.

4. **Determine the TEQ-WHO_{98} congener profile of the dietary dose by multiplying the TEQ-WHO_{98} fractional contribution of each congener by food intake rate for that food product.** A multiplication of each food product's overall TEQ-WHO_{98} concentration, in pg/g, and the corresponding food consumption rate, in g/day, gives the pg TEQ-WHO_{98} consumed per day by that food product. Further multiplication of this pg TEQ-WHO_{98}/day and each congener's fractional contribution gives the pg TEQ-WHO_{98}/day contributed by each congener. The representative food TEQ-WHO_{98} concentrations described in Section 4.4.2 to determine background dose were expressed on a whole weight basis, to be consistent with the consumption rates of the food products, which were also on a whole weight basis. The whole concentration, in pg TEQ_{DF}-WHO_{98}/g for CDD/CDFs and TEQ_{P}-WHO_{98}/g for coplanar PCBs for all food products were: beef - 0.18 pg/g CDD/CDFs and 0.084 pg/g PCBs; pork - 0.28 pg/g CDD/Fs and 0.012 pg/g PCBs; poultry - 0.068 pg/g CDDs/CDFs and 0.026 pg/g PCBs; dairy - 0.12 pg/g CDD/CDFs and 0.058 pg/g PCBs; milk - 0.018 pg/g CDDs/CDFs and 0.0088 pg/g PCBs, freshwater fish - 1.2 pg/g CDD/CDFs and 1.2 pg/g PCBs; and marine fish - 0.36 pg/g CDD/Fs and 0.25 pg/g PCBs. The consumption rates for this exercise were expressed in g/day, which were calculated using the g/kg-day consumption rates given in Section 4.4.2 multiplied by a 70 kg adult: beef - 49.7 g/day, pork - 15.4 g/day, poultry - 35 g/day, dairy - 55 g/day, milk - 175 g/day, freshwater fish - 5.9 g/day, and marine fish - 9.6 g/day.

The results of this four-step procedure are demonstrated in Table 4-42 for the beef consumption pathway for CDDs/CDFs. Tables 4-43 and 4-44 show the average congener concentrations of CDDs/CDFs and PCBs, respectively, derived for the food groups, the total TEQ-WHO_{98} concentration for each food group from this profile, and the TEQ-WHO_{98} percentage contributions for each congener and food group. Tables 4-45 and 4-46 show

the final results of this exercise for CDDs/CDFs and PCBs, respectively. Results suggest that 72 percent of the total TEQ_{DF}-WHO_{98} background dose of CDDs/CDFs comes from four congeners: 1,2,3,7,8-PCDD (33 percent), 2,3,4,7,8-PCDF (17 percent), 2,3,7,8-TCDD (10 percent), and 1,2,3,6,7,8-HxCDF (12 percent). PCB 126 comprises 61 percent of the TEQ_P-WHO_{98} dose of dioxin-like PCBs. When adding the doses of the CDDs/CDFs to the coplanar PCBs, PCB 126 and 1,2,3,7,8-PCDD are the largest contributors at 21 percent, followed by the three CDD/CDF congeners at 2,3,4,7,8-PCDF (11 percent), 2,3,7,8-TCDD (7 percent), and 1,2,3,6,7,8-HxCDD (8 percent).

4.4.8.2. *Background Tissue Concentrations*

For the purposes of this exercise, the tissue concentrations from the CDC studies reported in Table 4-18 were used. For coplanar PCBs, the main issue was that data for only four PCB congeners were included (i.e., PCBs 77, 81, 126, and 169). As a result of the exclusion of the other PCBs, their percent contribution to the TEQ tissue concentration could not be calculated.

Once the concentrations were derived, the TEQ-WHO_{98} contributions of individual congeners to the total TEQ-WHO_{98} were derived in a manner similar to the food results. Tables 4-47 and 4-48 show the final results of this exercise for CDDs/CDFs and coplanar PCBs, respectively, giving the derived actual congener concentrations, and the percentage contribution to TEQ-WHO_{98} for each congener. The studies used in this exercise are the same as those used in Section 4.2.3 to estimate recent (i.e., 1990s) body burden levels.

Table 4-47 indicates that four congeners contribute 82 percent of CDD/CDF TEQ_{DF}-WHO_{98}: 1,2,3,6,7,8-HxCDD (34 percent), 1,2,3,7,8-PCDD (24 percent), 2,3,4,7,8-PCDF (14 percent), and 2,3,7,8-TCDD (10 percent). These are the same four congeners contributing the most to background dose. From Table 4-48, it is seen that PCB 126 overwhelms all other congeners, and for all tissue types. PCB 126 comprises 90 percent of the dose of dioxin-like PCBs. Figures 4-12 and 4-13 compare the fractional TEQ-WHO_{98} contributions of each congener to the total TEQ-WHO_{98} background dose of CDD/CDFs (Figure 4-12) and coplanar PCBs (Figure 4-13), to the TEQ-WHO_{98} contributions of each congener to average body tissue TEQ-WHO_{98} concentration of CDD/CDFs (Figure 4-12) and coplanar PCBs (Figure 4-13). The match between the

highest contributors is noteworthy from this figure, as is the lack of contribution from other congeners. Some key observations that can be gleaned from this exercise include:

1) As noted, five congeners dominate the TEQ-WHO_{98} body burden as well as the TEQ dose. These are, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PCDF, and 2,3,7,8-TCDD from the CDD/CDFs, and PCB 126 from the coplanar PCBs.

2) For the four dominant CDD/CDF congeners combined, the body burden had a higher TEQ-WHO_{98} contribution than the food: contributions from the four congeners to body burden TEQ-WHO_{98} equaled 82 percent while for food they equaled 72 percent.

3) While 2,3,7,8-TCDD has been the focus of past exposure and health studies, it would appear that the other CDD/CDF congeners found to be high contributors in this exercise may also be important from an exposure and health standpoint.

4.5. Comparison of Assessment Approaches and Best Estimates of Intake

Two approaches were used in this chapter to estimate background exposures to dioxin-like compounds among the general population of the Unites States. The first approach used pharmacokinetic modeling to calculate a dose from tissue concentrations. This was done using either a steady state or non-steady state approach. Using the steady state approach, the TEQ_{DF}-WHO_{98} dose was estimated to be 126 pg/day, when the half life for TCDD (i.e., 7.1 years) was assumed to apply to the total TEQ, and 87 pg/day, when congener specific half-lives were used. PCB doses could not be estimated in this way because of the lack of congener-specific half-life information. The advantage of modeling doses from tissue concentrations is that all pathways of exposure are accounted for. However, because the half-lives of dioxin-like compounds in the body are relatively long (i.e., 7.1 years for TCDD), modeled doses may reflect the cumulative effect of previous doses and not current doses. This was demonstrated by a non-steady state model used to reconstruct past doses of 2,3,7,8-TCDD. The results of the modeling exercise indicated that current doses would be expected to be less than past doses. Assuming that these results would apply to all dioxin-like congeners, and not just 2,3,7,8-TCDD, the current total TEQ_{DF}-WHO_{98} dose would be expected to be somewhat lower than 88 pg/day, as estimated using the steady state approach.

The second approach used for estimating background doses to dioxin-like compounds was to evaluate dioxin-like compounds in various dietary components (i.e.,

meats, dairy products, fish, etc.) and environmental media (i.e., air, soil, water) to which humans are exposed. By combining TEQ_{DFP}-WHO_{98} concentrations in foods and these media with the contact rates (i.e., ingestion, inhalation, dermal contact rates) for these foods and media, CDD/CDF and PCB doses were calculated. Using this approach, the daily TEQ_{DF}-WHO_{98} dose was estimated to be 43 pg/day and the TEQ_{P}-WHO_{98} was estimated to be 23 pg/day. The advantage of using this approach is that, if current media concentrations and intake estimates are used, the estimated doses should reflect current exposures. In this analysis, the most recent data on the concentrations of dioxin-like compounds in beef, pork, poultry, milk, and vegetable oil, collected by EPA, have been used. Recent data from the published literature have also been used for freshwater and marine fish and shellfish. Likewise, intake rates are based on EPA's recently published *Exposure Factors Handbook* (U.S. EPA, 1997)which presented data from USDA's 1989-1991 Continuing Survey of Food Intake Among Individuals (USDA, 1995) (a more recent USDA data set has been released since the *Exposure Factors Handbook* was published, but EPA has not yet completed its analysis of these data), and the most current data for establishing contact rates for other media. It should be noted, however, that the dose component approach may underestimate current doses if important pathways of exposure are not accounted for in the component analysis. For example, in this assessment, fruits and vegetables have not been considered as significant contributors to the overall dose. Data for the concentrations of dioxin-like compounds in fruits and vegetables are limited, but it expected that the concentrations would be lower in these foods than in fatty foods such as meat, fish and dairy products. Thus, a fruit and vegetable component has not been included in this analysis. If fruits and vegetables actually account for a more significant portion of the exposure than expected, the dose estimated here may be lower than that experienced by the general population of the United States. Other uncertainties introduced by this approach include the use of soil ingestion rates that may or may not account for all types of inadvertent soil ingestion (e.g., outdoor soil, household dust), the lack of PCB residue data for soils and air, and non-representative sampling data for air. For example, the adult soil ingestion rate cited in the *Exposure Factors Handbook* (U.S. EPA, 1997) is based on a limited data set, but is used as a reasonable surrogate for all forms of soil ingestion. The accuracy of this assumption is difficult to assess; however, because soil ingestion accounts for a small percentage of the overall dose, this uncertainty

is not expected to significantly affect one's confidence in the dose estimates. Likewise, the lack of PCB soil and air data, and the non-representative nature of the CDD/CDF air data would be expected to have little effect on the overall dose estimate, because these pathways account for a small percentage of the overall dose.

Despite these uncertainties, the dose component approach is believed to provide the best estimate of the mean current background dose to the general U.S. population. Variability was evaluated using dietary fat data, high-end intake rates, and by evaluating variability in body burden. In general, these data indicate that the high-end dose of dioxin-like compounds is likely to be 2 to 3 times higher than the mean.

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Table 4-1. NHATS Mean Adipose Tissue Data (ppt, lipid adjusted)

Congener	Congener Concentration (pg/g)	I-TEQ_{DF} Concentration (pg/g)	TEQ_{DF}-WHO_{98} Concentration (pg/g)	Percent Detected[a]
2,3,7,8-TCDD	5.38	5.38	5.38	97
2,3,7,8-PeCDD	10.7	5.35	10.7	97
2,3,7,8-HxCDD	86.8	8.68	8.68	97
2,3,7,8-HpCDD	110	1.1	1.1	100
OCDD	724	0.72	0.072	100
2,3,7,8-TCDF	1.88	0.19	0.19	100
1,2,3,7,8-PeCDF	0.31	0.016	0.016	14
2,3,4,7,8-PeCDF	9.7	4.85	4.85	95
2,3,7,8-HxCDF	14.2	1.42	1.42	2 to 92
2,3,7,8-HpCDF	16	0.16	0.16	4 to 89
OCDF	2.28	0.002	0.0002	30
TOTAL		27.9	32.6	

[a] Based on analysis of 48 samples composited from 865 samples

Source: U.S. EPA (1991a).

Table 4-2. Estimated Mean I-TEQ_{DF} Concentrations (ppt) in Adipose Tissue for U.S. Subpopulations from the 1987 NHATS

	I-TEQ_{DF} Concentration (ppt)	Percent of Population[a]
Census Regions		
Northeast	31.1	22
North Central	29.7	26
South	26.6	33
West	24.4	19
Age Groups		
0-14 years	9.7	23
15-44 years	24.6	46
45 + years	46.5	31
Race		
Caucasian	26.5	83
Non-Caucasian	35.2	17
Sex		
Male	26.1	49
Female	29.9	51
Total Population	27.9	100

[a] Population percentage based on 1980 U.S. Census.

Source: Orban et al. (1994).

Table 4-3. Human Adipose Tissue Data (ppt, lipid adjusted)

Chemical	Range (ppt)	Mean (ppt)
2,3,7,8-TCDD	1.6 to 38	10.4
PCB 77	Nondetect to 27.9	11.7
PCB 126	14.6 to 371	135
PCB 169	29.5 to 174	69
PCB 81	1.5 to 21.3	10.5

Source: Patterson et al. (1994).

Table 4-4. Mean Levels in Human Serum (ppt, whole weight basis)

Chemical	1982	1988	1989
2,3,7,8-TCDD	Not Measured	0.159	0.0165
PCB 77	1.38	0.481	0.251
PCB 126	0.281	0.183	0.135
PCB 169	0.282	0.151	0.192
PCB 105	Not Measured	33.2	Not Measured
PCB 118	Not Measured	366	Not Measured
PCB 180	Not Measured	466	Not Measured
Total PCBs	Not Measured	3,100	Not Measured

Source: Patterson et al. (1994).

Table 4-5. Mean TEQ Levels in Pooled Serum Samples

	$I\text{-}TEQ_{DF}$ (ppt, lipid basis)	$TEQ_P\text{-}WHO_{94}$ (ppt, lipid basis)
Cornwall		
Sports Fishers		
<38 years, lower	20.8	--
higher	22.2	3.6
38 years, lower	28.4	3.1
higher	31.4	9.5
> 50 years, higher	33.5	17.3
Nonfish Eaters		
<38 years	24.7	2.6
38-50 years	29.8	6.8
>50 years	36.8	9.7
Mississauga		
Sports Fishers		
<38 years	32.4	--
38-50 years	40.1	--
>50 years	41.2	--
Nonfish Eaters		
<38 years	34.0	--
38-50 years	29.1	--
>50 years	34.3	--

Source: Adapted from Cole et al. (1995).

Table 4-6. CDD/CDF Levels in Human Blood from Various Countries

Country	Mean Blood Level (ppt I-TEQ_{DF}, lipid)	Number of Samples
USA	41 (50 ppt TEQ_{DF}-WHO_{98})	100
Germany	42 (49 ppt TEQ_{DF}-WHO_{98})	85
S. Vietnam (Ho Chi Minh)	28	50
S. Vietnam (Dong Nai)	49	33
N. Vietnam (Hanoi)	12	32
Guam	32	10
Soviet Union (St. Petersburg)	17	50
Siberia (Baikalsk)	18	8
Japan	31 (35 ppt TEQ_{DF}-WHO_{98})	50-100

Source: Schecter et al. (1992a; 1994a).

Table 4-7. CDD/CDF Levels in Human Adipose Tissues from Various Countries

Country	Mean Tissue Level (ppt I-TEQ_{DF})	Number of Samples
USA	24 (27 ppt TEQ_{DF}-WHO_{98})	15
Germany	69 (79 ppt TEQ_{DF}-WHO_{98})	4
China	18	7
Japan	38 (43 ppt TEQ_{DF}-WHO_{98})	6
Canada	36 (40 ppt TEQ_{DF}-WHO_{98})	46
S. Vietnam	30	41
N. Vietnam	4	26

Source: Schecter (1991).

Table 4-8. Levels of CDDs and CDFs 2,3,7,8-Substituted Found in Spanish Human Adipose Tissue on Fat Weight Basis in pg/g (ppt). (17 samples)

Isomers	No. of Pos.	Range (pg/g)	Mean (pg/g)	S.D. (pg/g)	I-TEQ_{DF} (pg/g)
2,3,7,8-TCDD	6	ND-13.86	3.28	5.03	3.28
2,3,7,8-TCDF	11	ND-18.52	3.98	5.24	0.39
1,2,3,7,8-PCDF	4	ND-25.87	2.01	6.47	0.02
2,3,4,7,8-PCDF	13	ND-44.77	25.14	15.86	12.7
1,2,3,7,8-PCDD	12	ND-22.57	10.74	8.89	5.37
1,2,3,4,7,8-HCDF	10	ND-83.63	18.77	25.43	1.87
1,2,3,6,7,8-HCDF	10	ND-68.10	14.92	19.05	1.49
2,3,4,6,7,8-HCDF	8	ND-66.31	10.87	21.05	1.87
1,2,3,7,8,9-HCDF	10	ND-76.40	20.63	38.6	2.06
1,2,3,4,7,8-HCDD	5	ND-54.5	6.52	14.62	0.65
1,2,3,6,7,8-HCDD	12	ND-152.4	65.64	54.60	6.56
1,2,3,7,8,9-HCDD	13	ND-41.28	19.9	13.31	1.99
1,2,3,4,6,7,8-HCDF	14	ND-102.2	23.63	25.45	0.23
1,2,3,4,7,8,9-HCDF	6	ND-106.6	9.40	26.55	0.09
1,2,3,4,6,7,8-HCDD	17	60.4-707.4	187.4	146.35	1.87
OCDF	11	ND-293.7	72.30	99.59	0.072
OCDD	17	91-2847.5	1318.1	742.49	1.31
CDDs	17	313.9-3457	1608.3	839.6	21.03
CDFs	17	23.9-649.7	203.4	188.3	20.79
CDDs + CDFs	17	963.7-3604.2	1811.7	813.8	41.8 (TEQ_{DF}-WHO_{98} = 46 pg/g)

ND = Not detected

Source: Gonzalez et al. (1993).

Table 4-9. Concentration of CDDs, CDFs, and PCBs in Human Milk on a Fat Basis (pg/g)

Congener	Primipara (n = 7)		Multipara (n = 8)		Ratio Pri/Multi
	Mean	SD	Mean	SD	
2,3,7,8-TCDD	2.0	0.4	1.2	0.3	1.7***
1,2,3,7,8-PeCDD	8.9	1.7	5.0	2.6	1.8**
1,2,3,4,7,8-HxCDD	4.7	4.3	2.6	1.1	1.8
1,2,3,6,7,8-HxCDD	32.3	8.1	18.9	6.4	1.7**
1,2,3,7,8,9-HxCDD	6.9	2.7	3.6	1.2	1.9**
1,2,3,4,6,7,8-HpCDD	29.8	15.4	31.3	15.6	0.9
OCDD	174.2	137.0	194.6	75.5	0.9
2,3,7,8-TCDF	2.3	0.8	2.0	0.5	1.1
1,2,3,7,8-PeCDF	0.6	0.5	0.6	0.5	1.1
2,3,4,7,8-PeCDF	11.4	1.3	7.8	3.0	1.5*
1,2,3,4,7,8-HxCDF	4.3	0.5	3.3	1.2	1.3
1,2,3,6,7,8-HxCDF	4.5	0.5	3.2	1.3	1.4*
1,2,3,7,8,9-HxCDF	1.9	0.8	1.6	0.4	1.2
2,3,4,6,7,8-HxCDF	2.0	1.3	1.5	0.7	1.3
1,2,3,4,6,7,8-HpCDF	2.0	0.7	2.1	0.5	1.0
1,2,3,4,7,8,9-HpCDF	0.2	0.2	0.7	0.9	0.3
OCDF	2.7	1.3	3.0	1.3	0.9
3,3',4,4'-TeCB	10.4	6.4	13.7	7.3	0.8
3,3',4,4',5-PeCB	134.5	70.7	165.9	87.4	0.8
3,3',4,4',5,5'-HxCB	60.0	33.4	50.1	21.1	1.2
Total CDD	258.7	144.7	257.2	78.9	1.0
Total CDF	27.0	4.2	21.5	5.7	1.3*
Total CDD/CDF	285.7	145.8	278.7	83.5	1.0
Total Dioxin-like PCB	204.9	94.3	229.8	105.9	0.9
I-TEQ_{DF}	32.6	9.6	28.9	8.9	1.1
Fat (%)	4.6	1.8	3.5	0.9	1.3
Age	27.4	3.8	32.1	4.2	0.9

*** $p < 0.01$
** $p < 0.1$
* $p < 0.5$

Source: Hirakawa et al. (1995).

Table 4-10. CDD/CDF Concentrations and I-TEQ_{DF} Levels in Human Milk
(ppt, lipid basis)

Congener	Concentration (pg/g fat)		Toxicity Equivalents (pg/g fat, as I-TEQ_{DF})	
	Mean	Range	Mean	Range
2,3,7,8-T_4CDD	4.2	2.9 - 5.1	4.21	2.92 - 5.06
1,2,3,7,8-P_5CDD	11.9	8.4 - 16.6	5.94	4.18 - 8.30
1,2,3,4,7,8-H_6CDD	7.1	5.0 - 11.0	0.71	0.50 - 1.10
1,2,3,6,7,8-H_6CDD	35.3	27.8 - 45.5	3.53	2.78 - 4.55
1,2,3,7,8,9-H_6CDD	8.0	6.5 - 11.1	0.80	0.65 - 1.11
1,2,3,4,6,7,8-H_7CDD	81.4	40.8 - 142	0.81	0.41 - 1.42
O_8CDD	272	154 - 455	0.27	0.15 - 0.46
2,3,7,8-T_4CDF	1.3	0.7 - 1.9	0.13	0.07 - 0.19
1,2,3,7,8-P_5CDF	0.9	0.5 - 1.8	0.045	0.02 - 0.09
2,3,4,7,8-P_5CDF	31.1	24.7 - 42.6	15.56	12.35 - 21.30
1,2,3,4,7,8-H_6CDF	8.6	6.8 - 11.0	0.86	0.68 - 1.10
1,2,3,6,7,8-H_6CDF	7.8	6.3 - 10.4	0.77	0.63 - 1.04
1,2,3,7,8,9-H_6CDF	0.5	<0.1 - 1.0	0.05	<0.01 - 0.10
2,3,4,6,7,8-H_6CDF	4.9	2.0 - 7.0	0.49	0.20 - 0.70
1,2,3,4,6,7,8-H_7CDF	13.4	5.4 - 30.1	0.13	0.05 - 0.30
1,2,3,4,7,8,9-H_7CDF	5.0	2.5 - 15.0	0.05	0.03 - 0.15
O_8CDF	3.4	1.6 - 7.0	0.0034	0.00 - 0.01
Total CDD/CDFs	497	333 - 715	34.4 (TEQ_{DF}-WHO_{98} = 40 ppt)	27.3 - 43.2

Source: Van Cleuvenbergen et al. (1994).

Table 4-11. CDD/CDF and PCB TEQ Concentrations in Breastmilk from Various Countries and Regions Based on 1992/93 Sampling[a]

Country	Area	Indiv. Samples in Pool	Fat (wt%)	CDD/CDF (pg I-TEQ_{DF}/g)	Non-Ortho PCBs (pg TEQ_P-WHO_{94}/g)	Mono-Ortho PCBs (pg TEQ_P-WHO_{94}/g)	∑ [Marker PCBs] (ng/g)
Albania	Tirana	10	5.84	4.8	1.3	1.1	63
	Librazhd	10	4.72	3.8	1.0	0.7	43-46
Austria	Vienna (urban)	13	4.10	10.7	8.3	3.4	381
	Tulln (rural)	21	3.80	10.9	9.4	3.0	303
	Brixlegg (industrial)	13	3.40	14.0	15.1	3.8	449
Belgium	Brabant Wallou	8	3.79	20.8	3.8	3.6	275-277
	Liege	20	2.98	27.1	1.7	3.1	306-308
	Brussels	6	2.81	26.6	4.0	3.9	260-261
Canada	Maritimes 92	20	2.76	10.8-11.0	2.9	1.2-1.4	86-87
	Québec 92	20	3.06	13.4-13.6	5.1	1.7-1.9	137-138
	Ontario 92	20	3.09	18.1-18.3	5.8	1.8-2.0	128-129
	Prairies 92	20	3.20	14.6-14.8	2.3	0.9-1.1	58-59
	British Columbia 92	20	2.97	15.7-15.8	2.5	1.0-1.2	70-71
	All Provinces 92	100	2.96	14.5-14.6	3.8	1.5-1.7	112-113
	Gaspe	12	3.52	23.2-23.4	9.5	3.2-3.4	220-221
	Basse Côte-Nord	4	3.63	14.6-14.7	19.6	5.7-6.0	559-560
	Ungave Bay	4	3.31	14.3-14.5	9.8	4.3-4.6	576
	Hudson Bay	5	3.26	20.9-21.1	13.3	8.0-8.3	1361
Croatia	Kirk	10	3.80	8.4	3.8	2.2	218-219
	Zagreb	13	3.26	13.5	5.2	2.7	219
Czech	Kladno	11	5.41	12.1	2.5	3.5	532-533
	Uherske Hradiste	11	4.92	18.4	4.1	5.7	1068
Denmark	7 Different Cities	48	3.61	15.2	2.3	2.2	209-210
Finland	Helsinki	10	4.14	21.5	1.9	2.7	189
	Kuopio	24	4.49	12.0	1.0	1.4	133-135
Germany	Berlin	10	5.00	16.5-16.6	9.0	2.7	375
Hungary	Budapest	20	4.97	8.5-8.6	0.8	0.8	61-65
	Scentes	10	4.97	7.8	0.9	0.5	45-47
Netherlands	Whole Country	17	2.73	22.4-22.5	8.8	2.5	253-256
Norway	Tromsø (coastal)	10	2.56-2.70	10.1	16.1	3.4	273
	Hamar (rural)	10	2.51-2.76	9.3	7.4	3.0	265-266
	Skien/Porsgrumm (ind)	10	2.75-3.00	12.5-12.6	6.7	2.9	302
Lithuania	Palanga (coastal)	12	4.00-4.83	16.6	12.8	7.6	361
	Anykshchiai (rural)	12	3.56-4.10	14.4	12.9	7.8	287
	Vilnius City (urban)	12	2.69-2.87	13.3	11.6	8.9	322
Pakistan	Lahore	14	4.31	3.9	1.9	0.4	19-20
Russia	Arkhankelsk	1	5.17	15.2	2.9	5.7	197
	Karhopol	1	3.64	5.9	2.0	2.9	102
Slovak	Michalovce	10	4.77	15.1-15.2	6.4	7.0	1015
	Nitra	10	3.61	12.6	3.6	2.5	489-490
Spain	Bizkaia	19	3.75	19.4	6.7	3.9	461
	Gipuzkoa	10	3.86	25.5	3.8	4.4	452-453
Ukraine	Kiev nr.1	5	3.40	11.0	9.3	5.6	264
	Kiev nr.2	5	3.76	13.3	6.0	5.6	191-192
United Kingdom	Birmingham	20	3.09-3.10	17.9	2.5	1.8	129-131
	Glasgow	23	3.40-3.45	15.2	2.6	1.3	131-133

[a] Results from the second round of WHO-coordinated exposure studies on levels of PCBs, PCDDs, and PCDFs (on fat basis) in human milk. In calculating sums of the six marker PCBs and levels of PCDDs, PCDFs, non-*ortho*, and mono-*ortho* PCBs expressed in TEQ, both data are shown when non-detect values are equal to zero and non-detect values are equal to the limit of detection. If no differences appeared, a single value is presented.

I-TEF_{DF}s used in calculating TEQ_{DF}s for CCD/CDFs; TEF_P-WHO_{94}s used in calculating TEQ_Ps for PCBs.

Source: Liem et al. (1996).

Table 4-12. Comparison of Results from the First and Second Round of WHO-Coordinated Human Milk Study

Country	Area	CDDs and CDFs (pg I-TEQ_{DF}/g)				∑ [Marker PCBs] (ng/g)			
		1987/88[b]	n	1992/93	n	1987/88	n	1992/93	n
Austria	Vienna (urban)	17.1	54	10.7	13			381	13
	Tulln (rural)	18.6	51	10.9	21			303	21
Belgium	Brabant Wallou	33.7		20.8	8	558	12	275	8
	Liege	40.2		27.1	20	609	21	306	20
	Brussels	38.8		26.6	6			260	6
Canada	All Provinces 1981			28.6	200			212	200
	All Provinces 1982			14.5	100			112	100
	Maritimes	15.6	19	10.8	20			86	20
	Québec	18.1	34	13.4	20			137	20
	Ontario[c]	17.6	76	18.1	20			128	20
	Prairies	19.4	31	14.6	20			58	20
	British Columbia	23.0	23	15.7	20			70	20
Croatia	Kirk	12.0	14	8.4	10	500[a]	14	218	10
	Zagreb	11.8	41	13.5	13	450[a]	41	219	13
Denmark	Several Regions/Cities	17.8	42	15.2	48	830[a]	10	209	48
Finland	Helsinki	18.0	38	21.5	10	150	38	189	10
	Kuopio	15.5	31	12.0	24	203	31	133	24
Germany	Berlin	32.0	40	16.5	10			375	10
	North Rhine-Westphalia	31.6	79	20.7[e]		762	143		
Hungary	Budapest	9.1	100	8.5	20			61	20
	Scentes	11.3	50	7.8	10			45	10
Netherlands	Rural Area	37.4	13			416	10		
	Urban Area	39.6	13			392	10		
	All Regions	34.2	10	22.4	17	272	96	253	17
Norway[d]	Tromsø (coastal)	18.9	11	10.1	10	562[a]	10	273 (536[a])	10
	Hamar (rural)	15.0	10	9.3	10	507[a]	10	265 (483[a])	10
	Skien/Porsgrumm (ind)	19.4	10	12.5	10	533[a]	8	302 (468[a])	10
United Kingdom	Birmingham	37.0		17.9	20			129	20
	Glasgow	29.1		15.2	23			131	23

NOTE: Results are expressed on a fat basis. ∑ (marker PCBs) and TEQs are calculated assuming non-detect values are equal to zero.

[a] Analyzed using packed column technique.
[b] Calculated using Nordic TEF-model.
[c] Ontario-1988 denotes proportional mean of two pooled samples analyzed in the first round.
[d] To compare results between first and second round, samples from 1992/93 have been reanalyzed using (old) packed column technique (Becher and Skåre, personal communication).
[e] Dioxin levels in human milk samples from North Rhine-Westphalia collected in 1992 as reported by Fürst[19]).

Source: Liem et al. (1996).

Table 4-13. PCB Concentrations in Cow's Milk and Human Milk from The Netherlands (ppt, lipid basis)

	Cow's Milk (background site)	Human Milk
PCB 77	3.5	13.7
PCB 126	14.4	88.1
PCB 169	2.8	55.2

Source: Van der Velde et al. (1994).

Table 4-14. I-TEQ_{DF}s in Mother's Milk and Blood, and Infant's Blood (ppt)

Time Period	Samples Taken	Mother/Child Pair 1	Mother/Child Pair 2	Mother/Child Pair 3	Mother/Child Pair 4
Before 2nd pregnancy	Mother's blood Milk 1st Infant's blood	12.3 16.3 29.2 (age 11 months	10.5 12.8 37.5 (age 12 months)	NA	NA
At or after birth*	Mother's blood Milk Placenta Cord blood	10.3 11.9 14.5	11.9 15.6 18.5 8.4	13.4 11.8 9.7 4.1	14.5 10.9 24.4 9.1
5 Months after birth	Mother's blood Milk	11.2 11.0	6.0 11.3	No Data	 11.1
11 Months after birth	Mother's blood Infant's blood	10.1 10.8 (2nd infant)	5.6 16.0 (2nd infant)	11.5 4.2 (2nd infant)	15.8 23.7 (2nd infant)

NA - Not applicable
* Represents second birth for mothers 1 and 2, and first birth for mothers 3 and 4.

Source: Abraham et al. (1998).

Table 4-15. Mean Concentrations of CDD/CDFs and Coplanar PCB Congeners from the Times Beach Exposure Study

	Target Population (n = 76)					Comparison Population (n = 74)				
	Sep, 1995	July, 1996	June, 1997	Mean	n*	Sep, 1995	July, 1996	June, 1997	Mean	n*
CDD Congeners										
2,3,7,8-TCDD	1.79	1.27	1.23	1.43	66	1.46	1.38	1.23	1.36	61
1,2,3,7,8-PCDD	4.93	4.04	2.95	3.97	67	4.53	4.96	3.45	4.31	60
1,2,3,7,8,9-HxCDD	7.24	5.98	5.15	6.12	64	6.28	7.25	5.47	6.33	59
1,2,3,4,6,7,8-HpCDD	88.0	75.4	60.5	74.6	60	83.7	84.7	64.8	77.8	61
1,2,3,4,6,7,9-HpCDD	0.89	1.06	0.68	0.88	58	0.99	0.93	0.79	0.90	59
OCDD	650.0	542.0	435.0	542.3	64	535.0	512.0	404.0	483.7	46
TEQ_D-WHO_{98}	8.4	6.7	5.3	6.8		7.5	8.0	5.9	7.1	
CDF Congeners										
2,3,7,8-TCDF	0.48	0.56	0.53	0.52	62	0.56	0.54	0.45	0.52	51
1,2,3,7,8-PCDF	0.42	0.46	0.46	0.45	66	0.48	0.49	0.46	0.48	60
2,3,4,7,8-PCDF	5.73	5.00	4.12	4.95	61	5.43	5.82	4.52	5.26	59
1,2,3,4,7,8-HxCDF	7.36	6.40	5.03	6.26	64	6.18	7.24	4.91	6.11	59
1,2,3,6,7,8-HxCDF	6.40	5.07	4.01	5.16	65	5.19	5.86	4.03	5.03	58
2,3,4,67,8-HxCDF	0.46	0.45	0.47	0.46	63	0.77	0.80	0.63	0.73	55
1,2,3,4,6,7,8-HpCDF	14.4	12.1	9.0	11.83	63	11.5	11.7	8.30	10.5	59
1,2,3,4,7,8,9-HpCDF	0.40	0.47	0.42	0.43	65	0.45	0.42	0.40	0.42	58
OCDF	1.13	1.08	0.56	0.92	53	1.22	1.08	1.46	1.25	48
TEQ_F-WHO_{98}	4.5	3.9	3.2	3.9		4.1	4.5	3.4	4.0	
Coplanar PCB Congeners										
77	2.43	1.90	2.52	2.28	63	1.90	2.47	2.22	2.20	59
81	1.97	1.92	1.91	1.93	65	2.13	2.10	2.07	2.10	54
126	9.97	8.80	8.15	8.97	66	12.8	14.2	12.3	13.1	59
169	16.4	14.4	10.8	13.9	63	16.2	16.4	13.1	15.2	59
WHO_{98} TEQ_P	1.2	1.0	0.9	1.0		1.4	1.6	1.4	1.5	

* n = number of individuals with measurements of this congener for all three sampling dates.

Source: MDOH (1999).

Table 4-16. Results of Blood Sampling for the Comparison Population at Vertac in Jacksonville, AK

	1991 Sampling of 71 individuals	1994 Resampling of 18 individuals		1995 Resampling of 14 individuals	
	1991	1991	1994	1991	1995
CDD Congeners					
2,3,7,8-TCDD	2.5	3.0	2.7	3.1	3.3
1,2,3,7,8-PCDD	6.1	6.6	5.7	5.9	5.9
1,2,3,4,7,8-HxCDD	7.7	7.9	12.4	7.4	NR
1,2,3,6,7,8-HxCDD	70.8	70.4	56.0	66.4	68.1
1,2,3,7,8,9-HxCDD	8.6	8.9	7.2	9.8	10.2
1,2,3,4,6,7,8-HpCDD	124.1	115.0	77.2	102.9	81.7
OCDD	970.8	944.7	608.7	690.6	650.9
TEQ_D- WHO_{98}	18.6	19.6	16.8	18.4	17.9
CDF Congeners					
2,3,7,8-TCDF	2.0	0.6	0.2	0.6	0.1
1,2,3,7,8-PCDF	0.1	0.3	0 (ND)	0.2	0 (ND)
2,3,4,7,8-PCDF	5.4	6.4	5.6	5.9	5.6
1,2,3,4,7,8-HxCDF	8.1	8.0	6.8	7.4	6.6
1,2,3,6,7,8-HxCDF	5.0	5.6	4.4	5.1	4.9
1,2,3,7,8,9-HpCDF	0 (ND)	0 (ND)	0 (ND)	0 (ND)	0 (ND)
2,3,4,6,7,8-HxCDF	3.2	4.0	2.6	4.0	2.5
1,2,3,4,6,7,8-HpCDF	19.9	18.0	13.5	18.9	14.6
1,2,3,4,7,8,9-HpCDF	0.1	0.3	0.2	0 (ND)	0 (ND)
OCDF	0.6	0.8	0 (ND)	1.0	0 (ND)
TEQ_F-WHO_{98}	4.7	5.2	4.3	4.9	4.4
Coplanar PCB Congeners					
77	5.9	3.1	0 (ND)	4.4	NR
81	0 (ND)	0 (ND)	0 (ND)	0 (ND)	0.4
126	17.2	17.6	13.2	15.4	15.1
169	16.3	20.8	18.5	18.2	17.9
WHO_{98} TEQ_P	1.9	2.0	1.5	1.7	1.7

Source: ADH (1995) and Cranmer (1996).

Table 4-17. Congener-specific Average Concentrations for 29 North Carolina Adults

	North Carolina Adults, n = 29, sampled in 1996
CDD Congeners	
2,3,7,8-TCDD	2.38
1,2,3,7,8-PCDD	4.51
1,2,3,4,7,8-HxCDD	3.46
1,2,3,7,8,9-HxCDD	3.99
1,2,3,4,6,7,8-HpCDD	54.04
OCDD	391.3
TEQ_D-WHO_{98}	8.22
CDF Congeners	
2,3,7,8-TCDF	1.01
1,2,3,7,8-PCDF	1.16
2,3,4,7,8-PCDF	6.26
1,2,3,4,7,8-HxCDF	5.44
1,2,3,6,7,8-HxCDF	4.67
2,3,4,6,7,8-HxCDF	1.66
1,2,3,7,8,9-HxCDF	1.37
1,2,3,4,6,7,8-HpCDF	11.77
1,2,3,4,7,8,9-HpCDF	1.32
OCDF	2.80
TEQ_F-WHO_{98}	4.74
Coplanar PCB Congeners	
77*	51.00
81*	4.11
126*	17.95
169*	14.95
WHO_{98} TEQ_P	2.00

* PCBs 77 and 81 were not detected in any sample, so the concentrations shown are the average of ½ detection limit for the 29 samples. PCBs 126 and 169 were detected in most of the samples, so the average concentrations calculated at ½ detection limits reported above are very similar to average concentrations calculated at ND = 0.

Source: Masten (2000).

Table 4-18. Results of CDC Compilation of Blood Data from Six Study Sites (all results in pg/g lipid; n = 316)

Congener	Mean	75th Percentile	90th Percentile	95th Percentile
CDD Congeners				
2,3,7,8-TCDD	2.1	2.7	3.5	4.2
1,2,3,7,8-PCDD	5.2	6.5	7.8	9.2
1,2,3,4,7,8-HxCDD	6.2	7.8	10.9	12.0
1,2,3,6,7,8-HxCDD	73.1	87.6	116.9	127.3
1,2,3,7,8,9-HxCDD	7.1	8.8	10.7	12.6
1,2,3,4,6,7,8-HpCDD	79.2	94.9	131.3	161.5
OCDD	664.0	793.6	1084.7	1394.0
CDF Congeners				
2,3,7,8-TCDF	0.7	0.9	1.2	1.5
1,2,3,7,8-PCDF	0.8	1.0	1.4	1.7
2,3,4,7,8-PCDF	6.2	7.5	10.2	12.2
1,2,3,4,7,8-HxCDF	6.5	7.8	10.5	12.2
1,2,3,6,7,8-HxCDF	5.3	6.2	8.4	9.8
1,2,3,7,8,9-HxCDF	0.7	0.8	1.2	1.4
2,3,4,6,7,8-HxCDF	2.2	2.6	3.3	4.0
1,2,3,4,6,7,8-HpCDF	13.2	15.4	21.2	25.8
1,2,3,4,7,8,9-HpCDF	1.3	1.5	2.1	2.6
OCDF	2.1	2.6	3.3	4.0
Coplanar PCB Congeners				
77	31.1	32.6	51.7	72.7
81	3.2	3.9	5.4	6.9
126	18.1	21.8	32.2	45.8
169	19.4	25.1	32.7	37.7
Toxic Equivalent Concentrations for the Entire Data Base*				
TEQ_{DFP}-WHO_{98}	22.1	26.7	33.9	38.8

* This TEQ concentration was derived separately from the congener profile, and cannot be derived from the profile. See text for more detail.

Table 4-19. CDD/CDF Levels in Human Tissues in North America (ppt TEQ_{DF}-WHO_{98}, lipid basis) (late 1980s to early 1990s)

	2,3,7,8-TCDD	1,2,3,7,8-PECDD	Total HXCDD	1,2,3,4,6,7,8-HPCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PECDF	2,3,4,7,8-PECDF	Total HXCDF	1,2,3,4,6,7,8-HPCDF	OCDF	Total TEQ*
ADIPOSE TISSUE												
NHATS, U.S. EPA, 1991a U.S. (n = 865; 48 composites)	5.4	10.7	8.7	1.1	0.072	0.19	0.016	4.9	1.4	0.16	0.0002	32.6
Patterson et al., 1994 U.S. (n = 4)	4.4	11.6	11.6	0.56	0.045	0.11	-	1.9	0.95	0.12	-	31.3
Schecter, 1991 U.S. (n = 15)	6.9	7.7	6.6	0.83	0.043	0.16	-	3.4	1.1	0.16	0.00005	26.8
Schecter, 1991 Canada (n = 46)	7.1	11	9.7	1.5	0.095	-	-	8.5	1.8	0.3	-	40.0
MEAN	6.0	10.3	9.1	1.00	0.064	0.15	0.02	4.7	1.3	0.19	0.0001	32.7
SD	1.1	1.5	1.8	0.35	0.021	0.03	0.00	2.5	0.33	0.07	0.0001	
WEIGHTED MEAN	5.5	10.7	8.7	1.1	0.073	0.19	0.02	5.0	1.4	0.17	0.0002	32.8
BLOOD												
Cole et al., 1995 Canada (n = 132; 14 composites)	4.4	9.9	8.5	1.1	0.053	0.18	-	8.3	3.0	0.12	-	35.8
Schecter et al., 1993 U.S. (n = 5; composite)	3.4	7.0	8.1	1.6	0.12	0.3	0.1	3.5	2.1	0.5	0.001	26.4
Schecter et al., 1993 U.S. (n = 50)	3.8	9.2	9.1	1.2	0.08	0.2	0.1	4.4	2.3	0.23	0.001	30.9
Schecter et al., 1994a U.S. (n = 100)	5.2	21.0	11.2	1.9	0.12	0.31	0.14	6.5	3.3	0.36	0.0004	50.0
MEAN	4.20	11.8	9.3	1.4	0.093	0.27	0.08	5.7	2.7	0.26	0.0008	35.8
SD	0.68	5.4	1.2	0.32	0.028	0.04	0.04	1.9	0.48	0.06	0.0003	
WEIGHTED MEAN	4.5	13.6	9.6	1.4	0.081	0.28	0.11	6.9	3.0	0.28	0.0006	39.8
HUMAN MILK												
Schecter et al., 1989b U.S. (n = 42)	3.3	6.7	4.2	0.42	0.023	0.29	0.023	3.65	1	0.043	0.0004	19.7
ALL TISSUE TYPES												
MEAN	4.9	10.5	8.7	1.1	0.072	0.23	0.06	5.00	1.9	0.20	0.001	32.7
SD	1.3	4.1	2.2	0.45	0.032	0.07	0.04	2.2	0.80	0.09	0.0004	
WEIGHTED MEAN	5.2	11.2	8.8	1.2	0.073	0.21	0.03	5.4	1.8	0.19	0.0003	34.0

* Sum of mean TEQ_{DF}-WHO_{98} concentrations for all congeners.

Table 4-20. CDD/CDF Levels in Human Tissues in Europe and Japan (ppt TEQ_{DF}-WHO_{98}, lipid basis) (ate 1980s to early 1990s)

	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	Total HxCDD	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PeCDF	2,3,4,7,8-PeCDF	Total HxCDF	1,2,3,4,6,7,8-HpCDF	OCDF	Total TEQ*
ADIPOSE TISSUE												
Beck et al., 1994 Germany (n=20)	7.2	21.0	11.9	1.0	0.059	0.25	0.02	20.0	3.6	0.2	0.00004	65.2
Gonzalez et al., 1993 Spain (n=17)	3.3	10.7	9.2	1.9	0.13	0.39	0.02	12.7	7.3	0.32	0.0072	45.9
Schecter, 1991 Germany (n=4)	5.1	21.5	10.9	1.5	0.065	0.39	-	35.4	3.8	0.23	0.00042	78.9
Schecter, 1991 Japan (n=6)	6.6	13.0	8.6	0.69	0.14	0.31	-	6.5	6.9	0.71	-	43.4
MEAN	5.6	16.6	10.2	1.3	0.098	0.34	0.02	18.7	5.4	0.37	0.003	58.4
SD	1.5	4.8	1.32	0.46	0.036	0.06	0.00	10.8	1.7	0.20	0.003	
WEIGHTED MEAN	5.5	16.3	10.4	1.3	0.095	0.32	0.02	17.0	5.4	0.31	0.003	56.6
BLOOD												
Schecter et al., 1992a Germany (n=102)	3.6	13.8	7.6	0.92	0.061	0.23	0.1	18.5	3.5	0.25	0.00042	48.5
Schecter et al., 1992a Japan (n=50-100)	3.2	11.7	6.1	0.59	0.14	0.51	0.038	10.3	2.5	0.13	0.00031	35.1
MEAN	3.4	12.8	6.8	0.76	0.10	0.37	0.07	14.4	3.0	0.19	0.0004	41.8
SD	0.20	1.1	0.78	0.17	0.040	0.14	0.03	4.10	0.49	0.06	0.0001	
WEIGHTED MEAN	3.4	12.9	7.0	0.78	0.095	0.35	0.07	15.0	3.1	0.20	0.0004	42.9

Table 4-20. CDD/CDF Levels in Human Tissues in Europe and Japan (ppt TEQ_{DF} = WHO_{98}, lipid basis) (late 1980s to early 1990s) (continued)

	2,3,7,8-TCDD	1,2,3,7,8-PeCDD	Total HxCDD	1,2,3,4,6,7,8-HpCDD	OCDD	2,3,7,8-TCDF	1,2,3,7,8-PeCDF	2,3,4,7,8-PeCDF	Total HxCDF	1,2,3,4,6,7,8-HpCDF	OCDF	Total TEQ*
HUMAN MILK												
Bates et al., 1994 New Zealand (n = 37)	5.1	7.4	4.0	0.52	0.021	0.089	-	2.7	0.85	0.071	-	20.7
Beck et al., 1994 Germany (n = 112)	3.6	12.0	6.6	0.51	0.034	0.25	0.05	10	1.9	0.084	0.00016	35.0
Furst et al., 1994 Germany (n = 526)	3.2	10.1	5.1	0.41	0.021	0.17	0.025	13.4	1.8	0.055	0.00014	34.2
Pluim et al., 1994b The Netherlands (n = 35)	3.8	10.6	5.7	0.54	0.030	0.2	0.01	11.0	1.6	0.061	0.00013	33.5
Schecter et al., 1989b Germany (n = 185)	3	9.3	4.6	0.46	0.019	0.2	0.035	12	1.6	0.052	0.00099	31.3
Schecter et al. 1989c Japan (n = 6)	4.5	4.6	3.9	0.62	0.098	0.3	0.053	12.8	0.94	0.040	-	27.7
Startin et al., 1989 United Kingdom (n = 80)	5.6	13.0	7.0	0.71	0.027	0.12	0.02	11	1.7	0.083	0.00069	39.2
Tuinstra et al., 1994 The Netherlands (n = 200)	4.1	11.5	6.2	0.63	0.079	0.09	0.03	11.3	1.7	0.077	0.00013	35.7
Van Cleuvenbergen et al., 1994 Belgium (n = 9)	4.2	11.9	5.04	0.81	0.027	0.13	0.045	15.6	2.2	0.18	0.00034	40.1
MEAN	4.2	10.0	5.3	0.58	0.041	0.17	0.04	11.1	1.6	0.08	0.0004	33.1
SD	0.83	3.5	1.1	0.12	0.028	0.07	0.01	3.5	0.43	0.04	0.0003	-
WEIGHTED MEAN	3.6	10.5	5.4	0.50	0.033	0.16	0.03	11.9	1.7	0.06	0.0003	34.0
ALL TISSUE TYPES												
MEAN	4.4	12.1	6.9	0.81	0.066	0.24	0.04	13.7	2.9	0.18	0.001	41.0
SD	1.3	4.2	2.4	0.40	0.043	0.12	0.02	7.3	1.9	0.17	0.002	-
WEIGHTED MEAN	3.6	11.0	5.8	0.56	0.043	0.19	0.04	12.5	2.0	0.09	0.0004	35.8

* Sum of mean TEQ concentrations for all congeners.

Table 4-21. PCB Levels in Human Tissues in North America (ppt TEQ_P-WHO_{98}, lipid basis) (late1980s to early 1990s)

PCB Congeners	77	105	114	118	123	126	156	157	167	169	189	**Total TEQ***
ADIPOSE TISSUE												
Mes and Weber, 1989 Canada (n = 1)	0.0003	-	-	-	-	2.0	-	-	-	0.0016	-	2.0
Patterson et al., 1994 U.S. (n = 28)	0.0012	-	-	-	-	13.5	-	-	-	0.69	-	14.2
Schecter el al., 1989a U.S. (n = 3)	-	6.0	-	1.5	-	-	4.0	-	-	-	-	11.5
Williams and LeBel, 1991 Canada (n = 62)	-	-	-	-	-	26.7	-	-	-	1.6	-	28.3
MEAN	0.0008	6.00	-	1.50	-	14.1	4.0	-	-	0.76	-	26.3
SD	0.0004	0.00	-	0.00	-	10.1	0.00	-	-	0.65	-	
WEIGHTED MEAN	0.0012	6.00	-	1.50	-	22.4	4.0	-	-	1.3	-	35.2
BLOOD												
Cole et al., 1995 Canada (n = 7; pooled from 132)	0.013	-	-	-	-	6.9	-	-	-	0.57	-	7.5
Dewailly et al., 1994 Canada (n = 10-57)	-	-	-	2.5 (n = 51)	-	4.8 (n = 10)	-	-	-	0.29 (n = 10)	-	7.6
Kang et al., 1997 U.S. (n = 14-16)	-	-	-	-	-	1.8 (n = 14)	-	-	-	0.27 (n = 16)	-	2.1
Patterson et al., 1994 U.S. (n = 2,3, pooled from 240)	0.010	0.72	-	7.9	-	3.95	-	-	-	0.33	-	12.9
Schecter et al., 1993 U.S. (n = 1, pooled from 5)	0.003	0.32	-	1.1	-	5.0	2.1	-	-	0.3	-	8.9
Schecter et al., 1993 U.S. (n = 50)	0.008	0.69	-	1.6	-	10.4	3.0	-	-	0.46	-	16.2
MEAN	0.009	0.58	-	3.3	-	5.5	2.6	-	-	0.37	-	12.3
SD	0.004	0.18	-	2.7	-	2.7	0.45	-	-	0.11	-	-
WEIGHTED MEAN	0.011	0.71	-	6.1	-	5.5	2.9	-	-	0.41	-	15.6

Table 4-21. PCB Levels in Human Tissues in North America (ppt TEQ_P-WHO_{98}, lipid basis) (late 1980s to early 1990s) (continued)

PCB Congeners	77	105	114	118	123	126	156	157	167	169	189	**Total TEQ***
HUMAN MILK												
Dewailly et al., 1994 Canada (n = 96; pooled to 16)	0.0008	-	-	1.7	-	8.0	-	-	-	0.33	-	10.1
Hong et al., 1992 U.S. (n = 5)	0.034	0.64	0.75	2.6	0.017	5.8	2.2	0.50	0.011	0.58	0.04	13.2
Mes and Weber, 1989 Canada (n = "several" pooled samples)	0.0012	-	-	-	-	5.1	-	-	-	0.006	-	5.1
She et al., 1995 U.S. (n = 12)	0.0007	1.7	-	3.8	-	5.8	2.8	-	-	0.15	-	14.3
MEAN	0.0009	1.7	0.75	2.7	0.02	6.1	2.5	0.50	0.01	0.27	0.04	14.2
SD	0.014	0.53	0.00	0.84	0.00	1.1	0.31	0.00	0.00	0.21	0.00	-
WEIGHTED MEAN	0.002	1.4	0.75	2.0	0.02	7.7	2.7	0.50	0.01	0.32	0.04	15.3
ALL TISSUE TYPES												
MEAN	0.007	1.7	0.75	2.9	0.02	7.7	2.8	0.50	0.01	0.43	0.04	16.7
SD	0.010	2.0	0.00	2.1	0.00	6.3	0.68	0.0	0.00	0.39	0.00	-
WEIGHTED MEAN	0.009	0.79	0.75	5.1	0.02	8.2	2.9	0.50	0.01	0.52	0.04	18.8

* Sum of mean TEQ concentrations for all congeners.

Table 4-22 . PCB Levels in Human Tissues in Europe (ppt TEQ_P-WHO_{98}, lipid basis, using WHO TEFs) (late 1980s to early 1990s)

PCB Congeners	77	105	114	118	123	126	156	157	167	169	189	**Total TEQ***
ADIPOSE TISSUE												
Beck et al., 1989 Germany (n = 7)	0.006	-	-	-	-	-	-	-	-	-	-	0.006
HUMAN MILK												
Beck et al., 1989 Germany (n = 10)	0.0022	-	-	-	-	-	-	-	-	-	-	0.0022
Georgii et al., 1995 Germany (n = 68)	-	-	-	4.4	-	-	13.5	-	-	-	-	17.9
Johansen et al., 1994 Norway (n = 28)	0.046	0.77	2.0	2.6	-	15.6	5.8	0.8	-	1.9	-	29.6
Noren et al., 1990 Sweden (n = 2)	0.0024	1.2	-	2.8	-	12.4	10.1	-	-	0.86	-	27.4
Noren and Lunden, 1991 Sweden (n = 6,7; pooled from 120,140)	0.0027	0.65	-	-	-	9.8	7.2	-	-	0.47	-	18.1
Koopman-Esseboom et al., 1994 The Netherlands (n = 195)	0.002	0.9	-	3.6	-	15.2	10.5	-	-	0.8	-	31.0
Van der Velde et al., 1994 The Netherlands (n = "several")	0.0014	-	-	-	-	8.8	-	-	-	0.55	-	9.4
Dwarka et al., 1995 United Kingdom (n = 193)	-	-	-	2.3	-	-	-	-	-	-	-	2.3
Startin et al., 1989; Duarte-Davidson et al., 1992 United Kingdom (n = 6; pooled from 57)	-	0.99	-	1.8	-	-	-	-	-	-	-	2.8
MEAN	0.009	0.89	2.0	2.9	-	12.4	9.4	0.80	-	0.92	-	29.3
SD	0.016	0.17	0.00	0.86	-	2.8	2.7	0.00	-	0.52	-	-
WEIGHTED MEAN	0.006	0.83	2.0	3.0	-	13.1	9.7	0.80	-	0.76	-	30.2
BREAST TISSUE												
Dahl et al., 1994 Sweden (n = 16)	-	1.1	1.5	5.5	-	-	17.0	2.4	-	-	0.38	27.8
ALL TISSUE TYPES												
MEAN	0.009	0.93	1.7	3.3	-	12.4	10.7	1.6	-	0.92	0.38	31.9
SD	0.015	0.18	0.28	1.2	-	2.8	3.8	0.78	-	0.52	-	

Table 4-23. Weighted Mean CDD/CDF Profiles for Human Tissues from Studies in the 1980s and Early 1990s

2,3,7,8-Substituted CDD/CDFs	Adipose Tissue[a]		Blood[b]		Human Milk[c]	
	Concentration (ppt, lipid)	Fraction of Total 2,3,7,8-substituted CDD/CDFs	Concentration (ppt, lipid)	Fraction of Total 2,3,7,8-substituted CDD/CDFs	Concentration (ppt, lipid)	Fraction of Total 2,3,7,8-substituted CDD/CDFs
2,3,7,8-TCDD	5.49	0.0055	4.54	0.0040	3.30	0.0093
1,2,3,7,8-PeCDD	10.7	0.0107	13.6	0.0119	6.70	0.0188
1,2,3,4,7,8-HxCDD	3.82	0.0038	9.93	0.0086	4.95	0.0139
1,2,3,6,7,8-HxCDD	70.6	0.0711	73.0	0.0636	30.5	0.0856
1,2,3,7,8,9-HxCDD	12.7	0.0128	13.0	0.0113	6.20	0.0174
1,2,3,4,6,7,8-HpCDD	111.4	0.1121	138.1	0.1202	42.0	0.1178
OCDD	725.6	0.7306	811.7	0.7069	233.0	0.6537
2,3,7,8-TCDF	1.89	0.0019	2.77	0.0024	2.85	0.0080
1,2,3,7,8-PeCDF	0.32	0.0003	1.20	0.0010	0.45	0.0013
2,3,4,7,8-PeCDF	12.1	0.0122	13.9	0.0121	7.30	0.0205
1,2,3,4,7,8-HxCDF	5.89	0.0059	12.6	0.0110	5.55	0.0156
1,2,3,6,7,8-HxCDF	9.24	0.0093	8.22	0.0072	3.20	0.0090
1,2,3,7,8,9-HxCDF	--	--	6.93	0.0062	1.85	0.0050
2,3,4,6,7,8-HxCDF	--	--	3.54	0.0031	0.25	0.0007
1,2,3,4,6,7,8-HpCDF	21.6	0.0218	25.2	0.0219	4.00	0.0112
1,2,3,4,7,8,9-HpCDF	--	--	4.27	0.0037	0.25	0.0007
OCDF	1.97	0.0020	5.74	0.0050	4.10	0.0115
TOTAL	993.2	1.0	1,148.2	1.0	356.5	1.0

[a] Based on data from Patterson et al. (1994); Schecter (1991); and U.S. EPA (1991a).
[b] Based on data from Schecter et al. (1993, 1994a), and Cole et al. (1995).
[c] Based on data from Schecter et al. (1992b).

Table 4-24. Estimated Dose Based on Congener-Specific Half-Lives and Adipose Tissue TEQ_{DF}-WHO_{98} Concentrations, and Pharmocokinetic Modeling

	½ Life [d]	Adipose Tissue Conc. (ppt TEQ_{DF}-WHO_{98})	Dose [e,f] (pg/day)
2,3,7,8-TCDD	7.2	2.1	7.8
1,2,3,7,8-PECDD	15.7	5.2	8.8
1,2,3,4,7,8-HXCDD	8.4	0.62	2.0
1,2,3,6,7,8-HXCDD	13.1	7.3	14.8
1,2,3,7,8,9-HXCDD	4.9	0.71	3.9
1,2,3,4,6,7,8-HPCDD	3.7	0.79	5.7
OCDD	6.7	0.066	0.26
2,3,7,8-TCDF	7.2	0.07	0.26
1,2,3,7,8-PECDF	15.7	0.04	0.07
2,3,4,7,8-PECDF	19.6	3.1	4.2
1,2,3,4,7,8-HXCDF	6.2	0.65	2.8
1,2,3,6,7,8-HXCDF	6	0.53	2.4
1,2,3,7,8,9-HXCDF	6	0.070	0.3
2,3,4,6,7,8-HXCDF	5.8	0.22	1.0
1,2,3,4,6,7,8-HPCF	3	0.13	1.2
1,2,3,4,7,8,9-HPCDF	3.2	0.013	0.11
OCDF	6.7	0.00021	0.0008
TOTAL TEQ_{DF}-WHO_{98}		21.6	87

[a] Represents the mean half-life for all 2,3,7,8-substituted congeners in this class.
[b] Half-life for this congener not available; half-life assumed to be the same as for the CDD with the same chlorination pattern.
[c] No half-life data available for this congener; assumed to be the same as for 1,2,3,6,7,8-HxCDF
[d] Half-life data from Flesch-Janys et al. (1996).
[e] Assumes a body fat volume of 17.5 kg.
[f] Dose = [(ln2/T 0.5 yrs)*17.5 kg*Conc. (pg/g)*(1,000 g/kg)*(1 yr/365 days) / (0.8 absorption).

Table 4-25. Predicted Average Daily Intake of 2,3,7,8-TCDD by the General Population of the United States

Media	Predicted Media Concentration[a]	Media Intake (person/day)	Daily Intake of 2,3,7,8-TCDD (pg/day)	Percent of Daily Intake
Inhalation	0.02 (pg/m^3)	20 (m^3)	0.4	1.1
Water	0.003 (pg/L)	1.33 L[b]	0.004	0.01
Soil ingestion	0.96 (ng/kg)	20 mg	0.02	0.05
Food				
Produce	0.06 (ng/kg)	20 g[b]	1.2	3.4
Milk and dairy products				
Beef	0.03 (ng/kg)	266 g[b]	8.0	23.0
Fish	0.20 (ng/kg)	90 g[b]	18.0	51.7
Eggs	0.38 (ng/kg)	18 g[b]	6.7	19.3
	0.01 (ng/kg)	25 g[b]	0.5	1.4
TOTAL			34.8	100

[a] Values predicted by the Fugacity Food Chain model.

[b] Inferred consumption rate calculated by dividing reported daily intake (column 4) by predicted concentration (column 2).

Source: Travis and Hattemer-Frey (1991).

Table 4-26. Predicted Average Daily Intake of 2,3,7,8-TCDD from Foods by the General Population of the United States

Media	2,3,7,8-TCDD Concentration in Food (ng/kg)	Food Intake (g/person/day)	Daily Intake of 2,3,7,8-TCDD (pg/day)	Percent of Daily Intake
Milk	0.0018	108.9	0.20	1.2
Cream	0.0072	2.0	0.01	<0.1
Sour cream	0.010	0.7	0.01	<0.1
Cheese	0.016	19.4	0.31	1.9
Ice cream	0.0055	7.5	0.04	0.3
Butter	0.044	2.6	0.11	0.7
Cottage cheese	0.0021	5.5	0.01	<0.1
Meats	0.035	187	6.55	41.2
Ocean fish	0.500	17.2	8.6	54.1
Coffee	0.0001	363.6	0.04	0.3
Orange juice	0.0002	33.5	0.01	<0.1
TOTAL			15.9	100

Source: Henry et al. (1992).

Table 4-27. Daily Exposure to 2,3,7,8-TCDD and I-TEQ_{DF} from Air, Soil, Food, and Nonfood in The Netherlands

Media	Media Intake (g/person/day)	Daily Intake of 2,3,7,8-TCDD (pg/day)	Daily Intake of I-TEQ_{DF} (pg/day)
Air inhaled	20[a] m^3	0.05	2
Air ingested (particulates)	[b]	0.025	1
Soil dermal	150 mg	0.004	0.15
Soil ingested		0.003	0.10
Uptake from air and soil		0.08	3.2
Leafy vegetables	27 g	0.2-2	1.8-7
Pork	15 g fat	0.45	4.2
Beef	5 g fat	3	13
Chicken and eggs	2.5 g fat	0.6	4.8
Milk	8 g fat	3.2	17
Cheese, butter	12.5 g fat	5	26
Sea fish	0.4 g fat	2	14
Freshwater fish	0.4 g fat	4	10
Fish oil	5.5 g	1.1	7.2
Vegetable oil	40 g	NDA	14
Intake from food		19.5-21.3	112-117
Intake from paper food packaging		NDA	9.1
TOTAL INTAKE		19.6-21.4	121-126

[a] Intake rate could not be determined from Theelen (1991).

[b] Assumes exposure of 2,000 cm^2 of skin to 1 mg of soil/cm^2. Soil concentrations assumed to be 7,000 mg I-TEQ_{DF}/kg and 175 mg of 2,3,7,8-TCDD/kg. Dermal absorption of 1 percent assumed.

NDA = No data available.

Source: Theelen (1991).

Table 4-28. Estimated Lifetime Average Daily Exposure of Canadians to Dioxin I-TEQ_{DF}

Media	Daily Intake of Dioxin[a] (I-TEQ_{DF}) (pg/day)		
	Adult A[b]	Adult B[c]	Adult C[d]
Food	132 - 282	291 - 441	132 - 282
Air	3.5	3.5	12
Soil	1.75 - 1.90	1.75 - 1.90	1.75 - 1.90
Water	<0.7 - 3.5	<0.7 - 3.5	<0.7 - 3.5
Consumer Products	<0.7	<0.7	<0.7
Total Estimated Lifetime Intake[e]	140 - 290	300 - 450	150 - 300

[a] These estimates represent the lifetime average daily intake calculated by dividing the total estimated intakes for each life stage (i.e., adult, child, infant, neonate) by the 70-year exposure period. The estimates in this table are based on the upper range of average national values and conservative assumptions that overestimate rather than underestimate exposures. These estimates are only approximations and not absolute values.

[b] Adult a is an average 70-kg adult consuming average amounts of air (20 m^3/day), water (1 liter/day), and soil (20 mg/day). Food intakes based on Nutrition Canada 1977 survey.

[c] Adult B is similar to Adult a except that consumption of fish contaminated with CDDs and CDFs is in excess of current Canadian guidelines.

[d] Adult C is similar to Adult a except that he/she lives in close proximity to an incineration/combustion source.

[e] These estimates have been rounded off because of the uncertainty in the data.

Source: Gilman and Newhook (1991).

Table 4-29. Estimated Upper Bound Dietary Intakes of CDD/CDFs by the Average UK Consumer in 1982 and 1992

Food Group	1982			1992		
	Consumption (kg/person/day) Mean	CDD/CDF Concentration (ng I-TEQ_{DF}/kg fresh weight) Mean	CDD/CDF Intake (pg I-TEQ_{DF}/person/day) Mean	Consumption (kg/person/day) Mean	CDD/CDF Concentration (ng I-TEQ_{DF}/kg fresh weight) Mean	CDD/CDF Intake (pg I-TEQ_{DF}/person/day) Mean
Bread	0.125	0.02	3	0.118	0.03	4
Other Cereal Products	0.105	0.13	14	0.098	0.17	17
Carcass Meat	0.032	0.49	16	0.029	0.13	4
Offals (internal organs)	0.002	1.57	3	0.001	0.59	1
Meat Products	0.048	0.32	15	0.046	0.08	3
Poultry	0.017	0.50	8	0.018	0.13	2
Fish	0.016	0.41	7	0.014	0.21	3
Oils and Fats	0.030	1.26	38	0.031	0.20	6
Eggs	0.024	0.92	22	0.017	0.17	3
Milk	0.303	0.16	48	0.293	0.06	17
Milk Products	0.055	1.20	66	0.056	0.16	9
TOTAL	--	--	240	--	--	69

Note: Estimated total dietary intakes were calculated before rounding.

Source: MAFF (1995).

Table 4-30. Estimated CDD/CDF Mean Background Exposures for Adults in the United States

Media	Conc. TEQ_{DF}-WHO_{98}[a]	Contact Rate[b]	Daily Intake[c] (mg/kg-day)	Daily Intake (pg/kg-day)	% of Total
Soil ingestion	9.3 ppt[e]	50 mg/day	6.6×10^{-12}	6.6×10^{-3}	1.1
Soil dermal contact	9.3 ppt	12 mg/day[f]	1.6×10^{-12}	1.6×10^{-3}	0.3
Freshwater fish and shellfish ingestion	1.0 ppt[i]	5.9 g/day	8.4×10^{-10}	8.4×10^{-2}	13.9
Marine fish and shellfish ingestion	0.26 ppt[i]	9.6 g/day	3.6×10^{-11}	3.6×10^{-2}	5.9
Inhalation	0.12 pg/m^3	13.3 m^3/day	2.3×10^{-11}	2.3×10^{-2}	3.7
Water ingestion	0.00056 ppq	1.4 L/day	1.1×10^{-14}	1.1×10^{-5}	<0.01
Milk ingestion	0.018 ppt	175 g/day	4.5×10^{-11}	4.5×10^{-2}	7.4
Dairy ingestion	0.12 ppt	55 g/day	9.4×10^{-11}	9.4×10^{-2}	15.5
Eggs ingestion	0.081 ppt	0.24 g/kg/day	1.9×10^{-11}	1.9×10^{-2}	3.2
Beef ingestion	0.18 ppt	0.71 g/kg/day	1.3×10^{-10}	1.3×10^{-1}	21.0
Pork ingestion	0.28 ppt	0.22 g/kg/day	6.2×10^{-11}	6.2×10^{-2}	10.1
Poultry ingestion	0.068 ppt	0.50 g/kg/day	3.4×10^{-11}	3.4×10^{-2}	5.6
Other meat ingestion	0.18 ppt[g]	0.35 g/kg/day[h]	6.2×10^{-11}	6.2×10^{-2}	10.1
Vegetable fat ingestion	0.056 ppt[e]	17 g/day	1.4×10^{-11}	1.4×10^{-2}	2.2
	Total		6.1×10^{-10}	6.1×10^{-1} [d]	100.0

[a] Values from Table 3-64.

[b] Values for adult soil ingestion, inhalation, water ingestion, and eggs, beef pork, and poultry ingestion from Exposure Factors Handbook (U.S. EPA, 1997). Contact rates for milk, dairy, and vegetable fats are based on data from USDA (1995). Contact rates for fish from U.S. EPA (2000).

[c] Daily intake (mg/kg-day) = [Contact rate (g/day; m^3/day; L/day; mg/day) x Conc. TEQ x Unit Conversion (soil unit conversion = 10^{-12}, all other media unit conversion = 10^{-9})/Body Weight (kg)] or Contact rate (g/kg-day) x Conc. TEQ x Unit Conversion.

[d] Approximately equivalent to 43 pg/day, assuming an adult body weight of 70 kg.

[e] Calculated by setting nondetects to zero.

[f] Calculated as the surface area of the body that contacts the soil (5,700 cm^2/day) x the rate that soil adheres to the skin (0.07 mg/cm^2) x the fraction of CDD/CDFs absorbed through the skin (0.03); exposure factors based on recommendations in U.S. EPA (1999) for an adult resident, which assumes that the lower legs, forearms, hands, and head are exposed to the soil.

[g] Estimated as the average of beef, pork, and poultry.

[h] Calculated as the total meat intake rate minus the intake rates for beef, pork, and poultry (U.S. EPA, 1997).

[i] This concentration is a species-specific ingestion-weighted average value.

Table 4-31. Estimated Dioxin-Like PCB Mean Background Exposures for Adults in the United States

Media	Conc. WHO98-TEQ[a]	Contact Rate[b]	Daily Intake[c] (mg/kg-day)	Daily Intake (pg/kg-day)	% of Total
Soil ingestion	2.3 ppt[e]	50 mg/day	1.6×10^{-12}	1.6×10^{-3}	0.5
Soil dermal contact	2.3 ppt	12 mg/day[f]	3.9×10^{-13}	3.9×10^{-4}	0.1
Freshwater fish and shellfish ingestion	1.2 ppt	5.9 g/day	1.0×10^{-10}	1.0×10^{-1}	30.9
Marine fish and shellfish ingestion	0.25 ppt	9.6 g/day	3.4×10^{-11}	3.4×10^{-2}	10.5
Inhalation	--	--	--	--	--
Water ingestion	--	--	--	--	--
Milk ingestion	0.0088 ppt	175 g/day	2.2×10^{-11}	2.2×10^{-2}	6.7
Dairy ingestion	0.058 ppt	55 g/day	4.6×10^{-11}	4.6×10^{-2}	13.9
Eggs ingestion	0.10 ppt	0.24 g/kg/day	2.4×10^{-11}	2.4×10^{-2}	7.3
Beef ingestion	0.084 ppt	0.71 g/kg/day	6.0×10^{-11}	6.0×10^{-2}	18.2
Pork ingestion	0.012 ppt	0.22 g/kg/day	2.6×10^{-12}	2.6×10^{-3}	0.8
Poultry ingestion	0.026 ppt	0.50 g/kg/day	1.3×10^{-11}	1.3×10^{-2}	4.0
Other meat ingestion	0.041[g]	0.35 g/kg/day[h]	1.4×10^{-11}	1.4×10^{-2}	4.3
Vegetable fat ingestion	0.037 ppt	17 g/day	9.0×10^{-12}	9.0×10^{-3}	2.7
	Total		3.3×10^{-10}	3.3×10^{-1} [d]	100.0

[a] Values from Table 3-64.

[b] Values for adult soil ingestion, eggs, beef pork, and poultry ingestion from Exposure Factors Handbook (U.S. EPA, 1997). Contact rates for milk, dairy, and vegetable fats are based on data from USDA (1995). Contact rates for fish from U.S. EPA (2000).

[c] Daily intake (mg/kg-day) = [Contact rate (g/day; m^3/day; L/day; mg/day) x Conc. TEQ x Unit Conversion (soil unit conversion = 10^{-12}, all other media unit conversion = 10^{-9})/Body Weight (kg)] or Contact rate (g/kg-day) x Conc. TEQ x Unit Conversion.

[d] Approximately equivalent to 23 pg/day, assuming an adult body weight of 70 kg.

[e] Calculated by setting nondetects to zero.

[f] Calculated as the surface area of the body that contacts the soil (5,700 cm^2/day) x the rate that soil adheres to the skin (0.07 mg/cm^2) x the fraction of CDD/CDFs absorbed through the skin (0.03); exposure factors based on recommendations in U.S. EPA (1999) for an adult resident, which assumes that the lower legs, forearms, hands, and head are exposed to the soil.

[g] Estimated as the average of beef, pork, and poultry.

[h] Calculated as the total meat intake rate minus the intake rates for beef, pork, and poultry (U.S. EPA, 1997).

Table 4-32. Comparison of Adult Contact Rates, TEQ_{DF} Concentrations, and Background Exposure Estimates from the 1994 Draft and Current Version of This Document

Media	Previous I-TEQ_{DF} Concentration	Current TEQ_{DF}-WHO_{98} Concentration	Previous Contact Rate	Current Contact Rate	Previous Daily Intake Rate (pg/kg-day)	Current Daily Intake Rate (pg/kg-day)
Soil Ingestion	8.0 ppt[a]	9.3 ppt[b]	100 mg/day	50 mg/day	1.1×10^{-2}	6.6×10^{-3}
Soil Dermal Contact	--	9.3 ppt	--	12 mg/day	--	1.6×10^{-3}
Freshwater Fish and Shellfish Ingestion	1.2 ppt	1.0 ppt[c]	6.5 g/day	5.9 g/day	1.1×10^{-1}	8.4×10^{-2}
Marine Fish and Shellfish Ingestion	--	0.26 ppt[c]	--	9.6 g/day	--	3.6×10^{-2}
Inhalation	0.095 pg/m^3	0.12 pg/m^3	23 m^3/day	13.3 m^3/day	3.1×10^{-2}	2.3×10^{-2}
Water Ingestion	0.0056 ppq	0.00056 ppq	1.4 L/day	1.4 L/day	1.1×10^{-4}	1.1×10^{-5}
Milk Ingestion	0.07 ppt	0.016 ppt	251 g/day	175 g/day	2.5×10^{-1}	4.5×10^{-2}
Dairy Ingestion	0.36 ppt	0.12 ppt	67 g/day	55 g/day	3.4×10^{-1}	9.4×10^{-2}
Eggs Ingestion	0.14 ppt	0.081 ppt	29 g/day	0.24 g/kg/day	5.8×10^{-2}	1.9×10^{-2}
Beef Ingestion	0.48 ppt	0.18 ppt	77 g/day	0.71 g/kg/day	5.3×10^{-1}	1.3×10^{-1}
Pork Ingestion	0.26 ppt	0.28 ppt	47 g/day	0.22 g/kg/day	1.7×10^{-1}	6.2×10^{-2}
Poultry Ingestion	0.19 ppt	0.068 ppt	68 g/day	0.50 g/kg/day	1.8×10^{-1}	3.4×10^{-2}
Other Meat Ingestion	--	0.18 ppt	--	0.35 g/kg/day	--	6.2×10^{-2}
Vegetable Ingestion	--	0.056 ppt	--	17 g/day	--	1.4×10^{-2}
TOTAL	--	--	--	--	1.7×10^{0} (119 pg/day)	6.1×10^{-1} (43 pg/day)

a Rural/pristine background sites
b Urban background sites
c This concentration is a species-specific ingestion-weighted average value.

Table 4-33. Background Exposures via Consumption of German Food

Food	I-TEQ_{DF}[a] concentration (fat basis)	Intake Rate[b] (g fat/day)	TCDD - Equivalent[a] (pg/day)
Cow's milk	1.35	6.0	8.1
Cheese	0.98	5.2	5.1
Butter	0.66	12	7.9
Beef	1.69	10	16.9
Veal	3.22	0.1	0.3
Pork	<0.4	14	5.6
Chicken	1.41	1	1.4
Canned meat	1.29	2	2.6
Lard	0.47	1.5	0.7
Salad oil	<0.4	5	1
Margarine	<0.4	14	2.8
Fish and Fish Products		1.8	27
Freshwater fish	13.25		
Saltwater fish	16.82		
Fish oil	2.64		
Cod liver oil	13.31		
Total I-TEQ_{DF}			**79.4**

[a] Milk data based on Fürst et al. (1991); other data based on Fürst et al. (1990).
[b] Based on data reported by Fürst et al. (1990).

Table 4-34. Comparison of Contact Rates and Background TEQ_{DF}-WHO_{98} Exposures for Three Age Groups of Children to Adults

Media	TEQ_{DF}-WHO_{98} Concentrations (whole weight)	Age 1-5 Years[a]		Age 6-11 Years[b]		Age 12-19 Years[c]		Adult[d]	
		Contact Rate	Daily Intake (pg/kg-day)	Contact Rate	Daily Intake (pg/kg-day)	Contact Rate	Daily Intake (pg/kg-day)	Contact Rate	Daily Intake (pg/kg-day)
Soil Ingestion	9.3 ppt[g]	100 mg/day	6.2×10^{-2}	50 mg/day	1.6×10^{-2}	50 mg/day	8.0×10^{-3}	50 mg/day	6.6×10^{-3}
Soil Dermal Contact	9.3 ppt[g]	2.2 mg/day[e]	1.3×10^{-3}	3.2 mg/day[e]	9.8×10^{-4}	11 mg/day[e]	1.8×10^{-3}	12 mg/day[e]	1.6×10^{-3}
Freshwater Fish and Shellfish Ingestion	1.0 ppt[h]	1.5 g/day[f]	1.0×10^{-1}	1.9 g/day[f]	6.3×10^{-2}	2.3 g/day[f]	4.0×10^{-2}	5.9 g/day	8.4×10^{-2}
Marine Fish and Shellfish Ingestion	0.26 ppt[h]	2.5 g/day[f]	4.3×10^{-2}	3.1 g/day[f]	2.7×10^{-2}	3.7 g/day[f]	1.7×10^{-2}	9.6 g/day	3.6×10^{-2}
Inhalation	0.12 pg/m^3	7.5 m^3/day	6.0×10^{-2}	12 m^3/day	4.8×10^{-2}	14 m^3/day	2.9×10^{-2}	13.3 m^3/day	2.3×10^{-2}
Water Ingestion	0.00056 ppq	0.69 L/day	2.6×10^{-5}	0.79 L/day	1.5×10^{-5}	0.97 L/day	9.4×10^{-6}	1.4 L/day	1.1×10^{-5}
Milk Ingestion	0.018 ppt	348 g/day	4.2×10^{-1}	357 g/day	2.1×10^{-1}	308 g/day	9.6×10^{-2}	175 g/day	4.5×10^{-2}
Dairy Ingestion	0.12 ppt	103 g/day	8.2×10^{-1}	88 g/day	3.5×10^{-1}	77 g/day	1.6×10^{-1}	55 g/day	9.4×10^{-2}
Eggs Ingestion	0.081 ppt	0.75 g/kg/day	6.1×10^{-2}	0.41 g/kg/day	3.3×10^{-2}	0.24 g/kg/day	1.9×10^{-2}	0.24 g/kg/day	1.9×10^{-3}
Beef Ingestion	0.18 ppt	1.4 g/kg/day	2.5×10^{-1}	1.1 g/kg/day	2.0×10^{-1}	0.83 g/kg/day	1.5×10^{-1}	0.67 g/kg/day	1.3×10^{-1}
Pork Ingestion	0.28 ppt	0.48 g/kg/day	1.3×10^{-1}	0.35 g/kg/day	9.8×10^{-2}	0.27 g/kg/day	7.6×10^{-2}	0.22 g/kg/day	6.2×10^{-2}
Poultry Ingestion	0.068 ppt	1.1 g/kg/day	7.5×10^{-2}	0.87 g/kg/day	5.9×10^{-2}	0.56 g/kg/day	3.8×10^{-2}	0.49 g/kg/day	3.4×10^{-2}
Other Meats Ingestion	0.18 ppt	1.1 g/kg/day	1.9×10^{-1}	0.69 g/kg/day	1.2×10^{-1}	0.42 g/kg/day	7.4×10^{-2}	0.35 g/kg/day	6.2×10^{-2}
Vegetable Fat Ingestion	0.056 ppt[g]	4 g/day	1.5×10^{-2}	9 g/day	1.7×10^{-2}	12 g/day	1.2×10^{-2}	17 g/day	1.4×10^{-2}
TOTAL	--	--	2.2×10^{0} (34 pg/day)	--	1.3×10^{0} (37 pg/day)	--	7.2×10^{-1} (42 pg/day)	--	6.1×10^{-1} (43 pg/day)

a 15 kg body weight assumed
b 30 kg body weight assumed
c 58 kg body weight assumed
d 70 kg body weight assumed
e Dermal contact rates based on the calculation: skin surface area contacting soil (cm^2/day) x soil adherence rate (mg/cm^2) x absorption fraction (0.03). Exposure factor values based on recommended data and procedures in U.S. EPA (1999) for adult and child residents. For all ages it was assumed that the head, hands, lower legs, and forearms were exposed to soil. Adherence factors for ages 1-5 years and 6-11 years were calculated using data for children playing in dry soil. For ages 12-19 years and adults, a gardening scenario was assumed. Surface areas were assumed to be 2,400, 3,500, 5,300, and 5,700 cm^2/day for ages 1-5 years, 6-11 years, 12-19 years, and adults, respectively. Adherence factors for these age groups were estimated to be 0.03, 0.03, 0.07, and 0.07 mg/cm^2, respectively.
f Fish intake rates for children based on data in Table 10-46 of EPA's Exposure Factors Handbook (U.S. EPA, 1997). Total fish intake values apportioned among various fish categories based on the proportions for adults.
g Calculated by setting nondetects to zero.
h This concentration is a species-specific ingestion-weighted average value.

NOTE: Contact rates derived from U.S. EPA (1997) except for milk, dairy, and vegetable fats which were derived from USDA (1995). Dairy intake is assumed to be intake of total milk and milk products minus fluid milk intake.

Table 4-35. Comparison of Contact Rates and Background TEQ_P-WHO_{98} Exposures for Three Age Groups of Children to Adults

Media	TEQ_P-WHO_{98} Concentrations (whole weight)	Age 1-5 Years[a]		Age 6-11 Years[b]		Age 12-19 Years[c]		Adult[d]	
		Contact Rate	Daily Intake (pg/kg-day)	Contact Rate	Daily Intake (pg/kg-day)	Contact Rate	Daily Intake (pg/kg-day)	Contact Rate	Daily Intake (pg/kg-day)
Soil Ingestion	2.3	100 mg/day	1.5×10^{-2}	50 mg/day	3.8×10^{-3}	50 mg/day	2.0×10^{-3}	50 mg/day	1.6×10^{-3}
Soil Dermal	2.3	2.2 mg/day	3.3×10^{-4}	3.2 mg/day	2.4×10^{-4}	11 mg/day	4.4×10^{-4}	12 mg/day	3.9×10^{-4}
Freshwater Fish and Shellfish Ingestion	1.2 ppt	1.5 g/day[e]	1.2×10^{-2}	1.9 g/day[e]	7.6×10^{-2}	2.3 g/day[e]	4.8×10^{-2}	5.9 g/day	1.0×10^{-1}
Marine Fish and Shellfish Ingestion	0.25 ppt	2.5 g/day[e]	4.2×10^{-2}	3.1 g/day[e]	2.6×10^{-2}	3.7 g/day[e]	1.6×10^{-2}	9.6 g/day	3.4×10^{-2}
Inhalation	--	7.5 m^3/day	--	11 m^3/day	--	14 m^3/day	--	13.3 m^3/day	--
Water Ingestion	--	0.7 L/day	--	0.8 L/day	--	1.0 L/day	--	1.4 L/day	--
Milk Ingestion	0.0088 ppt	348 g/day	2.0×10^{-1}	357 g/day	1.1×10^{-1}	308 g/day	4.7×10^{-2}	175 g/day	2.2×10^{-2}
Dairy Ingestion	0.058 ppt	103 g/day	4.0×10^{-1}	88 g/day	1.7×10^{-1}	77 g/day	7.7×10^{-2}	55 g/day	4.6×10^{-2}
Eggs Ingestion	0.10 ppt	0.75 g/kg/day	7.5×10^{-2}	0.41 g/kg/day	4.1×10^{-2}	0.24 g/kg/day	2.4×10^{-2}	0.24 g/kg/day	2.4×10^{-2}
Beef Ingestion	0.084 ppt	1.4 g/kg/day	1.2×10^{-1}	1.1 g/kg/day	9.2×10^{-2}	0.83 g/kg/day	7.0×10^{-2}	0.71 g/kg/day	6.0×10^{-2}
Pork Ingestion	0.012 ppt	0.48 g/kg/day	5.8×10^{-3}	0.35 g/kg/day	4.2×10^{-2}	0.27 g/kg/day	3.2×10^{-3}	0.22 g/kg/day	2.6×10^{-3}
Poultry Ingestion	0.026 ppt	1.1 g/kg/day	2.9×10^{-2}	0.87 g/kg/day	2.3×10^{-2}	0.56 g/kg/day	1.5×10^{-2}	0.50 g/kg/day	1.3×10^{-2}
Other Meats Ingestion	0.041 ppt	1.1 g/kg/day	4.5×10^{-2}	0.69 g/kg/day	2.8×10^{-2}	0.42 g/kg/day	1.7×10^{-2}	0.35 g/kg/day	1.4×10^{-2}
Vegetable Fat Ingestion	0.037 ppt	4 g/day	9.9×10^{-3}	9 g/day	1.1×10^{-2}	12 g/day	7.7×10^{-3}	17 g/day	9.0×10^{-3}
TOTAL	--	--	1.1×10^{0} (16 pg/day)	--	5.8×10^{-1} (17 pg/day)	--	3.3×10^{-1} (19 pg/day)	--	3.3×10^{-1} (23 pg/day)

a 15 kg body weight assumed
b 30 kg body weight assumed
c 58 kg body weight assumed
d 70 kg body weight assumed
e Fish intake rates for children based on data in Table 10-46 of EPA's Exposure Factors Handbook (U.S. EPA, 1997). Total fish intake values apportioned among various fish categories based on the proportions for adults.

NOTE: Contact rates derived from U.S. EPA (1997) except for milk, dairy, and vegetable fats which were derived from USDA (1995). Dairy intake is assumed to be intake of total milk and milk products minus fluid milk intake.

Table 4-36. Percentage TEQ_{DFP}-WHO_{98} Contribution of Each Media to Total Dose by Age Group

Media	CDD/CDFs				PCBs			
	1-5 Years	6-11 Years	12-19 Years	Adult	1-5 Years	6-11 Years	12-19 Years	Adult
Soil Ingestion	2.8	1.2	1.1	1.1	1.4	0.7	0.6	0.5
Soil Dermal Contact	0.06	0.08	0.2	0.3	0.03	0.04	0.1	0.1
Freshwater Fish and Shellfish	4.5	5.1	5.5	13.9	11.3	13.1	14.6	30.9
Marine Fish and Shellfish	1.9	2.2	2.3	5.9	3.9	4.5	4.9	10.5
Inhalation	2.7	3.8	4.0	3.7	--	--	--	--
Water	0.001	0.001	0.001	0.002	--	--	--	--
Milk	18.7	17.2	13.3	7.4	19.2	18.1	14.3	6.7
Dairy	36.8	28.2	22.2	15.5	37.5	29.3	23.6	13.9
Eggs	2.7	2.7	2.7	3.2	7.1	7.1	7.4	7.3
Beef	11.3	15.9	20.8	21.0	11.1	15.9	21.4	18.2
Pork	6.0	7.9	10.5	10.1	0.5	0.7	1.0	0.8
Poultry	3.3	4.7	5.3	5.6	2.7	3.9	4.5	4.0
Other Meat	8.6	9.7	10.3	10.1	4.2	4.8	5.2	4.3
Vegetable Fat	0.7	1.3	1.6	2.2	0.9	1.9	2.3	2.7

Table 4-37. Variability in Fat Intake from the Bogalusa Heart Study

Age (Years)	Total Fat Intake (g) 1973-1982 Data[a]			Animal Fat Intake (g) 1973-1982 Data[a]			Total Fat Intake (g) 1992-1994 Data[b]			Total Fat Intake (g) 1988-1991 Data[c]		
	Mean	Maximum	Max/Mean	Mean	Maximum	Max/Mean	Mean	Mean + 3SD	Mean + 3SD/Mean	Mean	Mean + 3SD	Mean + 3SD/Mean
0.5	37.1	107.6	2.9	18.4	61.1	3.3	--	--	--	--	--	--
1	59.1	152.7	2.6	36.5	127.1	3.5	--	--	--	--	--	--
2	86.7	236.4	2.7	49.5	153.1	3.1	--	--	--	--	--	--
3	91.6	232.5	2.5	50.1	182.6	3.6	--	--	--	--	--	--
4	98.6	584.6	5.9	50.8	242.2	4.8	--	--	--	--	--	--
10	93.2	529.5	5.7	54.1	412.3	7.6	84.6	205.8	2.4	--	--	--
13	107.0	282.2	2.6	56.2	209.6	3.7	--	--	--	--	--	--
15	97.7	251.3	2.6	53.8	182.1	3.4	--	--	--	--	--	--
17	107.8	327.4	3.0	64.4	230.0	3.6	--	--	--	--	--	--
19-28	--	--	--	--	--	--	--	--	--	98.5	290.2	2.9

a Frank et al. (1986)
b Nicklas et al. (1993)
c Nicklas et al. (1995)

Table 4-38. Fat Intake (g/day) Among the Adult U.S. Population, Based on Data from the 1987 NHIS

Age (yrs)	Men				Women			
	N	Mean (g/day)	SD [a] (g/day)	Mean + 35D / Mean	N	Mean (g/day)	SD [a] (g/day)	Mean + 35D / Mean
18-34	3,166	116.5	69.5	2.9	4,296	67.6	32.8	2.5
35-49	2,346	103.6	48.4	2.4	2,923	65.4	43.3	3.0
50-64	1,512	90.2	46.7	2.6	2,092	57.8	27.4	2.4
65-79	1,148	76.0	40.7	2.6	1,926	50.7	26.3	2.6
80+	213	73.8	39.4	2.6	521	50.5	18.3	2.1

a Standard deviation calculated from standard error (SE) as follows: $SD = SE \times \sqrt{n}$.

Table 4-39. Estimated CDD/CDF Upper Percentile Background Exposures for Adults in the United States

Media	Conc. TEQ_{DF}-WHO_{98}[a]	Contact Rate[b]	Daily Intake[c] (mg/kg-day)	Daily Intake (pg/kg-day)	% of Total
Soil ingestion	9.3 ppt[e]	100 mg/day	1.3×10^{-11}	1.3×10^{-2}	1.2
Soil dermal contact	9.3 ppt	51.3 mg/day[f]	6.8×10^{-12}	6.8×10^{-3}	0.6
Freshwater fish and shellfish ingestion	1.0 ppt[g]	10.3 g/day	1.5×10^{-10}	1.5×10^{-1}	13.3
Marine fish and shellfish ingestion	0.26 ppt	16.7 g/day	6.2×10^{-11}	6.2×10^{-2}	5.6
Inhalation	0.12 pg/m^3	15.2 m^3/day	2.6×10^{-11}	2.6×10^{-2}	2.4
Water ingestion	0.00056 ppq[g]	2.0 L/day	1.6×10^{-14}	1.6×10^{-5}	<0.01
Milk ingestion	0.018 ppt	421 g/day	1.9×10^{-10}	1.9×10^{-1}	16.8
Dairy ingestion	0.12 ppt	132 g/day	2.3×10^{-10}	2.3×10^{-1}	20.4
Eggs ingestion	0.081 ppt	0.39 g/kg/day	3.2×10^{-11}	3.2×10^{-2}	2.9
Beef ingestion	0.18 ppt	0.93 g/kg/day	1.7×10^{-10}	1.7×10^{-1}	15.1
Pork ingestion	0.28 ppt	0.30 g/kg/day	8.4×10^{-11}	8.4×10^{-2}	7.6
Poultry ingestion	0.068 ppt	0.68 g/kg/day	4.6×10^{-11}	4.6×10^{-2}	4.2
Other meats ingestion	0.18 ppt	0.48 mg/kg/day	8.6×10^{-11}	8.6×10^{-2}	7.8
Vegetable fat ingestion	0.056 ppt[e]	28.8 g/day	2.3×10^{-11}	2.3×10^{-2}	2.1
	Total		1.1×10^{-9}	$1.1 \times 10^{+0}$ [d]	100.0

[a] Values from Table 3-64.

[b] Values for adult soil ingestion based on data in U.S. EPA (1991b). Inhalation rate based on data for males in Exposure Factors Handbook (U.S. EPA, 1997). Water ingestion rate based on high-end value in U.S. EPA (1997). Contact rates for fish, milk, dairy, eggs, meats, and vegetable fats are based on data from an unpublished analysis of USDA's 1994-1996 CSFII data conducted by EPA.

[c] Daily intake (mg/kg-day) = [Contact rate (g/day; m^3/day; L/day; mg/day) x Conc. TEQ x Unit Conversion (soil unit conversion = 10^{-12}, all other media unit conversion = 10^{-9})/Body Weight (kg)] or Contact rate (g/kg-day) x Conc. TEQ x Unit Conversion.

[d] Approximately equivalent to 77 pg/day, assuming an adult body weight of 70 kg.

[e] Calculated by setting nondetects to zero.

[f] Calculated as the surface area of the body that contacts the soil (5,700 cm^2/day) x the rate that soil adheres to the skin (0.30 mg/cm^2) x the fraction of CDD/CDFs absorbed through the skin (0.03); exposure factors based on recommendations in U.S. EPA (1999) for an adult resident, which assumes that the lower legs, forearms, hands, and head are exposed to the soil.

[g] This concentration is a species-specific ingestion-weighted average value.

Table 4-40. Estimated Dioxin-Like PCB Upper Percentile Background Exposures for Adults in the United States

Media	Conc. WHO98-TEQ[a]	Contact Rate[b]	Daily Intake[c] (mg/kg-day)	Daily Intake (pg/kg-day)	% of Total
Soil ingestion	2.3 ppt[e]	100 mg/day	3.3×10^{-12}	3.3×10^{-3}	0.5
Soil dermal contact	2.3 ppt	51.3 mg/day	1.7×10^{-12}	1.7×10^{-3}	11.1
Freshwater fish and shellfish ingestion	1.2 ppt	10.3 g/day	1.8×10^{-10}	1.8×10^{-1}	28.5
Marine fish and shellfish ingestion	0.25 ppt	16.7 g/day	6.0×10^{-11}	6.0×10^{-2}	9.6
Inhalation	--	--	--	--	--
Water ingestion	--	--	--	--	--
Milk ingestion	0.0088 ppt	421 g/day	9.6×10^{-11}	9.6×10^{-2}	15.5
Dairy ingestion	0.058 ppt	132 g/day	1.1×10^{-10}	1.1×10^{-1}	17.6
Eggs ingestion	0.10 ppt	0.39 g/kg/day	3.9×10^{-11}	3.9×10^{-2}	6.3
Beef ingestion	0.084 ppt	0.93 g/kg/day	7.8×10^{-11}	7.8×10^{-2}	12.6
Pork ingestion	0.012 ppt	0.30 g/kg/day	3.6×10^{-12}	3.6×10^{-3}	0.6
Poultry ingestion	0.026 ppt	0.68 g/kg/day	1.8×10^{-11}	1.8×10^{-2}	2.9
Other meats ingestion	0.041 ppt	0.48 mg/kg/day	2.0×10^{-11}	2.0×10^{-2}	3.2
Vegetable fat ingestion	0.037 ppt	28.8 g/day	1.5×10^{-11}	1.5×10^{-2}	2.5
	Total		6.2×10^{-10}	6.2×10^{-1} [d]	100.0

[a] Values from Table 3-64.

[b] Contact rates for fish, milk, dairy, eggs, meats, and vegetable fats are based on data from an unpublished analysis of USDA's 1994-1996 CSFII data conducted by EPA.

[c] Daily intake (mg/kg-day) = [Contact rate (g/day; m^3/day; L/day; mg/day) x Conc. TEQ x Unit Conversion (unit conversion = 10^{-9})/Body Weight (kg)] or Contact rate (g/kg-day) x Conc. TEQ x Unit Conversion.

[d] Approximately equivalent to 43 pg/day, assuming an adult body weight of 70 kg.

[e] Calculated by setting nondetects to zero.

[f] Calculated as the surface area of the body that contacts the soil (5,700 cm^2/day) x the rate that soil adheres to the skin (0.07 mg/cm^2) x the fraction of CDD/CDFs absorbed through the skin (0.03); exposure factors based on recommendations in U.S. EPA (1999) for an adult resident, which assumes that the lower legs, forearms, hands, and head are exposed to the soil.

Table 4-41. Comparisons of Predicted Average Daily Intake of 2,3,7,8-TCDD and Total TEQ_{DF}s

Location	Daily Intake of 2,3,7,8-TCDD (pg/day)	Daily Total TEQ_{DF} intake (pg/day)	Media
United States[a]	34.8	--	beef, milk, produce, fish, eggs, water, inhalation
United States[b]	15.9	--	dairy, meat, fish
North America[c]	5.5	43	dairy, eggs, meat, poultry, fish, inhalation, soil ingestion, soil dermal contact
Canada[d]		140-290	air, water, soil, food
Germany[e]		85 (79)	dairy, meats, fish
Germany[f]	25.0	158	dairy, meat, fish
Netherlands[g]	20.0	121-126	dairy, meat, poultry, fish
United Kingdom[h]	--	69	meat, fish, dairy, poultry, eggs, milk products, breads, and cereals
United Kingdom[i]	--	175.5	meat, fish, dairy, poultry, eggs, milk products, breads, and cereals
Spain[j]	--	210	vegetables, lentils and beans, cereals, fruit, fish, meat, eggs, dairy, milk, and oil

[a] Travis and Hattemer-Frey (1991)
[b] Henry et al. (1992)
[c] Current Assessment; TEF_{DF}-WHO_{98}s used
[d] Gilman and Newhook (1991); I-TEF_{DF}s used
[e] Fürst et al. (1990); value in parentheses is the corrected I-TEQ_{DF} value based on the milk data from Fürst et al. (1991); I-TEF_{DF}s used
[f] Fürst et al. (1991); I-TEF_{DF}s used
[g] Theelen (1991); I-TEF_{DF}s used
[h] MAFF (1995); data from 1992; I-TEF_{DF}s used
[l] Jacobs and Mobbs (1997) I-TEF_{DF}s used
[j] Schuhmacher et al. (1997) and Domingo et al. (1999); I-TEF_{DF}s used

Table 4-42. Example of the Calculation of the Picograms of TEQ_{DF}-WHO_{98} Contributed by Individual CDD/CDF Congeners for the Beef Consumption Pathway

Congener	Average congener concentration, pg/g lipid	Average TEQ_{DF}-WHO_{98} concentration, pg/g lipid	Fraction of TEQ_{DF}-WHO_{98} contributed by each congener[1]	TEQ_{DF}-WHO_{98} contributions to the diet by each congener (pg/day)[2]
2378-TCDD	0.052	0.052	0.049	0.43
12378-PCDD	0.35	0.35	0.33	2.9
123478-HxCDD	0.46	0.064	0.044	0.39
123678-HxCDD	1.4	0.14	0.13	1.2
123789-HxCDD	0.53	0.053	0.050	0.45
1234678-HpCDD	4.5	0.045	0.042	0.38
OCDD	4.8	0.00050	0.00045	0.0040
2378-TCDF	0.030	0.0030	0.0030	0.026
12378-PCDF	0.31	0.016	0.015	0.13
23478-PCDF	0.36	0.18	0.17	1.5
123478-HxCDF	0.55	0.055	0.051	0.46
123678-HxCDF	0.40	0.040	0.038	0.33
234678-HxCDF	0.31	0.031	0.030	0.26
123789-HxCDF	0.39	0.039	0.036	0.33
1234678-HpCDF	1.0	0.01	0.0093	0.084
1234789-HpCDF	0.31	0.0031	0.0030	0.026
OCDF	1.9	0.00019	0.00018	0.0016
TOTAL		1.06	1.00	8.9

[1] This is calculated as the picograms TEQ_{DF}-WHO_{98} contributed by each congener divided by the total TEQ_{DF}-WHO_{98} concentration. For example, the 0.049 for 2,3,7,8-TCDD is calculated as 0.052/1.06.

[2] Picograms contributed by each congener = (0.18 pg/g) (0.71 g/kg/day) (70 kg) (TEQ_{DF}-WHO_{98} fraction), where 0.18 pg/g is whole weight beef concentration as derived in Section 4.4.2, 0.71 g/kg/day is the consumption rate, 70 kg is the average adult body weight, and the TEQ_{DF}-WHO_{98} fraction is shown in the fourth column above, just preceding this final column of results.

Table 4-43. Average Concentrations (not on a TEQ_{DF}-WHO_{98} basis) and the Fraction of TEQ_{DF}-WHO_{98} Contributed by Each CDD/CDF Congener for the Various Food Groups

	Beef		Pork		Chicken		Other Meat		Dairy		Milk		Fresh Fish		Marine Fish	
Congener	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac
2378-TCDD	0.052	0.049	0.10	0.068	0.16	0.21	0.10	0.094	0.070	0.071	0.070	0.071	3.1	0.18	7.1	0.20
12378-PCDD	0.35	0.33	0.45	0.31	0.24	0.32	0.35	0.31	0.32	0.33	0.32	0.33	5.2	0.31	17	0.47
123478-HxCDD	0.46	0.044	0.52	0.035	0.18	0.024	0.39	0.035	0.39	0.040	0.39	0.040	3.0	0.018	9.0	0.025
123678-HxCDD	1.4	0.13	1.1	0.075	0.40	0.053	0.98	0.089	1.9	0.19	1.9	0.19	5.3	0.032	47	0.13
123789-HxCDD	0.53	0.050	0.47	0.032	0.37	0.049	0.46	0.042	0.55	0.056	0.55	0.056	4.1	0.024	13	0.036
1234678-HpCDD	4.5	0.042	10	0.069	1.5	0.020	5.4	0.049	5.0	0.051	5.0	0.051	24	0.014	52	0.014
OCDD	4.8	0.00045	53	0.0036	5.0	0.00066	21	0.0019	4.9	0.00050	4.9	0.00050	120	0.00071	76	0.00021
2378-TCDF	0.030	0.0030	0.090	0.0061	0.29	0.038	0.14	0.012	0.080	0.0082	0.080	0.0082	14	0.083	11	0.031
12378-PCDF	0.31	0.015	0.45	0.015	0.21	0.014	0.33	0.015	0.050	0.0025	0.050	0.0025	3.8	0.011	3.5	0.0049
23478-PCDF	0.36	0.17	0.56	0.19	0.26	0.17	0.39	0.18	0.28	0.14	0.28	0.14	7.6	0.23	5.1	0.071
123478-HxCDF	0.55	0.051	0.98	0.066	0.22	0.029	0.58	0.053	0.39	0.040	0.39	0.040	1.7	0.010	2.5	0.0069
123678-HxCDF	0.40	0.038	0.58	0.039	0.20	0.026	0.39	0.036	0.25	0.025	0.25	0.025	10	0.060	2.1	0.0058
234678-HxCDF	0.31	0.030	0.57	0.039	0.20	0.026	0.36	0.033	0.28	0.029	0.28	0.029	1.3	0.0077	1.2	0.0033
123789-HxCDF	0.39	0.036	0.45	0.031	0.15	0.020	0.33	0.030	0.050	0.0051	0.050	0.0051	1.3	0.0077	0.21	0.00058
1234678-HpCDF	1.0	0.0094	3.6	0.024	0.26	0.0034	1.6	0.015	0.83	0.0085	0.83	0.0085	16	0.0095	2.1	0.00058
1234789-HpCDF	0.31	0.0030	0.57	0.0039	0.17	0.0022	0.35	0.0032	0.050	0.00051	0.050	0.00051	1.4	0.00083	0.22	0.000061
OCDF	1.9	0.00018	2.3	0.0016	0.33	0.000043	1.5	0.00014	0.050	5.1E-6	0.050	5.1E-6	2.6	0.000016	1.8	0.0000050
TEQ_{DF}-WHO_{98}, pg/g	1.1		1.5		0.76		1.1		0.98		0.98		17		36	

Note:
Conc = average concentration, pg/g lipid for all foods;
Frac = fractional contribution of each congener to TEQ concentration

Table 4-44. The Average Concentrations (not on a TEQ_P-WHO_{98} basis) and the Fraction of TEQ_P-WHO_{98} Contributed by Each Dioxin-Like PCB Congener for the Various Food Groups

Congener	Beef		Pork		Chicken		Other Meat		Dairy		Milk		Fresh Fish		Marine Fish	
	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac	Conc	Frac
PCB 77	0.17	0.00020	0.30	0.0025	0.81	0.0031	0.43	0.0010	1.3	0.0022	0.19	0.0022	25	0.021	6.2	0.0025
PCB 105	16	0.019	6.4	0.054	12	0.046	11	0.027	20	0.035	3.1	0.035	350	0.029	160	0.064
PCB 114	--	--	--	--	--	--	--	--	--	--	--	--	170	0.073	74	0.15
PCB 118	76	0.089	18	0.15	51	0.20	48	0.12	82	0.14	12	0.14	1900	0.16	330	0.13
PCB 123	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
PCB 126	0.69	0.81	0.063	0.53	0.17	0.65	0.31	0.75	0.43	0.74	0.065	0.74	5.5	0.47	0.83	0.34
PCB 156	10	0.058	4.1	0.17	3.9	0.075	6.0	0.073	7.2	0.061	1.1	0.061	390	0.17	83	0.17
PCB 157	2.3	0.013	0.97	0.041	0.98	0.019	1.4	0.017	1.7	0.014	0.25	0.14	210	0.089	68	0.14
PCB 167	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
PCB 169	0.12	0.014	0.049	0.042	0.019	0.0073	0.063	0.015	0.060	0.010	0.0090	0.010	0.7	0.0060	0.2	0.0081
PCB 189	--	--	--	--	--	--	--	--	--	--	--	--	33	0.0028	8.0	0.0032
TEQ_{DF}-WHO_{98}, pg/g	0.084	--	0.012	--	0.026	--	0.041	--	0.058	--	0.088	--	1.2	--	0.25	--

Note:

Conc = average concentration, pg/g whole for all foods;
Frac = fraction contribution of each congener to TEQ_P-WHO_{98} concentration;
blank spaces indicate that no information was available on the concentration

Table 4-45. TEQ_{DF}-WHO_{98} Contribution of Each CDD/F Congener to the Daily Dose for Each Group and Overall (pg/day)

Congener	Beef	Pork	Chicken	Other Meat	Dairy	Milk	Fresh fish	Ocean fish	TOTAL	Fraction
2378-TCDD	0.43	0.29	0.50	0.42	0.47	0.22	1.1	0.49	4.0	0.10
12378-PCDD	2.9	1.3	0.75	1.4	2.2	1.0	1.8	1.2	12.6	0.33
123478-HxCDD	0.39	0.15	0.056	0.16	0.26	0.13	0.11	0.062	1.3	0.034
123678-HxCDD	1.2	0.32	0.13	0.39	1.3	0.61	0.19	0.33	4.4	0.12
123789-HxCDD	0.45	0.14	0.12	0.18	0.37	0.18	0.14	0.090	1.7	0.044
1234678-HpCDD	0.38	0.30	0.047	0.22	0.34	0.16	0.084	0.036	1.6	0.041
OCDD	0.0040	0.015	0.0016	0.0084	0.0033	0.0016	0.0042	0.00053	0.039	0.0010
2378-TCDF	0.026	0.026	0.091	0.055	0.054	0.026	0.49	0.076	0.85	0.022
12378-PCDF	0.13	0.066	0.033	0.065	0.017	0.0080	0.067	0.012	0.40	0.010
23478-PCDF	1.5	0.82	0.41	0.79	0.95	0.45	1.3	0.18	6.4	0.17
123478-HxCDF	0.46	0.29	0.069	0.23	0.26	0.13	0.060	0.017	1.5	0.040
123678-HxCDF	0.34	0.17	0.063	0.16	0.17	0.080	0.35	0.015	1.3	0.035
234678-HxCDF	0.26	0.17	0.063	0.14	0.19	0.090	0.046	0.0083	0.97	0.025
123789-HxCDF	0.33	0.13	0.047	0.13	0.034	0.016	0.046	0.015	0.73	0.019
1234678-HpCDF	0.084	0.10	0.0081	0.064	0.056	0.027	0.056	0.015	0.40	0.010
1234789-HpCDF	0.025	0.017	0.0053	0.014	0.0034	0.0016	0.0049	0.00015	0.073	0.0019
OCDF	0.0016	0.00067	0.00010	0.00060	0.000034	0.000016	0.000091	0.000012	0.0031	0.000082
TOTAL	8.9	4.3	2.4	4.4	6.6	3.2	5.9	2.5	38	
Fraction	0.23	0.11	0.062	0.12	0.17	0.082	0.15	0.065		

Note: The total background dose is estimated to be 43 pg/day. The pathways above add to 38 pg/day, or about 90 percent of total. All numbers above were rounded and may not add up perfectly.

Table 4-46. TEQ_P-WHO_{98} Contribution of Each Coplanar PCB Congener to the Daily Dose for Each Group and Overall (pg/day)

Congener	Beef	Pork	Chicken	Other Meat	Dairy	Milk	Fresh fish	Ocean fish	TOTAL	Fraction
PCB 77	0.00083	0.00047	0.0028	0.0010	0.0070	0.0033	0.015	0.0060	0.037	0.0012
PCB 105	0.078	0.010	0.042	0.028	0.11	0.053	0.21	0.15	0.69	0.033
PCB 114	--	--	--	--	--	--	0.51	0.36	0.87	0.042
PCB 118	0.37	0.028	0.18	0.12	0.45	0.22	1.1	0.32	2.8	0.14
PCB 123	--	--	--	--	--	--	--	--	--	--
PCB 126	3.4	0.099	0.59	0.75	2.4	1.1	3.3	0.80	12	0.61
PCB 156	0.24	0.032	0.068	0.073	0.20	0.094	1.2	0.40	2.3	0.11
PCB 157	0.056	0.0076	0.017	0.017	0.046	0.022	0.63	0.33	1.1	0.055
PCB 167	--	--	--	--	--	--	--	--	--	--
PCB 169	0.059	0.0077	0.0066	0.015	0.033	0.016	0.042	0.019	0.20	0.0097
PCB 189	--	--	--	--	--	--	0.020	0.0077	0.030	0.0013
TOTAL	4.2	0.18	0.91	1.0	3.2	1.5	7.1	2.4	20	--
Fraction	0.20	0.0090	0.044	0.049	0.16	0.075	0.35	0.12	--	--

Note: All numbers above were rounded and may not add up perfectly.

Table 4-47. Average CDD/CDF Concentrations in Human Tissue and Fractional Contribution of CDD/CDF Congeners to Total TEQ_{DF}-WHO_{98} Tissue, Based on CDC Blood Data

Congener	Average	
	conc	frac
2378-TCDD	2.1	0.097
12378-PCDD	5.2	0.24
123478-HxCDD	6.2	0.029
123678-HxCDD	73	0.34
123789-HxCDD	7.1	0.034
1234678-HpCDD	79	0.037
OCDD	664	0.0031
2378-TCDF	0.7	0.0033
12378-PCDF	0.8	0.0019
23478-PCDF	6.2	0.14
123478-HxCDF	6.5	0.030
123678-HxCDF	5.3	0.025
234678-HxCDF	0.7	0.010
123789-HxCDF	2.2	0.0032
1234678-HpCDF	13.2	0.0061
1234789-HpCDF	1.3	0.00060
OCDF	2.1	9.7E-6
TEQ_{DF}-WHO_{98}	21.6	

Note:

conc = Actual, not TEQ_{DF}-WHO_{98}, lipid-based concentration profile in pg/g.
frac = Fractional contribution to TEQ_{DF}-WHO_{98} of each congener.

Table 4-48. Average Coplanar PCB Concentrations in Human Tissue and Percentage Contribution of CDD/F Congeners to Total TEQ_P-WHO_{98} Tissue, Based on CDC Blood Data

Congener	Average	
	conc	frac
PCB 77	31	0.0016
PCB 81	3.2	0.00016
PCB 105	--	--
PCB 114	--	--
PCB 118	--	--
PCB 123	--	--
PCB 126	18	0.90
PCB 156	--	--
PCB 157	--	--
PCB 167	--	--
PCB 169	19	0.095
PCB 189	--	--
TEQ_P- WHO_{98}	2.0	--

Note:

conc = Lipid-based concentration profile in pg/g; and
frac = fractional contribution to TEQ_P-WHO_{98} of each congener.

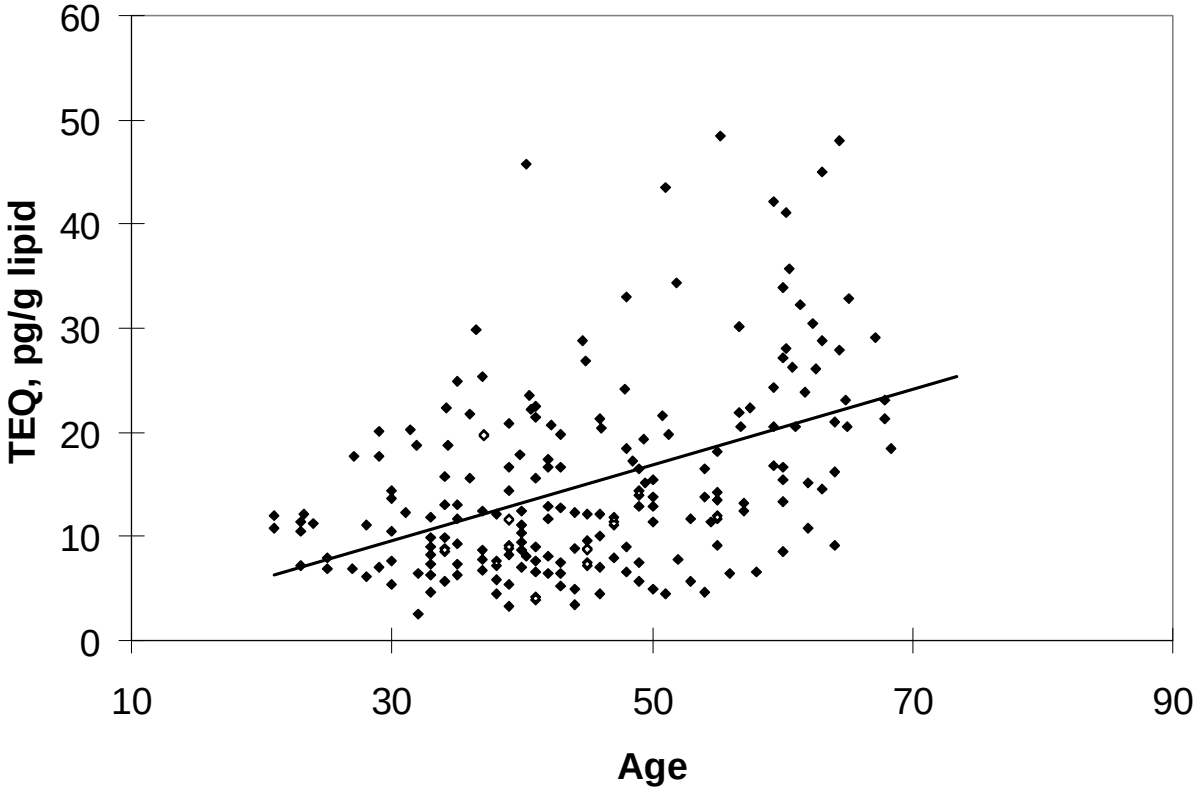


Figure 4-1. TEQ (I-TEQ for CDD/CDF + WHO_{94} for a Subset of Four Dioxin-Like PCBs) Lipid Concentrations for a Comparison Population and the Population of Mossville, Louisiana, as a Function of Age

Source: ATSDR, 1999b.

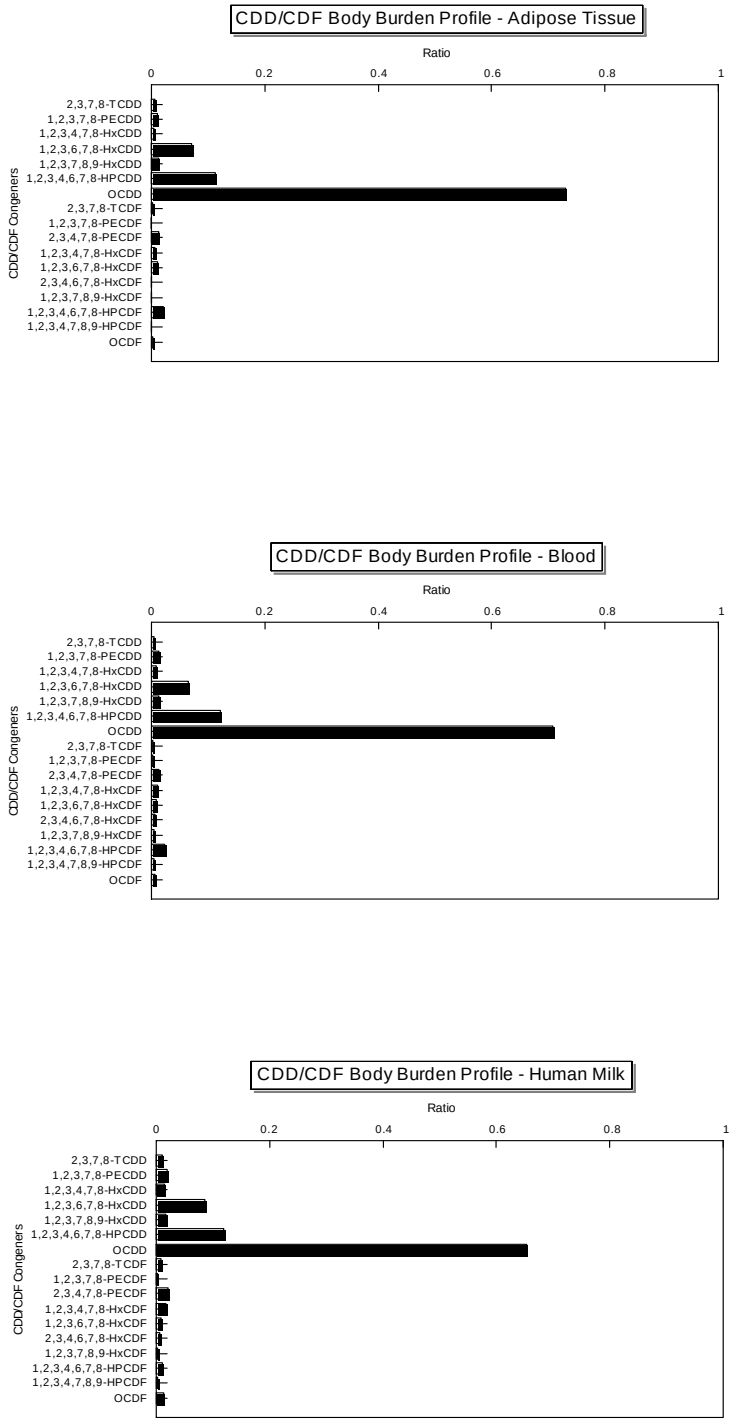


Figure 4-2. CDD/CDF Profiles for Adipose Tissue, Blood and Human Milk Based on Literature Studies from the 1980s to the Early 1990s

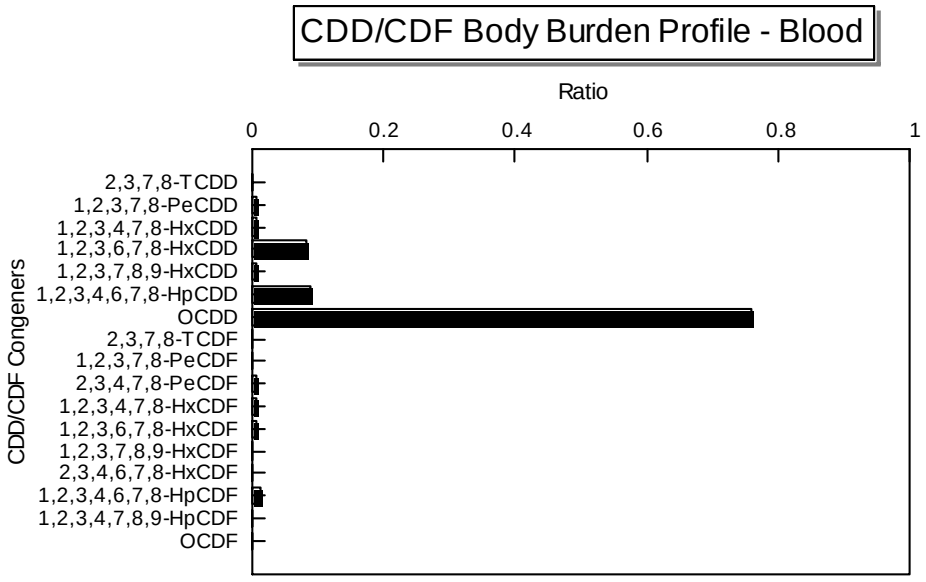


Figure 4-3. Congener Profile for the CDC Blood Data Set (1995-1997)

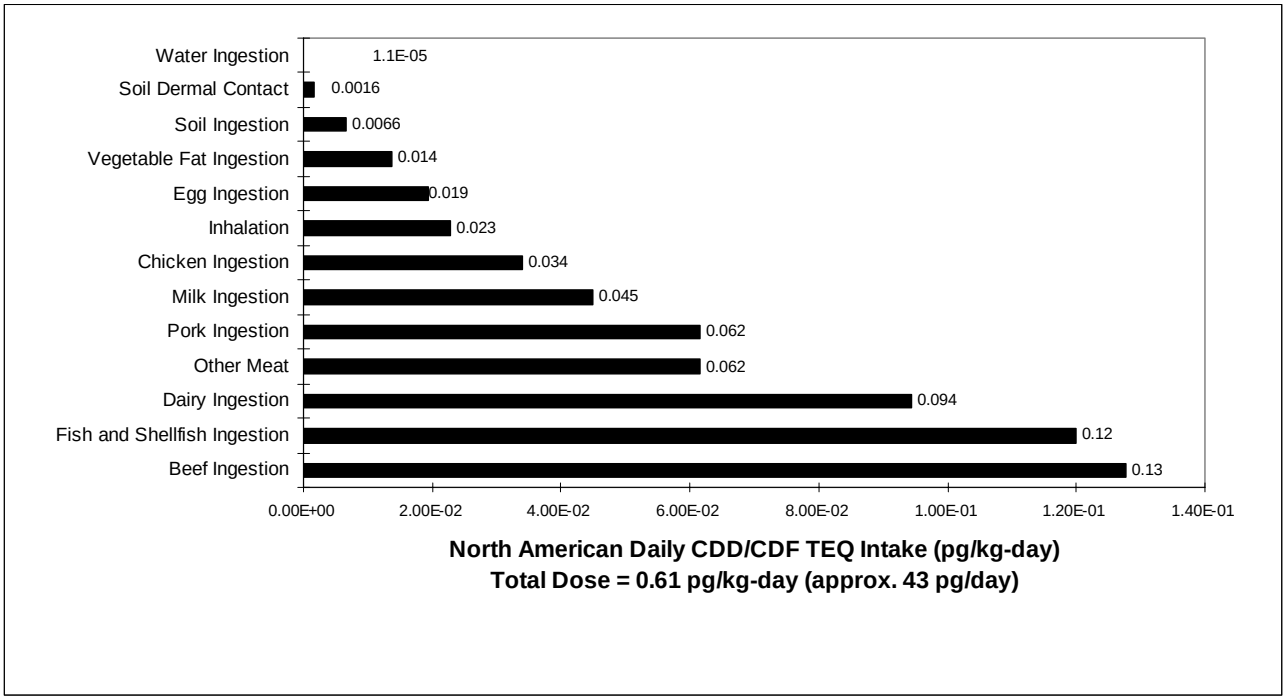
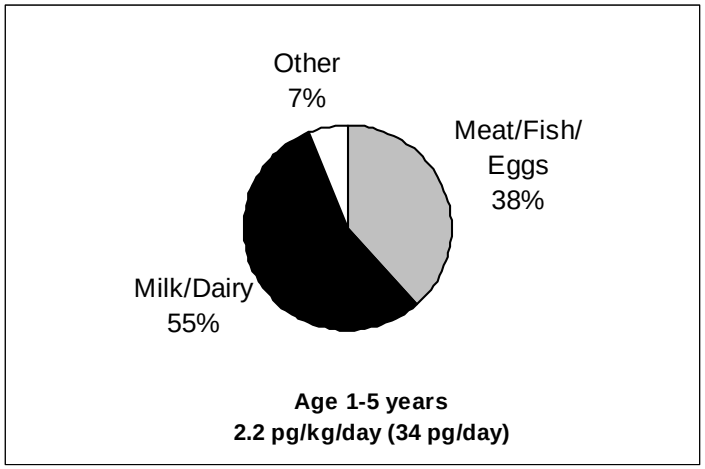
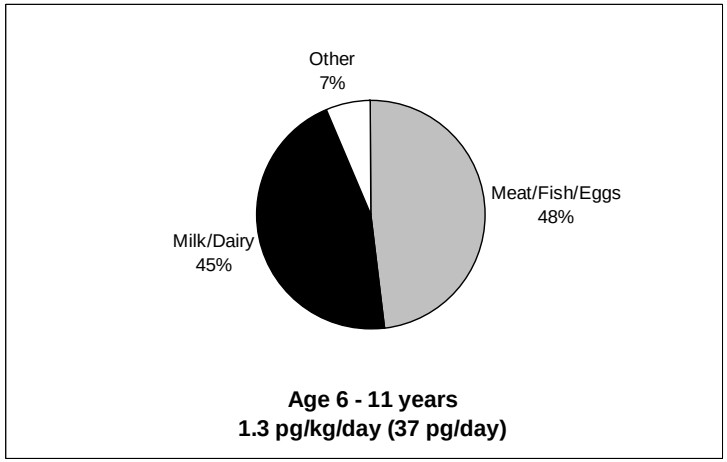
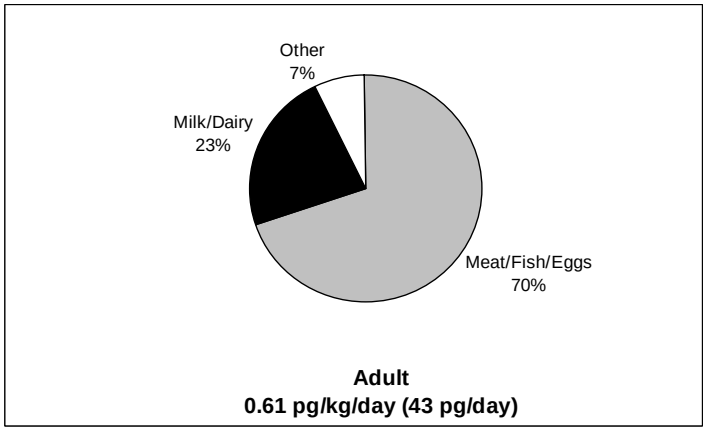
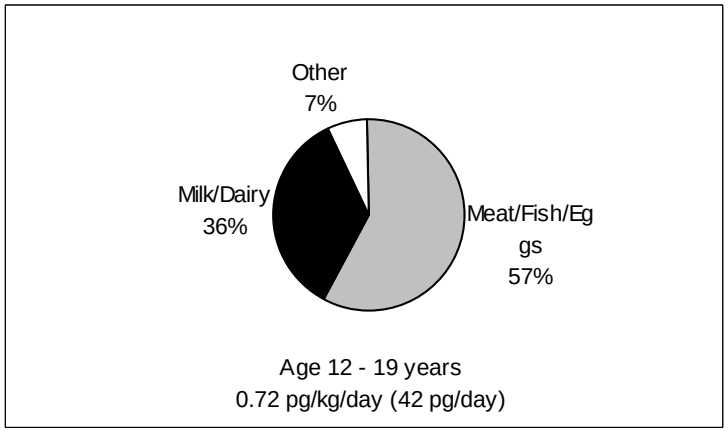


Figure 4-4. Background TEQ_{DF}-WHO_{98} Exposure for North America, by Pathway



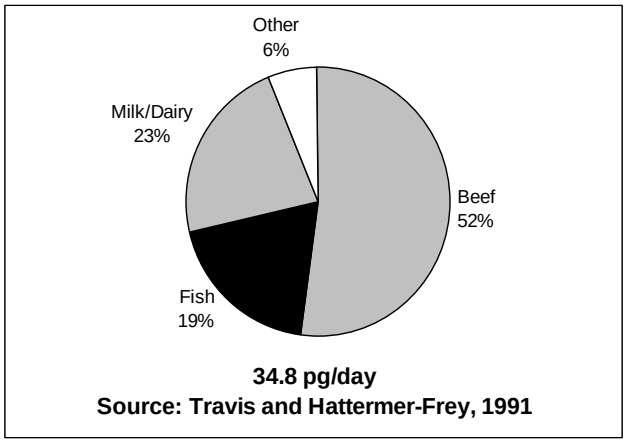


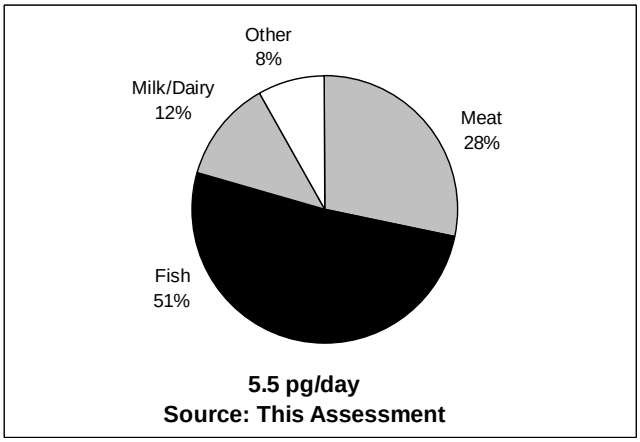


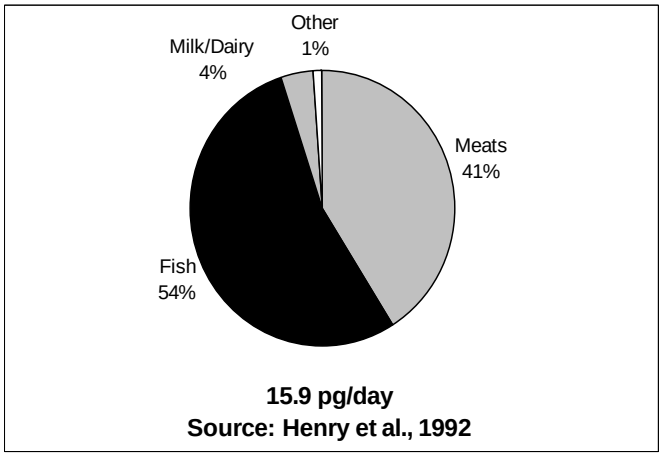


Note: See text for a discussion of the media concentrations and contact rates used to assess dose among these populations.

Figure 4-5. Percent Contribution of Various Media to TEQ_{DF}-WHO_{98} Dose, By Age Group

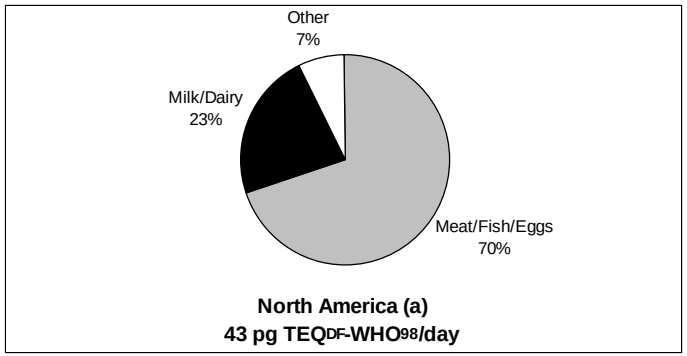


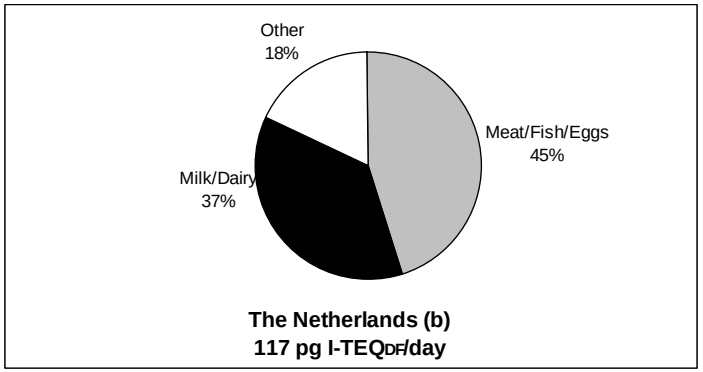


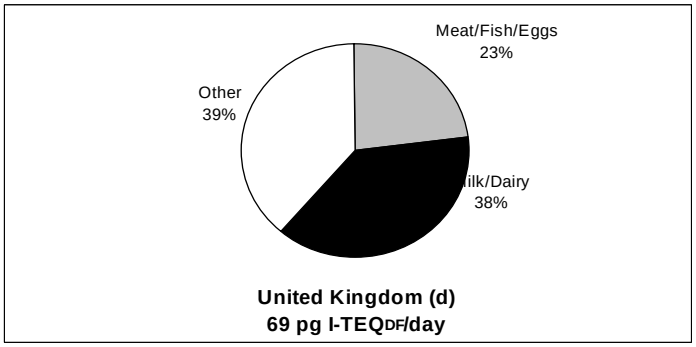


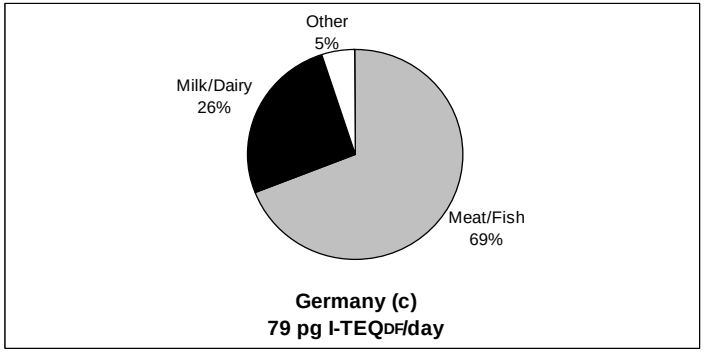
Note: Background exposures are the product of media-specific contact rates and residue concentrations. Reduction in the intake of one food type may not result in CDD/CDF exposure if dietary intake of that food type is replaced by other high CDD/CDF content foods.

Figure 4-6. Contribution of Various Media to 2,3,7,8-TCDD Exposure in North America









Note:
(a) Current assessment. See Table 4-30. Other category includes inhalation (3.7%), soil ingestion (1.1%), soil dermal contact (0.3%), vegetables oils (2.2%), and water (0.002%).
(b) Based on Theelen (1991). See Table 4-27. Other refers to inhalation (2.5%), soil ingestion (0.2%), leafy vegetables (3.4%), and vegetable oil (11.9%).
(c) Based on Furst et al. (1990, 1991). See Table 4-33. Other category includes salad oil (1.3%), and margarine (3.5%).
(d) Based on MAFF (1995). See Table 4-29. Other refers to breads and cereals (30%), and oils and fats (9%).
Percentages rounded to nearest whole number.
Reduction in the intake of one food type may not result in a reduction in CDD/CDF exposure if dietary intake of that food type is replaced by other high CDD/CDF content foods.

Figure 4-7. Comparison of North American and European Background CDD/CDF TEQ Exposures

Figure 4-8. TEQ_{DF}-WHO_{98} Derived from Pork Production Data

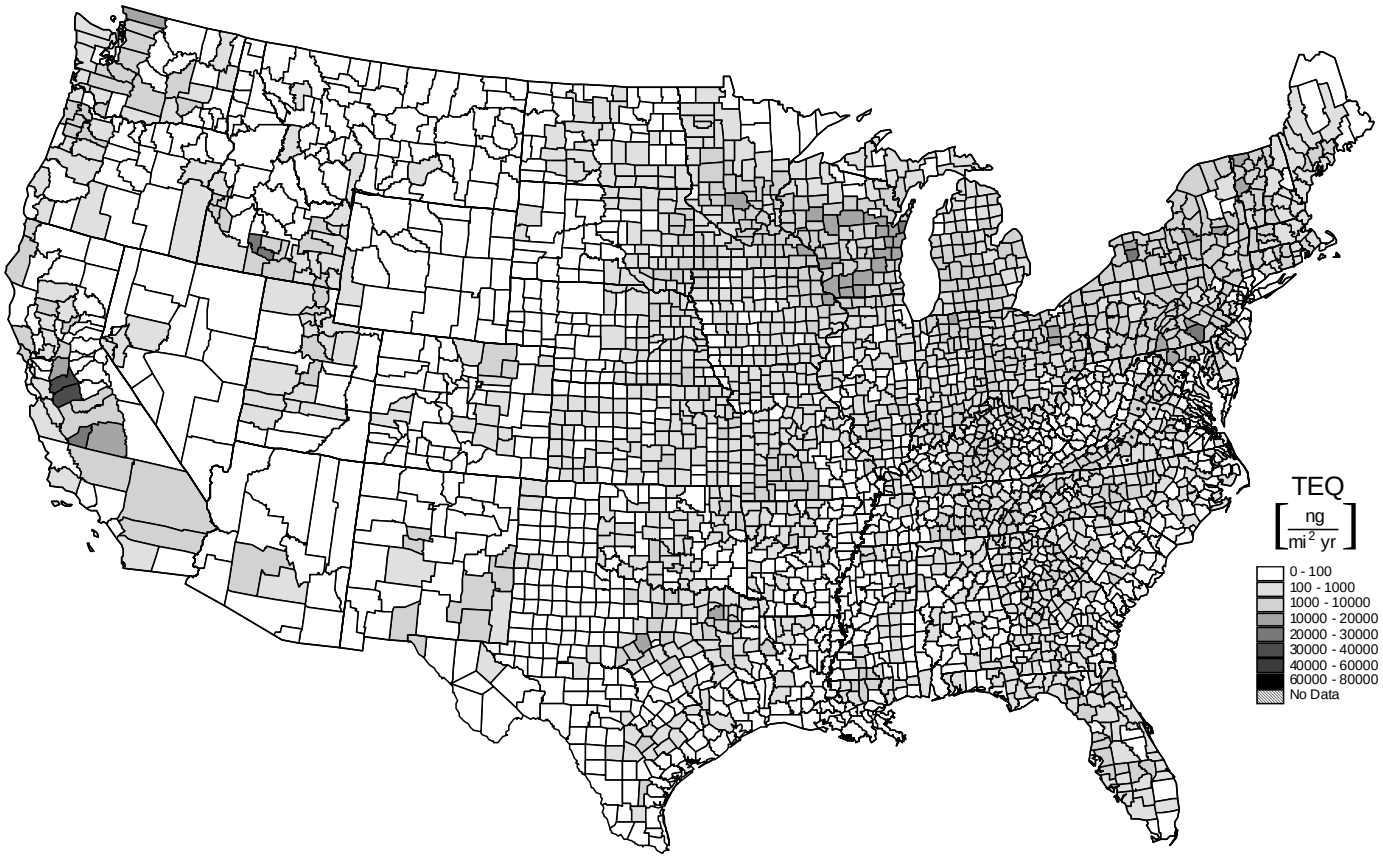


Figure 4-9. TEQ_{DF}-WHO_{98} Derived from Dairy Products Production Data

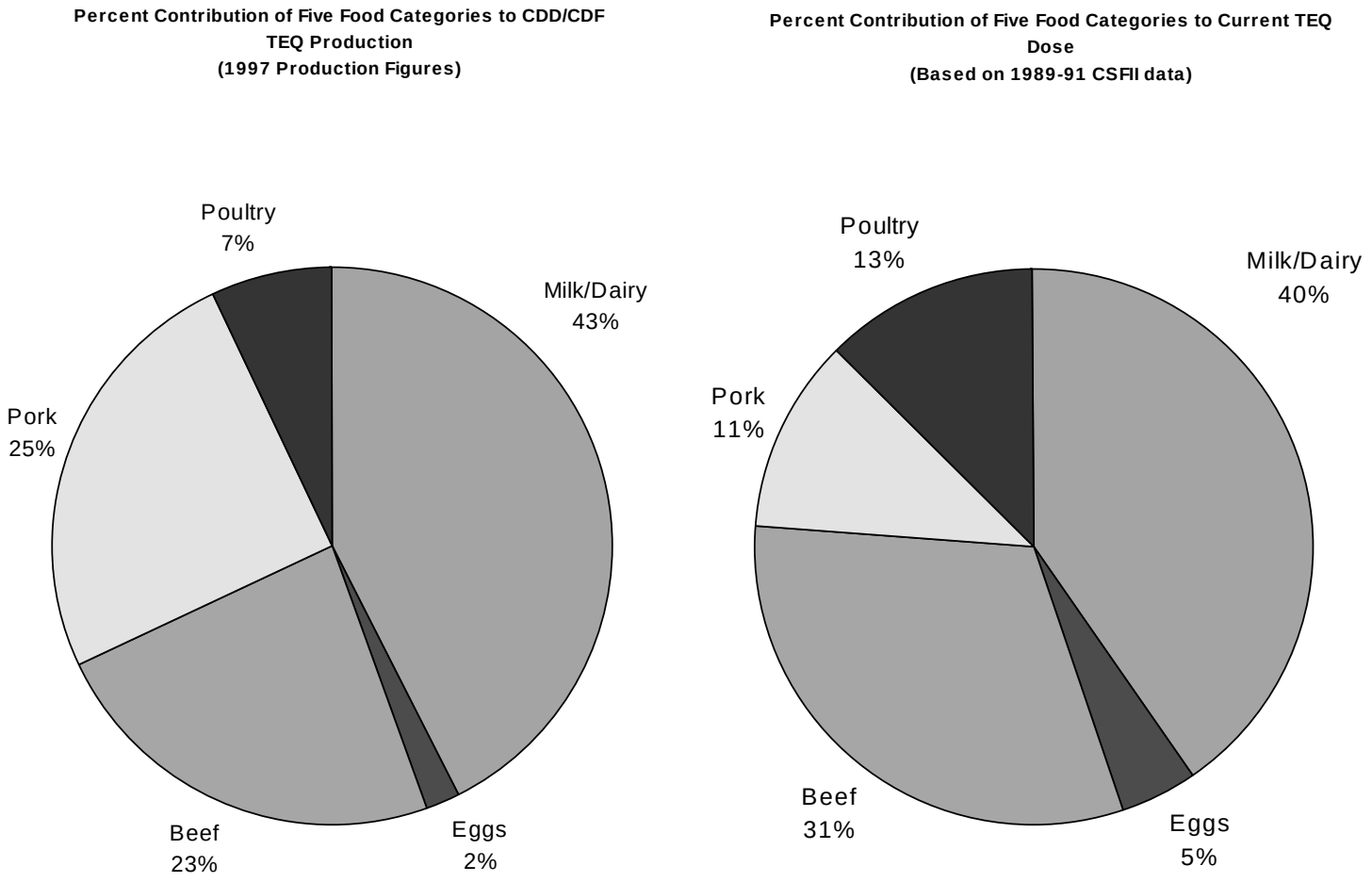


Figure 4-10. Comparison of Food Contributions to TEQ_{DF}-WHO_{98} Production Data and Dose

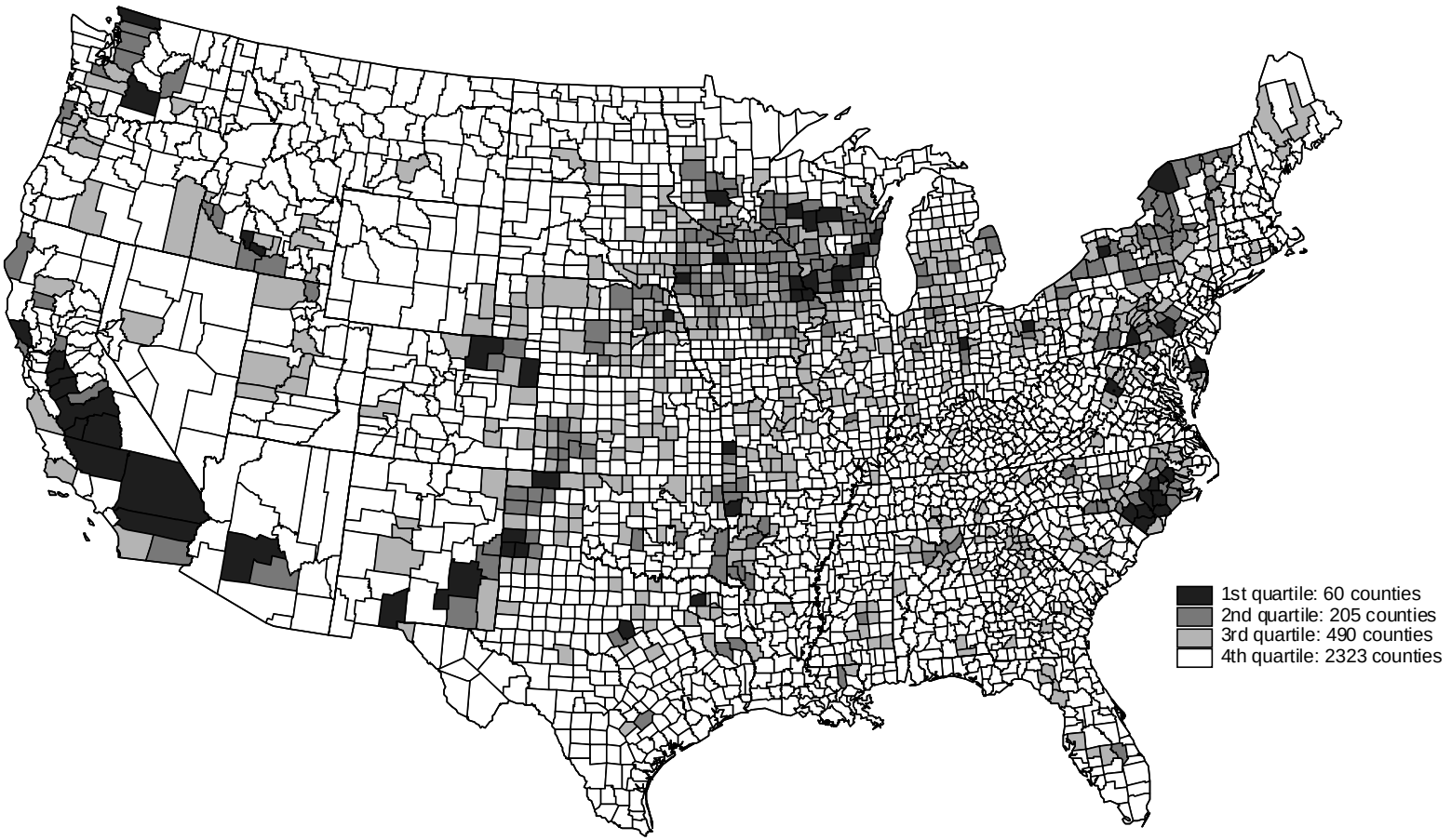


Figure 4-11. Total TEQ Production in Five Food Categories, Categorized by Quartile.

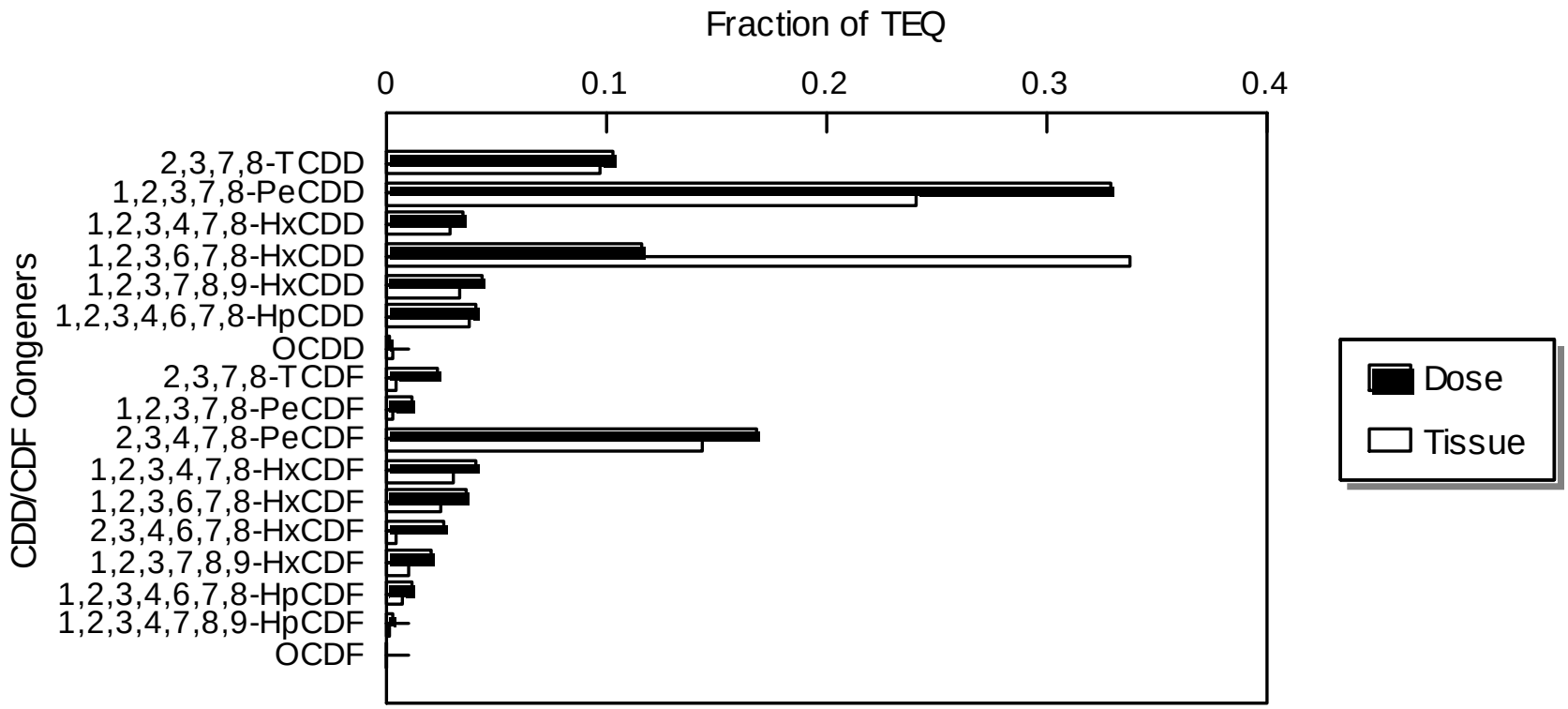


Figure 4-12. Fractions of the Background TEQ Dose and TEQ Tissue Concentration Contributed by Each CDD/CDF Congener

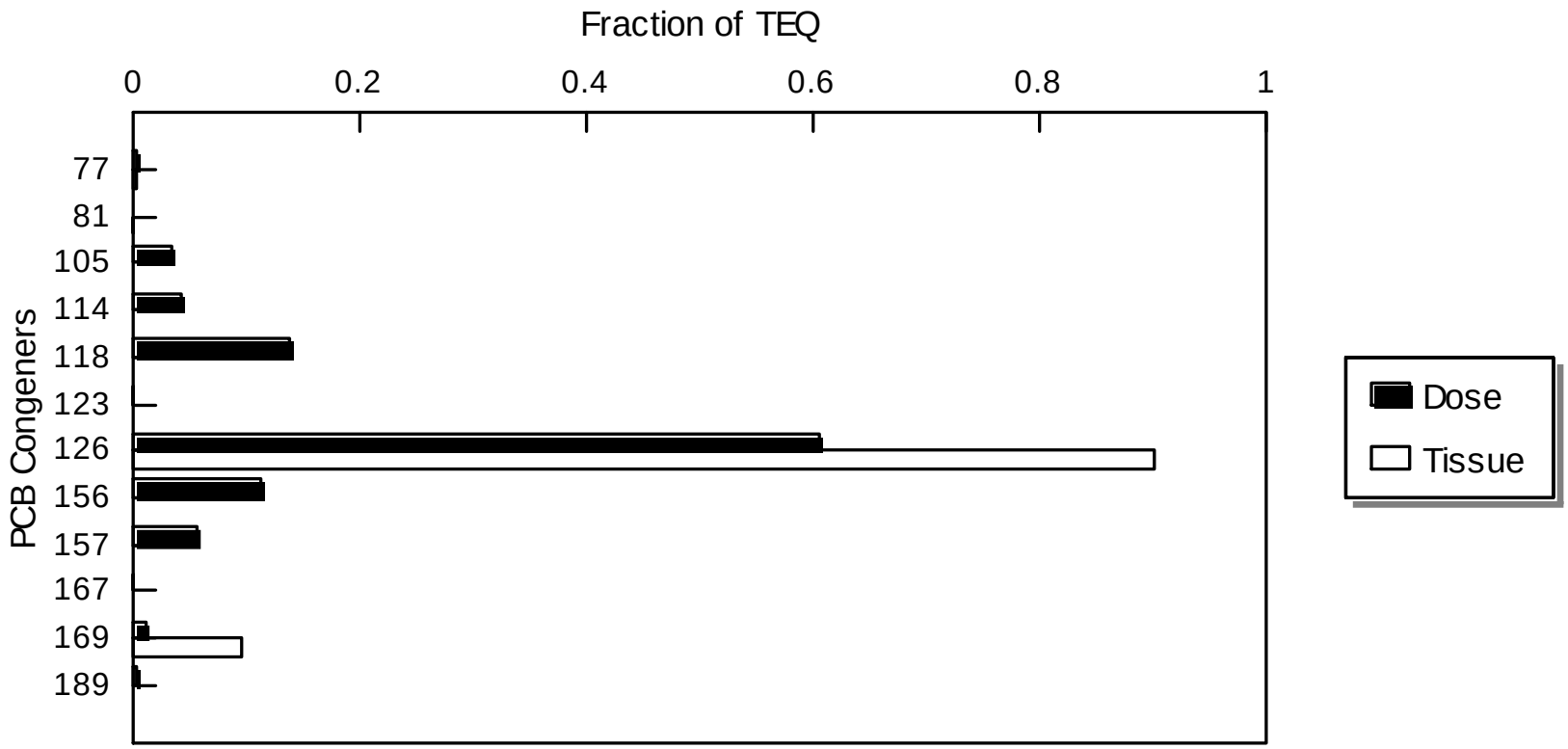


Figure 4-13. Fractions of the Background TEQ Dose and TEQ Tissue Concentration Contributed by Each PCB Congener

5.0. POTENTIALLY ELEVATED EXPOSURES

5.1. INTRODUCTION

Certain groups of people may have higher exposures to the dioxin-like compounds than the general population. The following sections discuss higher exposures that may result from dietary habits, localized impacts, and cigarette smoking. Other population segments can be highly exposed due to occupational conditions or industrial accidents. For example, several epidemiological studies have evaluated whether elevated dioxin exposure has occurred to certain workers in the chemical industry, members of the Air Force who worked with Agent Orange, and residents of Seveso, Italy, who were exposed as a result of a pesticide plant explosion. These epidemiological studies are fully discussed in the Epidemiology Chapter of the Dioxin Health Reassessment Document (U.S. EPA, 1996) and should be consulted if further details are desired. This chapter, however, does not address occupational or accidental exposure. Instead, it focuses on elevated exposures among the general population from dietary habits such as breast feeding or high rates of fish ingestion, localized sources, or cigarette smoking.

5.2. NURSING INFANTS

Nursing infants may be exposed to dioxin-like compounds via consumption of breast milk. These compounds are deposited in the fatty tissues (i.e., adipose tissue, blood lipids, and breast milk) of the mother and may be transferred to the infant during nursing. Based on data from 1989, approximately 52 percent of U.S. mothers initiate breastfeeding with their newborn infants, and 40 percent continue breastfeeding for 3 months or longer (NAS, 1991). At 5 to 6 months of age, only about 20 percent of infants are breast-fed (NAS, 1991). This section will show how breast milk ingestion exposures, which are higher during breast-feeding, on a body weight basis, than during any other period in an individual's life, impact lifetime exposures and body burdens. First, data showing the impact of breast milk ingestion to the infant body burden of CDD/CDF/PCBs are reviewed. Then, an estimate of the dose (average daily dose, ADD, and lifetime average daily dose, LADD) to the infant via breast milk is made. The section will close by developing, testing, and applying a model on the impact of breast-feeding to body burdens for growing infants.

5.2.1. The Impact of Breast Feeding on Infant Body Burden

Abraham et al. (1994, 1995) studied CDD/CDF/PCB levels in the blood of a breast-fed and a formula-fed infant at 11 and 25 months of age. Sampling of blood showed that the body burden of dioxin-like compounds was more than an order of magnitude higher for the breast-fed infant than the formula-fed infant during both time periods, with CDD/CDF ranging from 34.7 (11 months) to 43.9 (25 months) ppt TEQ_{DF}-WHO_{98} lipid-basis in the breast-fed infant compared to 2.7 to 3.3 ppt TEQ_{DF}-WHO_{98} for the formula-fed infant. Dioxin-like PCB concentrations were similarly an order of magnitude different, with the breast-fed infant having a concentration of 31.4 ppt TEQ_{P}-WHO_{98}, compared to 2.5 ppt TEQ_{P}-WHO_{98} for the formula-fed infant at 11 months (PCB 126 not measured at 25 months, so a comparison for that age is not informative). The full congener profiles for these results are shown in Table 5-1. The increase in the lipid-based CDD/CDF TEQ concentration in the blood of the breast-fed infant at 25 months was attributed to the relative decrease in body fat mass during the period between sampling and slight increases in body burden concentrations.

Abraham et al. (1994) also analyzed mother's milk at 1 month and mother's blood along with the infants' blood at 11 months. They found mother's milk to contain 23.5 ppt TEQ_{DF}-WHO_{98} at 1 month and mother's blood to contain 14.2 ppt TEQ_{DF}-WHO_{98} at 10 months. If blood and milk concentrations in a mother during lactation are the same at any given time, then these data suggest a reduction of about 40 percent in TEQ concentration in the mother between the 1st and 10th month of lactation. The reduction in mother's milk concentration of dioxins during nursing is discussed further in Section 5.2.3 below.

Kreuzer et al. (1997) developed and tested a toxicokinetic model of human lifetime body burden of TCDD, starting with a model for breast-feeding. To support their model, they presented adipose tissue and liver data on 3 stillborn and 17 infants who had died from sudden infant death syndrome (SIDS). Nine of the 17 infants had spent some portion of their lives breast-feeding, while the other 8 infants were formula-fed. Average congener and TEQ concentrations for these three groups are shown in Table 5-2. The highest TEQ concentrations were found in the infants who had some breast-feeding, with adipose concentrations at 15.9 ppt TEQ_{DF}-WHO_{98}, as compared to formula-fed infants who had concentrations at 4.3 ppt TEQ_{DF}-WHO_{98}. The breast-fed infants' concentrations included four infants who were weaned several weeks prior to their death from SIDS.

This may have generally led to reductions in their body burdens as their higher daily intake from breast-feeding was reduced after weaning. The average TEQ concentration for the five infants who died while still breast-feeding was 20.1 ppt TEQ_{DF}-WHO_{98}. The highest concentration found was for the infant who was breast-fed the longest at 19 weeks, and who died at that time; the TEQ concentration was 35 ppt TEQ_{DF}-WHO_{98}. Other breast-fed infants, however, did not have as much impact - infants who died while breast-feeding at 12 and 16 weeks had concentrations of 9 and 7.5 ppt TEQ_{DF}-WHO_{98}. While Kreuzer et al. (1997) concluded that breast-fed infants had elevated concentrations compared to formula-fed infants, they also observed that breast-fed infants had adipose TEQ concentrations that were within the range or lower than the values published for adults.

Abraham et al. (2000) reported on a study in Germany in which the blood of 80 breast-fed infants between the ages of 4 and 11 months were analyzed for the 17 CDD/CDFs . Of these 80 infants, 27 were from a region where a copper recycling plant led to elevations in the mother's milk. The I-TEQ_{DF} blood concentration in this group of 80 children at 11 months ranged between 2.0 and 107 pg/g lipid-basis, with a median of 25.3 ppt. Of these children, 6 had I-TEQ_{DF} concentrations greater that 50 ppt, and 5 of these 6 were from the region impacted by the copper recycling plant. From a control group of 21 children who had been formula-fed, individual dioxin measurements were performed in 5 children. Concentrations were found to range narrowly from 1.9 to 3.2 ppt I-TEQ_{DF} lipid-basis at 11 months. With several measurements over time, Abraham et al. (2000) found the blood concentrations of the breast-fed infants to increase over time. Infant or time-specific concentration data were not presented in Abraham et al. (2000). However, they did show the ratio between the concentration of specific compounds, as well as the I-TEQ_{DF} concentrations, in the children's blood and the blood of the mothers. When the ratio exceeded 1.0, this meant that the child's concentration was higher than the mother's. Abraham et al. (2000) showed the I-TEQ_{DF} ratio to increase from 1.12 at 16-24 weeks (n = 11 meaning there were 11 paired measurements at that time) to 2.12 at 25-32 weeks (n = 29) to 3.20 at 33-40 weeks (n = 33) to 3.73 at 41-48 weeks (n = 7). This was the most comprehensive data set found in the literature, although it was not fully described in the Abraham et al. (2000) abstract.

Patandin et al. (1997) looked at the plasma levels of four polychlorinated biphenyls (PCBs) in 173 Dutch children 3.5 years of age, 91 of which had been breast-fed and 82

of which had been formula-fed. Children in the breast-fed group had significantly higher median PCB levels in plasma ($p < 0.0001$) than children in the formula fed group. The four PCBs measured were 118, 138, 153, and 180. The median sums of these four PCBs in the two groups of children were 0.75 µg/L in the breast-fed group versus 0.21 µg/L in the formula fed group. By means of an extensive questionnaire on dietary history, combined with data on the concentrations of dioxin and PCBs in foods provided by the Dutch National Institute of Public Health and the Environment, Pantadin et al. (1997) were able to determine that the TEQ intake via the diet was virtually indistinguishable in the two groups. They found that PCB levels in the breast-fed children were significantly correlated with the period of breast-feeding ($r = 0.63$), milk PCB levels ($r = 0.39$), and the total TEQ in breast milk ($r = 0.36$). They concluded that the plasma PCB levels in Dutch children were the result of exposure through breast milk and in utero exposure, and that the influence of dietary intake of PCBs after weaning is small compared to the intake during breast-feeding.

5.2.2. Calculation of an Average Daily Dose from Breast-Feeding

Using the estimated dioxin concentration in breast milk, the administered dose to the infant can be estimated as follows:

$$ADD_{infant} = \frac{C_{milk\ fat} * f_3 * IR_{milk} * ED}{BW_{infant} * AT} \qquad \text{(Eqn. 5-1)}$$

where,

ADD_{infant} = Average daily dose to the infant (pg/kg-d);
$C_{milk\ fat}$ = Concentration in milk fat (pg/g);
IR_{milk} = Ingestion rate of breast milk (kg/d);
ED = Exposure duration (yr);
BW_{infant} = Body weight of infant (kg);
AT = Averaging time (yr); and
f_3 = Fraction of fat in breast milk.

The administered dose can be converted to an absorbed dose by multiplying by the fraction of ingested contaminant that is absorbed.

This approach assumes that all pertinent parameters, including the body weight of the infant, the infant ingestion rate of breast milk, and perhaps most importantly, the contaminant concentration in milk, represent the average over the breast feeding time period.

Smith (1987) reported that a study in Britain found that the breast milk ingestion rate for 7- to 8-month old infants ranged from 677 to 922 mL/d and that a study in Houston measured the mean production of lactating women to range from 723 to 751 g/d. Smith (1987) also reported that breast milk ingestion rates remain relatively constant over an infant's life. For purposes of estimating the dose to breast feeding infants, a milk ingestion rate of 800 mL/d was assumed in the analysis presented in this section. Smith (1987) also assumed that mother's milk has a 4 percent fat content, and that 80 percent of the ingested contaminant are absorbed. The infant weight varies with time. For example, a typical infant (average of male and female data) weighs about 3.3 kg at birth, 7.9 kg at 6 months, and 10.2 kg at 1.0 year (U.S. EPA, 1997; Walker and Watkins, 1997).

The concentration of dioxin in the mother's milk is also expected to change, since lactation provides a significant avenue of depuration. Lakind et al. (2000) cite several references where measurements of breast milk concentrations of lipophilic compounds (PCBs, DDE, DDT, CDD/CDFs) were shown to decline during the course of lactation. They fit available data on 2,3,7,8-TCDD to a curve, and their resulting relationship showed an 86 percent loss over 6 months. This is comparable to a modeling effort by Kreuzer et al. (1997), who modeled a 70 percent decline in TCDD concentrations after 6 months. Their model was more mechanistic, and added the loss by breast milk to an overall female body burden model which included inputs by food consumption and outputs by metabolic and non-metabolic pathways. Patandin et al. (1999), in their modeling of dioxin exposures from infancy to adulthood, cited data from Germany and England to conclude that breast milk concentrations of TCDD decline by 20 percent every 3 months. The data described in the previous section by Abraham et al. (1994) suggest a decline of 40 percent of TEQs from 1 month to 10 months of lactation.

For assignment of $C_{milk\ fat}$ in Equation 5-1, therefore, one would have to assign a concentration at birth and consider a decline in that concentration over time. For purposes of this discussion, a concentration of 25 ppt TEQ_{DFP}-WHO_{98} on a lipid basis is assumed for mother's milk when lactation begins (which is the average tissue concentration derived from recent studies of dioxins in blood in background settings of the US, reviewed in Chapter 4). It is then assumed to linearly drop by 50 percent after 6 months, with an additional linear drop of 50 percent by the end of 12 months, for a total decline of 75 percent from initial concentrations. These assignments in concentration decline are in the middle of the range reported above. They translate to concentrations of 12.5 ppt TEQ_{DFP}-WHO_{98} after 6 months and 6.3 ppt TEQ_{DFP}-WHO_{98} after a year, given a starting concentration of 25 ppt TEQ_{DFP}-WHO_{98}.

The proper way to derive an average dose to the child is to integrate Equation 5-1 over the time period of interest. At birth, for example, with a mother's milk concentration of 25 ppt TEQ_{DF}-WHO_{98}, an infant body weight of 3.3 kg, an average ingestion rate of 800 g/d breast milk, the administered dose is predicted to be 242 pg TEQ_{DF}-WHO_{98}/kg bw/day [(25 pg/g x 0.04 x 800 g/d) / (3.3 kg) = 242 pg/kg-d]. Table 5-3 shows infant body weights, as well as doses of dioxin TEQ_{DF}-WHO_{98} expressed in terms of pg/day for each of the first 12 months of life. These body weight data are the averages for male and female infants (U.S. EPA, 1997; Walker and Watkins, 1997), and along with other data, were used in the pharmacokinetic exercise described in the next section. Calculating monthly doses on the basis of body weight for each of the first twelve months of life and then dividing by 12, results in an average dose to the infant of 87 pg TEQ_{DF}-WHO_{98}/kg bw/day.

This value is much higher than the estimated average background TEQ_{DFP}-WHO_{98} dose for adults of approximately 1 pg TEQ_{DFP}-WHO_{98}/kg-d. However, if a 70 year averaging time is used for this one-year nursing scenario, then the LADD (Lifetime Average Daily Dose, calculated as ADD * ED/LT where LT is lifetime typically assumed to be 70 years) is estimated to be 1.2 pg TEQ_{DFP}-WHO_{98}/kg-d ([87 pg/kg-d] * 1 yr/70 yr). This is close to the adult background dose of 1.0 pg TEQ_{DFP}-WHO_{98}/kg-d. However, this can be misleading because it ignores the difference in daily intake during potentially sensitive stages in development. Also, it does not consider any exposures past the first year of life. In order to calculate a true lifetime average daily dose, one needs to incorporate the

changes in dose over various life stages. Using the estimates of dose derived in Chapter 4 for various ages in children: 1-5: 3.3 pg TEQ_{DFP}/kg-d, 6-11: 1.9 pg TEQ_{DFP}/kg-d, and 12-19: 1.1 pg TEQ_{DFP}/kg-d, the following calculates the LADD for lifetime background exposures considering one year of breast-feeding:

$$\text{LADD} = 87 \frac{1\text{yr}}{70\text{yrs}} + 3.3 \frac{4\text{yrs}}{70\text{yrs}} + 1.9 \frac{6\text{yrs}}{70\text{yrs}} + 1.1 \frac{8\text{yrs}}{70\text{yrs}} + 1.0 \frac{51\text{yr}}{70\text{yr}} \quad \text{(Eqn. 5-2)}$$

$$\text{LADD} = 2.45 \frac{\text{pg TEQ}_{DFP}}{\text{kg- day}} \quad \text{(Eqn. 5-3)}$$

On a mass basis, the cumulative dose to the infant after a year is about 238 ng TEQ_{DFP}-WHO_{98} (87 pg/kg-d x 7.5 kg x 365 d x ng/1,000 pg; 7.5 kg is an average annual weight based on the average of 12 monthly body weights). Using the age-dependent doses derived in Chapter 4 with assumed body weights, a dose from year 1 to year 70 in a 70-year lifetime is estimated to be about 1,687 ng TEQ_{DFP}-WHO_{98}, so that a total lifetime dose is 1,925 ng TEQ_{DFP}-WHO_{98} (1,687 + 238). This suggests that about 12 percent of lifetime dose (238/1925 * 100 percent) may occur as a result of breast feeding, if that feeding occurred for one year.

This exercise describes accumulated dose over a lifetime, given a year of breast-feeding. It was found that about 12 percent of lifetime dose came from breast-feeding. It was also found that the LADD for this scenario, including average dioxin doses after the first year until year 70, was 2.45 pg TEQ_{DFP}-WHO_{98}/kg-day. The issue of accumulative dose is explored in more detail in the next section, where the quantity, "area under the curve" is defined and used to assess overall exposure during a lifetime, or portions of a lifetime, under different breast-feeding scenarios as well as a formula-only scenario where the infant experiences only background exposures.

5.2.3. Modeling the Impact of Breast-Feeding on Infant Body Burden

The previous section described an approach to estimate doses received by an infant due to breast-feeding, which included a starting concentration in mother's milk, a decline of that concentration over time (and the resulting decline in dose delivered to the child),

and the child's changing body weight. That information will be used in this section to evaluate the impact of breast feeding on an infant's body burden of dioxins.

To better evaluate the impact of nursing on infants, a one-compartment non-steady state pharmacokinetic model was used to evaluate dioxin tissue levels. As described below, this model was validated using paired mother/child data on breast milk and infant blood concentrations of TEQ_{DF}-WHO_{98}. Following this validation, several breast-feeding scenarios were modeled and compared with a formula-feeding only scenario. Specifically, changes in infant TEQ_{DFP}-WHO_{98} tissue concentration over time were modeled for these scenarios: formula only, 6 weeks nursing, 6 months nursing, 1 year nursing, and 2 years nursing. The section closes with sensitivity analyses exercises which describe the model response to changes in the key parameters describing the dose received by the infant via breast milk and the rate of dissipation of dioxin TEQs in the infant.

5.2.3.1. *Description of the Model*

The pharmacokinetic model was based on the following differential equation describing the mass balance of dioxin in lipids (Pinsky and Lorber, 1998):

$$da(t)/dt = f\,D(t) - k(t)\,a(t) \qquad \text{Eqn. (5-4)}$$

$$c(t) = \frac{a(t)}{1000\,V(t)} \qquad \text{Eqn. (5-5)}$$

where:

- a(t) = total mass of dioxins in lipid (pg) at time t;
- c(t) = concentration of dioxins in lipid (pg/g) a time t;
- D(t) = ingested dose of dioxins (pg/yr) at time t;
- V(t) = lipid weight (kg) at time t;
- k(t) = elimination rate constant (yrs^{-1}) at time t;
- t = time (yrs); and
- f = fraction of ingested dose absorbed into lipid compartment (unitless).

The lipid weight, V(t), is calculated as the product of the percent body lipid and the full body weight of the infant, both of which are provided in Walker and Watkins (1997) for infant boys and girls. This section demonstrates the approach using the average for infant boys and girls. The dose regime for tested scenarios in this section, the body weight, lipid fraction, and assumed half-lives of TEQ_{DFP}-WHO_{98}, are shown with other model parameters in Table 5-3. The body lipid and body weight are also shown graphically in Figure 5-1, for the 70 year life span and in more detail for the early years of life.

One key assumption of this simplistic framework is that dioxins are instantaneously distributed to all body lipids. This is a common assumption for TCDD PK modeling in humans, adopted by the multi-compartment model of van der Molen et al. (1996), and the single-compartment models in Kreuzer et al. (1997), Campbell et al. (1996), and Lakind et al. (2000). The model of Carrier et al. (1995a,b) alternately has a nonlinear response to doses, with different partitioning to the liver and other body lipids as a function of body concentration; when the overall body concentration is high, more of the dioxin dose is partitioned to the liver, whereas at lower body concentrations, the partitioning to the liver is lower.

The other key and important assumption for the model is that the TEQ_{DFP}-WHO_{98} behaves as a single compound in humans, and can be described by a single dissipation half-life. Ayotte et al. (1994) modeled TEQ body burdens from infancy to adulthood, but it was unclear whether they modeled individual congeners or TEQs as one compound. Campbell et al. (1996) used a framework similar to the one used here and modeled individual congeners for an industrial exposure study.

The elimination rate constant, k(t), was developed in similar fashions by Pinsky and Lorber (1998), Michalek et al. (1996), and Flesch-Janys et al. (1996), for 2,3,7,8-TCDD. All three research groups derived a relationship in which the elimination rate constant was a function of percent body fat. All three also curve-fit their empirical algorithms for k(t) on data from adult individuals, whose percent body fat was about 25 percent. With body fat percent increasing over time, particularly in older individuals, the elimination rate constant decreased (equivalently, the half-life increased) significantly. Given a range of body fat over time, from about a low of 15 percent to a high over 40 percent (for elderly females), the relationship in Pinsky and Lorber (1998) results in a half-life of 2,3,7,8-TCDD ranging from about 6 to over 20 years.

None of these efforts, however, identified processes or factors critical for infants, other than percent body fat. With a body fat of around 15 percent at birth, the half-life is calculated to be about 6.4 years using the relationship in Pinsky and Lorber (1998). Kreuzer et al. (1997), however, developed a procedure for modeling the elimination half-lives for 2,3,7,8-TCDD in infants which considerd metabolic, t_m (breakdown by enzymes), and non-metabolic, t_f (fecal elimination) processes. Kreuzer et al. (1997) combined these two half-lives to solve for an overall half-life, $t_{1/2}$. Other key parameters included total body lipid mass and liver volumes, which change over time, and a reference half-life for an adult. For their "reference adult" at age 40, they cited an overall half-life of 5 years, based on information in Geyer et al. (1986). The Kreuzer et al. (1997) model showed a rise in half-lives from a low of less than 0.5 years at birth to a high of 5 years at the total body lipid mass of 20 kg. With their parameter assignments, perhaps most importantly this assignment of a 5 year half-life for a reference adult, the half-life will not go far beyond 5 years (as a function of body lipid mass, it would exceed 5 years when body lipid mass exceeds 20 kg), which makes the model of Kreuzer et al. (1997) importantly different than that of Pinsky and Lorber (1998), Michalek et al. (1996), and Flesch-Janys et al. (1996), all of whom have half-lives varying from a value of 6 to over 20 years. In short, the model of Kreuzer et al. (1997) has half-lives which mostly never exceed 5 years, while the other approaches have half-lives for TCDD which never go below 6 years.

As noted, the model of Kruezer et al. (1997) suggests relatively short half-lives for infants. For infants, the overall half-life is driven by non-metabolic processes and the resulting half-life for newborns is calculated to be about 0.4 years. It rises to about 2.0 years when the total body fat weight is about 5 kg, which occurs around ages 8-10 years (25-35 kg overall body weight, about 20 percent body fat). Very clearly, this rapid a half-life of dioxin intake will have an important impact on the accumulation of dioxin residues during breast-feeding as compared to a model showing a 6 year or higher half-life. Lakind et al. (2000) adopted the Kruezer et al. (1997) approach in their evaluation of the impacts of breast-feeding on the 2,3,7,8-TCDD body burdens of infants.

For purposes of this assessment, it was assumed that the overall half-life for the early years of life more closely follows the trend as derived in the modeling exercises by Kruezer et al. (1997). For later years, it was felt that the empirical data upon which Pinsky and Lorber (1998), Michalek et al. (1996), and Flesch-Janys et al. (1996) derived

the half-life relationship for 2,3,7,8-TCDD is more valid. Therefore, a hybrid of these assumptions, as shown in Figure 5-2, was adopted for this effort. The half-life at birth starts at the low value of 0.4 yr and then slowly rises to the levels as modeled by Pinsky and Lorber (1998) by about age 20. It is noted that had Kreuzer et al. (1997) established reference half-lives for 40 year-olds more in the 6-20 year range, they would still have had very low half-lives at birth, rising to these higher half-lives with age. The half-life assumptions remain an obvious uncertainty for this type of modeling approach. Not only is there a disparity in the literature with regard to this critical assumption, but the literature is also only specific to 2,3,7,8-TCDD, not TEQ_{DFP}-WHO_{98}. The impact of this assumption is examined later in the sensitivity analysis exercises.

The final assumption for the model is the initial lipid concentration in the infant. It was assumed to be 10 ppt TEQ_{DFP}-WHO_{98}, which was reasonably similar to the 11.9 ppt TEQ_{DF}-WHO_{98} found in stillborn adipose tissue in Kreuzer et al. (1997). All other assumptions and parameter assignments for this modeling exercise, including the half-life change over time, are shown in Table 5-3, and Figures 5-1 and 5-2.

5.2.3.2. *Validation of the Model*

While demonstrating the impact of breast-feeding, the studies reviewed in Section 5.2.1. do not contain the type of information needed for model validation. What is needed are breast milk concentrations that are taken at the same time infant body burden measurements are taken. The breast milk concentrations are used to provide the "independent" model driving term, the dose term, and the body burden measurements provide the "dependent" model prediction, the infant body lipid concentration.

One study had a set of this kind of data. Abraham et al. (1998) studied CDD/CDF/PCB levels in the blood of 6 breast-fed infants as well as the breast milk of the mothers of these infants. A portion of this data set had been reported in their earlier articles (Abraham et al., 1994; 1995). This analysis will focus on the TEQ_{DF}-WHO_{98} concentrations reported in Abraham et al. (1998), since PCB concentrations were not uniformly available for mother's milk and infant blood for all six mother/child pairs.

Two of the infants were the second children from mothers whose first child was also tracked by Abraham and colleagues. It was interesting to note that, for these two second children, both the mothers' milk and the infants' body burdens were significantly

lower. Specifically, the comparison of first and second children, respectively, were: 34.7 ppt TEQ_{DF}-WHO_{98} lipid compared to11.9 ppt TEQ_{DF}-WHO_{98}, and 44.2 ppt TEQ_{DF}-WHO_{98} compared to 18.8 ppt TEQ_{DF}-WHO_{98}. The comparison of the mothers' milk from the first to second children was similarly disparate: the first mother had concentrations ranging from 14 to 24 ppt TEQ_{DF}-WHO_{98} lipid for the first child, but 13 to 14 ppt TEQ_{DF}-WHO_{98} lipid only for the second child. The other mother showed a range of 15 to 27 ppt TEQ_{DF}-WHO_{98} lipid for the first child, but only 13 to 18 ppt TEQ_{DF}-WHO_{98} lipid for the second. Apparently, breast-feeding of the first child resulted in a higher body burden for this infant as compared to the second infant, and a lower body burden for the mother when the second infant was breast-fed.

Table 5-4 shows the observed data that were available in Abraham et al. (1998) for this model validation exercise. There were two concentrations measured in breast-milk for each of 5 of 6 children. The one child whose mother had only one measurement was only breast-fed for 7 weeks; all other children were breast-fed for periods ranging narrowly from 26 to 32 weeks. Concentrations within the breast-feeding period were linearly extrapolated from the two available data points. For example, for the first mother/child pair listed in Table 5-4, mother's milk was analyzed during month 2 and month 11. TEQ concentrations were 23.5 and 14.0 ppt TEQ_{DF}-WHO_{98} lipid, respectively. These concentrations were extrapolated backwards to give an estimated concentration at birth of 24.6 ppt TEQ_{DF}-WHO_{98}. Likewise, forwards extrapolation gave an estimated concentration for month 3 of 22.4 TEQ_{DF}-WHO_{98}, assuming linear decline. The infant body burden was ascertained by blood measurements at about 1 year of age for each child. The amount of time of full breast-feeding was supplied by Abraham et al. (1998), and this is also listed in Table 5-4.

Other assumptions for modeling the infant body burden were outlined above, and these include the intake rate of mother's milk (IR = 800 ml/d), the fraction of fat in mother's milk (0.04), the rate of absorption of dioxins (0.80), and the changing infant body weight and lipid fraction (and hence lipid volume, V(t); Table 5-3). After weaning, the dose to the infant was assumed to be 50 pg TEQ_{DF}-WHO_{98}/d. This is the dose developed for the age range of 1-5 in Chapter 4. The dose by formula feeding or other foods the infants may be consuming after weaning may be lower or higher, as little

information is available on the dioxin content of baby formula or baby food. The assumed initial body burden of the infant was 10 ppt TEQ_{DF}-WHO_{98}, as noted above.

The rate of dissipation of dioxin residues was identified as a principal uncertainty for this model. Two lines of thought discussed above include the rapid dissipation (half-life < 1 year) of TCDD residues in infants modeled in Kreuzer et al. (1997) and later adopted by Lakind et al. (2000), and the much longer dissipation (half-life around 7 years) of TCDD in adults described in Pinsky and Lorber (1998), Michalek et al. (1996), and Flesch-Janys et al. (1996). The model validation exercise described in this section tested the appropriateness of the lower infancy half-life approach adopted in this model, as shown in Figure 5-2, against an assumption of a constant 7 year half-life for TEQ_{DF}-WHO_{98} during the first year of life.

Table 5-4 shows the final results of this exercise. As seen, the model predictions at the selected and more rapid dissipation rate were significantly nearer to observations as compared to the predictions with the longer half-life. The average predicted concentration for the rapid dissipation rate for the 6 infants was 26 ppt TEQ_{DF}-WHO_{98} lipid, compared to the average observed concentration of 23.5 ppt TEQ_{DF}-WHO_{98} lipid. With a longer 7-year half-life, the predicted concentrations were all higher, with an average of 39 ppt TEQ_{DF}-WHO_{98} lipid. The model also seemed very adequately responsive to lower or higher infants' exposures. For the infant who was breast-fed for only 7 weeks with a low concentration in the mother's milk, the blood concentrations measured 5.0 ppt TEQ_{DF}-WHO_{98} lipid at 13 months, compared to a predicted 10 ppt TEQ_{DF}-WHO_{98} lipid (with the rapid dissipation assumption). The infant exposed to the highest mother's milk concentration had the highest body burden measurement at 44.2 ppt TEQ_{DF}-WHO_{98} lipid and also the highest predicted concentration at 36 ppt TEQ_{DF}-WHO_{98} lipid.

In summary, it appeared that, even with the key uncertainties identified above, including the use of a simple, one-compartment pharmacokinetic model and the modeling of TEQ_{DFP}-WHO_{98}s as though they were a single compound, this approach appears to predict infant TEQ_{DFP}-WHO_{98} body burdens within the range observed, and is adequately responsive to the different conditions of high and low exposure via breast-feeding.

5.2.3.3. *Scenario Evaluation*

The scenarios evaluated include: formula only, 6 weeks of breast-feeding, 6 months of breast-feeding, 1 year of breast-feeding, and 2 years of breast-feeding. These scenarios encompass current trends. In comprehensive documentation of statistics for children born between 1990 and 1993, CDC (1997) reported that 55 percent of all babies breastfed, with about half of those breastfeeding beyond 5 months. The average duration of breastfeeding was 28.7 weeks. In a policy statement, the American Academy of Pediatrics (1997) stated that exclusive breastfeeding is ideal nutrition and sufficient to support optimal growth and development for 6 months after birth. They recommend that breastfeeding continue for at least 12 months, and thereafter for as long as mutually desired. Ryan (1997) documented a resurgence in breastfeeding between 1989 and 1995. In comprehensive surveys conducted in 1989 and 1995, he found a 14 percent increase in the number of mothers who breastfed in the hospital, rising from 52 percent in 1989 to 59 percent in 1995. He also found a 19 percent increase in mothers who continued to breastfeed at 6 months, rising from 18 percent in 1989 to 22 percent in 1995.

The specifics of these scenarios are:

Scenario #1: Formula Only: In this scenario, the dose to the infant was assumed to be 50 pg TEQ_{DFP}-WHO_{98}/d. This is the dose developed for the age range of 1-5, as described in Chapter 4. The dose by formula feeding may be lower or higher, as little information is available on the dioxin content of baby formula. TEQ_{DFP}-WHO_{98} doses among individuals from 6 to 11, 12 to 18, and greater than 18 years of age were 54, 65, and 66 pg TEQ_{DFP}-WHO_{98}/d, respectively, as developed for these age ranges in Chapter 4.

Scenario #2: Six-Week Nursing: The dose to the infant was assumed to be a function of the starting concentration of dioxins in the mother's milk, 25 pg TEQ_{DFP}-WHO_{98}/g lipid, and other assumptions that have been described in this section: 800 g/day milk ingestion, 4 percent lipids in milk, resulting in an initial dose of 800 pg TEQ_{DFP}-WHO_{98}/d. This drops to 733 after 1 month, and then to 667 pg TEQ_{DFP}-WHO_{98}/d, when nursing stops. Doses from then are as in Scenario #1.

Scenario #3: Six-Month Nursing: It was assumed that the dose drops linearly from 800 to an ending dose of 400 pg TEQ_{DFP}-WHO_{98}/day at month 6. From there, doses are as in Scenario #1.

Scenario #4: It was assumed that the doses drop linearly from 800 to 400 at 6 months and then linearly again to 200 pg TEQ_{DFP}-WHO_{98}/day at the end of one year. From there, doses again are as in Scenario #1.

Scenario #5: The 1 year dose of 200 pg TEQ_{DFP}-WHO_{98}/day assumes a mother's milk concentration of 6.25 ppt TEQ_{DFP}-WHO_{98} lipid, which represented a drop from an initial concentration of 25 ppt TEQ_{DFP}-WHO_{98} lipid. For purposes of this demonstration, it was assumed that the mother's milk concentration stays at 6.25 ppt TEQ_{DFP}-WHO_{98} lipid for the second year of breast-feeding. From there, doses again are as in Scenario #1.

The results from this exercise are shown in Figures 5-3 and 5-4, which show the lipid concentrations and the body burdens from birth up to 70 years of age (on Figure 5-3), and then these two quantities for the narrower time frame of from birth to 10 years of age (Figure 5-4). The body burden, defined as the whole body concentration, is simply calculated as the lipid concentrations times the lipid fraction. Other results for these 5 scenarios are provided in Table 5-5, including the peak TEQ_{DFP}-WHO_{98} concentrations in the infant, the time when the peak occurred, the "area under the curve" (AUC), corresponding to different times, and the ratio of that AUC for the breast-feeding scenarios and the AUC for formula feeding only. The AUC is defined as:

$$\mathbf{AUC} = \mathbf{\Sigma\ c(t)} \qquad \text{Eqn. (5-6)}$$

where:

AUC = area under the curve, ppt TEQ_{DFP}-WHO_{98}-day

c(t) = lipid-based concentration in the infant each day, ppt TEQ_{DFP}-WHO_{98}

The AUC is a measure of accumulated exposure. For example, a year at a lipid-based concentration of 10 ppt TEQ_{DFP}-WHO_{98} would yield an AUC of 3,650 ppt TEQ_{DFP}-WHO_{98}-day (10 ppt * 365 days). A lifetime at an average body lipid concentration of 10 ppt would yield an AUC of 255,500 ppt TEQ_{DFP}-WHO_{98}-day (10 ppt * 70 yrs * 365 days/yr). The AUC provides a parameter to compare accumulated exposure for different scenarios. For that reason, the ratios of the AUCs of the various breast-feeding scenario and the formula-only scenario are provided in Table 5-5. A ratio for a particular breast-feeding scenario of 6, for example, would mean that the accumulated exposure for that scenario is 6 times that of the breast-feeding only scenario. This can easily be translated to a

corresponding measure of percent above or below the baseline scenario of formula feeding only. For example, if the ratio is 6, this is equivalent to saying that the accumulated exposure for the breast-feeding scenario is 500 percent higher than the formula-only scenario ((6-1)*100 percent); if the ratio is 0.7, this is equivalent to saying that the accumulated exposure for the breast-feeding scenario is 30 percent lower than the formula-only scenario (-(0.7-1)*100 percent).

The lipid concentrations are predicted to rise to about 44 ppt TEQ_{DFP}-WHO_{98} for the 6-month,1-year, and 2-year scenarios. The time that these peaks occur is uniformly at 9 weeks. For the 6 week breast-feeding scenario, the peak is at 34 ppt and it occurs at the 6 week mark. Body burdens follow a similar trend, rising to about 9 ppt TEQ_{DFP}-WHO_{98} for both the 6-month, 1-year, and 2-year scenarios at 9 weeks. The body burdens decline for these breast-feeding scenarios, but the decline is slower as the duration of time for breast-feeding increases. For the 2-year scenario, the body lipid concentration stays near 40 ppt past 2 years of age (Figure 5-4). The six-week scenario shows a rise in infant body burden to above 30 ppt TEQ_{DFP}-WHO_{98}, but then shows a rapid decline, tracking the formula-only scenario fairly well after about age 2. From Figure 5-3, it appears that all four scenarios begin to merge at about age 10 years. The rise in concentrations seen in the later years in Figure 5-3 is due to the rise in body fat percent and the subsequent rise in half-life as predicted by elimination rate model of Pinsky and Lorber (1998).

The AUC results in Table 5-5 show how the accumulated exposure is higher for each of the breast-feeding scenarios as compared to the formula-only scenarios. This exceedance after one year is about a factor of 6 for breast-feeding for 6 months or more. Even for the first 10 years of life, the accumulated exposure is about 2 times higher for these breast-feeding scenarios as compared to formula feeding only. After a lifetime, the ratios suggest that breast feeding results in a lifetime exposure only 1.03-1.18 times higher than formula feeding, or expressed in terms of a percentage, from 3 to 18 percent higher than formula feeding only.

5.2.3.4. *Sensitivity Analysis*

A brief sensitivity analysis was conducted to study the impact of key parameters and assumptions on this exercise. Sensitivity analysis exercises typically focus on the parameters with these two characteristics: those that are the most uncertain and those

that have an important impact on the results. It was ascertained that the parameters: absorption, body weight, and lipid fraction, while important, are reasonably well known and assigned appropriate mid-range values for this exercise. The initial concentration in the infant at birth of 10 ppt TEQ_{DFP}-WHO_{98} lipid is an unknown, but testing showed that infant concentrations rapidly declined to about 5 ppt regardless of the initial concentration. Therefore, this parameter does not appear to influence results like peak concentrations or accumulated exposures. The two most important parameters, or groups of parameters, were those used to determine dose to the infant - mother's milk concentration initially and over time, and the dissipation rate of dioxin-like compounds in the infant. To test the influence that these parameters have on results, six sensitivity analyses were devised. These were all variations on a baseline scenario selected to be the 6-month breast-feeding scenario. The six scenarios were:

Scenario #1: Use of the Pinsky and Lorber (1998) lipid-based function for dissipation rate instead of the hybrid function used. The Pinsky and Lorber (1998) lipid-based function is shown in Figure 5-2. This is expected to result in an increase in the predictions of infant and childhood body impacts.

Scenario #2: Use of the Kreuzer et al. (1997) modeled dissipation rate throughout life instead of the hybrid function used. The Kreuzer et al. (1997) function is shown in Figure 5-2. This is expected to result in a decrease in predictions of infant, childhood, and adult impacts.

Scenario #3: Use of the assumption that mothers' milk concentrations do not decline from 25 ppt TEQ_{DFP}-WHO_{98} lipid during the 6 months of breast-feeding. This will obviously result in an increase in the impact to the infant.

Scenario #4: Use of the assumption that mothers' milk concentrations begin at 15 ppt TEQ_{DFP}-WHO_{98} and decline to 7.5 ppt TEQ_{DFP}-WHO_{98} after 6 months (instead of using concentrations that begin at 25 ppt TEQ_{DFP}-WHO_{98} and decline to 12.5 ppt TEQ_{DFP}-WHO_{98} after 6 months). The assignment of an initial concentration of 25 ppt TEQ_{DFP}-WHO_{98} is based on the finding that this represents a reasonable average of adult body concentrations of the sum of dioxin, furan, and dioxin-like PCB TEQs, described in Chapter 4. However, this average includes a wide age range of populations, including older individuals. As will be discussed in the next chapter on trends, higher exposures in the past have resulted in higher concentrations in older adults compared to today's younger

adults. It may be more reasonable to assume a woman of child-bearing age today would have concentrations closer to 15 ppt TEQ_{DFP}-WHO_{98} rather than the full adult population average of 25 ppt TEQ_{DFP}-WHO_{98}. Also, for children after the first-born, reduction in a woman's body burden of dioxin-like compounds could occur from prior breast-feeding.

Scenario #5: For this scenario, both assumptions that would lead to a higher impact - use of the Pinsky and Lorber (1998) lipid-based function for dissipation rate and the assumption of mother's milk concentration not declining from 25 ppt TEQ_{DFP}-WHO_{98} lipid - were used.

Scenario #6: In contrast to Scenario #5, both assumptions that would lead to a lower impact - the use of the Kreuzer et al. (1997) modeled dissipation rate and the assumption of mothers' milk concentrations beginning at 15 ppt TEQ_{DFP}-WHO_{98} and declining to 7.5 ppt TEQ_{DFP}-WHO_{98} after 6 months - were used.

Results from this sensitivity analysis exercise are shown in Table 5-6 and Figure 5-5. It is seen that all results range from a reduction of 40 percent (AUC ratio of 0.6) from baseline or an increase of 160 percent (AUC ratio of 2.6). The peak concentration can rise as high as 54 ppt TEQ_{DF}-WHO_{98}, as seen in Table 5-6 for Scenario #5 or as low as 28.5 ppt TEQ_{DF}-WHO_{98} for Scenario #6. Perhaps the biggest impact is seen in assuming the higher dissipation rate (lower half-life) for the childhood years. This is seen in Scenarios #4 and #6, with the lowest peak concentration and the steepest reduction from baseline: 30-40 percent. While the results displayed on Table 5-6 focus on the difference between the baseline 6-month scenario and sensitivity analysis scenarios, also of note is the difference between the two extremes as modeled by Scenarios #5 and #6. The peak concentration predicted for Scenario #5 (infant impact maximized) is about twice that of Scenario #6 (infant impact minimized): 54.0 versus 28.5 ppt TEQ_{DFP}-WHO_{98}. More importantly, the accumulated exposure from Scenario #5 is significantly higher than from Scenario #6. This can be seen In Figure 5-5, where the body concentrations are higher in Scenario #5 than #6 throughout the modeled lifetime, particularly for the first 10 years of life. After 10 years, the accumulated exposure, as measured by AUC, is about 4 times higher for Scenario #5 as compared to #6 (this results from the 10-year ratios of 2.6 and 0.7 displayed on Table 5-6, divided by each other; 2.6/0.7 = 3.7).

In short, when using this modeling approach to evaluate exposure-related impacts to infants from breast feeding, the assessor needs to be aware that assumptions relating

to the dissipation of dioxin-like compounds from infants, and the dose they receive through breast milk, are the two most important inputs. Data should be sought to further validate the selected modeling procedure and parameters, if possible.

5.3. SPORT AND SUBSISTENCE FISHERS

The possibility of high exposure to dioxin as a result of fish consumption is most likely to occur in situations where individuals consume a large quantity of fish from one location where the dioxin level in the fish is elevated above background levels. Most people eat fish from multiple sources, and even if large quantities are consumed, they are not likely to have unusually high exposures. However, individuals who fish regularly for purposes of basic subsistence are likely to obtain their fish from one source and have the potential for elevated exposures. Such individuals may consume large quantities of fish. U.S. EPA (1997) presents studies that indicate that Native American subsistence fishermen consume 59 g fish/day (as a mean) and 170 g fish/day (as an upper estimate). Wolfe and Walker (1987) found Native American subsistence fish ingestion rates up to 770 g/day in a study conducted in Alaska. Assuming that subsistence fishermen consume 59 to 170 g of freshwater fish per day as their primary source of protein (i.e., no meat or eggs are consumed) adult daily intake of CDD/CDFs/PCBs would be 2.2 to 5.7 pg/kg-day (Table 5-7). This estimate is based on the same CDD/CDF/PCB media concentrations exposure assumptions, and exposure algorithms as those presented in Chapter 4. The estimated values for subsistence fishermen are two to six times higher than the adult general population mean daily intake from all food sources of 0.94 pg/kg-day, as estimated in Chapter 4. It should be noted that fish ingestion rate data for subsistence fishermen are limited. The ingestion rate values used here pertain only to Native American subsistence populations (U.S. EPA, 1997), but are used to demonstrate the potential for elevated exposures among groups of individuals whose diets are known to consist of higher proportions of fish than the general population. Fish ingestion rates for sports fishermen would generally be lower than for the Native American subsistence population, but higher than for the general population.

Studies are underway to evaluate whether Native Americans living on the Columbia River in Washington have high dioxin exposures as a result of fish consumption. These Tribes consume large quantities of salmon from the river. As cited in U.S. EPA (1997), a

study conducted by the Columbia River Intertribal Fish Commission (1994) suggested that these individuals have an average fish consumption rate of 59 g/day and a 95th percentile rate of 170 g/day. These data were used in the estimated dietary intake calculations for subsistence fishermen, as shown above. Currently, studies are underway to measure dioxin levels in fish from this region.

Svensson et al. (1991) found elevated blood levels of CDDs and CDFs in high fish consumers living near the Baltic Sea in Sweden. Three groups were studied: nonconsumers (n = 9), moderate consumers (n = 9, 220 to 500 g/wk), and high consumers (n = 11, 700 to 1,750 g/wk). The high consumer group was composed of fishermen or workers in the fish industry who consumed primarily salmon (30 to 90 pg I-TEQ_{DF}/g) and herring (8 to 18 pg I-TEQ_{DF}/g) from the Baltic Sea. The I-TEQ_{DF} blood level was found to average about 60 pg I-TEQ_{DF}/g lipid among the high consumers and 20 pg I-TEQ_{DF}/g lipid for the nonconsumers. This difference was particularly apparent for the PeCDFs.

Asplund et al. (1994) also found elevated plasma levels of dioxin-like PCBs in Swedish fishermen who consumed large amounts of fish. A total of 37 individuals with varying intake rates of fish from the Baltic Sea was studied. These individuals were categorized as high-fish eaters, moderate fish-eaters, and nonfish-eaters. The estimated weekly intake of fish correlated positively with plasma PCB levels among this group (Table 5-8).

Cole et al. (1995) reported on CDD/CDFs and PCBs in 132 serum samples (pooled to 14) from Ontario Great Lakes anglers and control populations. Based on a preliminary survey, anglers from the communities of Cornwall and Mississauga, Canada, were categorized based on the numbers, species, and locations of fish caught and kept for consumption, and on data reflecting the contaminant levels for the fish in these areas. Individuals categorized as having the highest and lowest potential for having elevated body burdens of CDD/CDFs and PCBs were selected for biological sampling. Individuals who did not consume fish served as controls. Study participants were further categorized by age (i.e., <38 years, 38-50 years, and >50 years). The results, however, indicated that mean I-TEQ_{DF} levels were similar for both eaters and noneaters of Great Lakes' fish in these communities. I-TEQ_{DF}s ranged from 20.8 to 41.2 ppt for fish eaters and 24.7 to 36.8 ppt for noneaters. In general, mean I-TEQ_{DF}s increased with age (Table 5-9). PCBs 77, 126, and 169 were also evaluated in the serum samples collected from Cornwall

residents. Mean TEQ_P-WHO_{98}s ranged from 2.6 to 17.3 ppt for fish eaters and noneaters combined. Again, significant differences between the two groups were not observed and the serum CDD/CDF and PCB levels are within the range of values observed for the general population, as presented in Chapter 4.

Health departments of five Great Lakes states: Wisconsin, Michigan, Ohio, Illinois, and Indiana, formed a consortium to study blood levels of chemical residues in fish consumers of three Great Lakes: Michigan, Huron, and Erie. Anderson et al. (1998) reported on a feasibility study to determine which compounds might be found in very frequent Great Lakes sport fish consumers. Anderson et al. (1998) selected 32 angling enthusiasts who reported eating at least one sport fish meal per week from one of three Great Lakes (i.e., 11 Lake Huron anglers, 11 Lake Erie anglers and 10 Lake Michigan anglers). The analysis included examination of serum levels of 7 CDDs, 10 CDFs, 4 coplanar PCBs (i.e., 77, 81,126, and 169), and 32 other PCB congeners. One individual was excluded from the data summary due to unusually high occupational/environmental exposures. The blood CDD/CDF/PCB levels for these anglers were compared to CDD/CDF/PCB blood levels for a comparison group (n = 70) from Jacksonville, Arkansas. Data for this Arkansas population are discussed in Chapter 4. The comparison groups represented the general population with no known exposure to the contaminants of concern (Anderson et al., 1998). The mean CDD/CDF lipid adjusted serum concentrations for both the sport fishing populations and the comparison group used by Anderson et al. (1998) are shown in Table 5-10. The mean coplanar and other PCB lipid adjusted serum concentrations are reported in Table 5-11. The average lipid-based I-TEQ_{DFP} concentration for Great Lakes fish consumers was calculated at 56.8 ppt, with the breakdown as follows: I-TEQ_D = 27.5 ppt; I-TEQ_F = 11.9 ppt, and TEQ_P-WHO_{94} = 17.4 ppt. Anderson et al (1998) suggested that these values were higher than the background population used in the comparison.

The Anderson et al. (1998) study led to a larger study, in which the blood of 100 additional sport fishers were sampled, and a comparison population of 100 other individuals were sampled. Falk et al. (1999) reported on the results of the blood sampling from 96 (of the 100) additional sport fishers. Results for the 100 comparison population were not provided. Falk et al. (1999) presented results in terms of I-TEQ_{DF} and TEQ_P-WHO_{94} (congener-specific data were not provided), and also examined relationships

between the CDD/CDF/PCB measurements in blood and factors such as: age, gender, which Great Lakes the fish came from, the type of sport fish consumed, and amount of sport fish consumed, as reported by the participants. The median lipid-based TEQ_{DFP}-WHO_{94} from the 96 participants was 21.3 ppt, with the breakdown as follows: I-TEQ_D = 9.6 ppt; I-TEQ_F = 7.4 ppt, and TEQ_P-WHO_{94} = 4.3 ppt. This finding of 21.3 ppt TEQ_{DFP}-WHO_{94} appears significantly lower than the original finding of 56.7 TEQ_{DFP}-WHO_{98}. One reason for this is that the lower finding from the 96 participants was a *median*, while the finding from the 31 individuals in the pilot study was a *mean*. It also appears that the smaller population had a few individuals with very high levels of dioxins which resulted in a higher mean concentration. Other differences that could be identified from Anderson et al. (1998) and Falk et al. (1999) include: 1) the time of sampling of the two studies; 2) the age of the participants; and 3) the sport fish consumption rates. Anderson et al. (1998) reported that sampling of the initial 31 individuals in the pilot study occurred in 1993. Although Falk et al. (1999) did not identify the date at which the followup study occurred, it appears likely to have been in 1995 or 1996. Although not expected to be a large factor explaining the differences in the populations, it is possible that average body burdens within the population decreased during this time period. The mean age of the 31 participants in the pilot study was 52 years (range 36 to 76), while the mean age in the second population of 96 participants was 46 years (range 27-67). A clear age relationship has been demonstrated in other studies, showing that older individuals have higher body burdens of dioxins. The followup study population of 96 individuals clearly showed lower consumption of Great Lakes fish as compared to the pilot population of 31 individuals, as evidenced by questionnaire response data. The followup study population reported an average of 52 fish meals consumed per year, while the pilot group reported an average of 77 fish meals per year. Likewise, consumption of Great Lakes fish was lower for the followup group than the pilot group: 43 Great Lakes fish meals per year and 49 Great Lakes fish meals per year, respectively. Also, the followup group reported a lower number of years consuming Great Lakes sports fish (26 years) than the pilot group (33 years). In summary, while the larger population of 96 sport fishers in the full survey appeared to show a much lower body burden of dioxin-like compounds as compared to pilot population of 31 sport fishers, the differences could be explained by factors of data description (median vs. mean), year of sampling, age of participants, and exposure to dioxins in fish.

Another observation from the Anderson et al. (1998) study was that Lake Erie sport fish consumers had consistently lower CDD/CDF/PCB serum concentrations than consumers of sport fish from Lakes Michigan and Huron. Serum levels observed for the Lake Michigan and Lake Huron fish consumers were similar and higher than those observed in consumers of Lake Erie sport fish. These interlake differences parallel the pattern observed in previously reported EPA sport fish tissue monitoring data from the respective lakes (Anderson et al., 1998) and indicate that serum concentrations may also be affected by variations in fish concentrations among the lakes.

Kolic et al. (2000) reported on sampling of fish for dioxin-like CDD/F/PCBs conducted by the Ontario Ministry of the Environment between 1996 and 1998 in the Ontario Great Lakes region. Table 5-12 presents the data on this sampling effort as it was reported in Kolic et al. (2000). A total of 193 samples are reported on in Table 5-12. TEQ concentrations were calculated using the WHO 1998 TEF scheme, with zero values used for non-detects. When no congeners were detected in the sample, the value was reported as zero. Fish were sampled for the Ontario Sports Fish Program. This program monitors sport fish in the Ontario fresh water lakes and issues consumption advisories through its biannual guide. Because of this purpose, the fish sampled are typically larger and from suspect areas in order to obtain positive results and therefore be able to set consumption advisories (Reiner et al., 1995). An initial set of data on CDD/CDFs from this program were reported on in Reiner et al. (1995). Sampling reported there occurred between 1991 and 1994. Kolic et al. (2000) examined the data taken between 1996 and 1998 for purposes of studying the relationship between dioxin-like PCBs and CDD/CDFs in the fish. They observed PCB TEQ concentrations substantially greater that CDD/CDF TEQ concentrations in most locations, as is evident from Table 5-12. Over all lakes, they observe an average ratio of 6.5 (omitting the large value of 86 from the Welland River, as well as all circumstances when CDD/CDF TEQ concentrations are zero).

Also noteworthy is that the concentrations reported for these fish are substantially higher than the fish concentrations used for background exposure calculations in Chapter 5. CDD/CDF concentrations for marine and freshwater sources were 1.0 and 0.26 pg/g whole weight TEQ_{DF}-WHO_{98}, respectively. PCB concentrations were 1.2 and 0.25 pg/g whole weight TEQ_{P}-WHO_{98}, respectively. In contrast, the overall concentrations for this Great Lakes data set were 5.4 and 26.6 TEQ_{DF}-WHO_{98}/g whole weight for CDD/CDFs and

PCBs, respectively. As observed by Kolic et al. (2000), CDD/CDF concentrations appeared to be declining since their earlier reporting in 1995. At that time, Reiner et al. (1995) reported on 198 samples, and the average I-TEQ_{DF} concentration was 11.5 pg/g whole weight.

Hong et al. (1994) analyzed PCBs in human milk from Mohawk and control women to evaluate the potential effect that relatively high levels of environmental contamination may have had on the body burdens of lactating Mohawk women in New York. PCBs were found to be present in fish and wildlife in the vicinity of the Mohawk Reservation, and the Mohawk people formerly depended on local fish and wildlife for food. However, no significant differences were observed between the mean total dioxin-like PCB levels in milk from 30 Mohawk women and the 20 control women. The mean PCB concentrations for these women were 49 ppb and 55 ppb, respectively. The age of the mother, the length of the nursing period, and the number of breastfed children were found to influence PCB levels in human milk. Older women, mothers of first born children, and smokers had higher levels of PCBs. PCB levels were also higher at the onset of lactation and in earlier samples during a breastfeeding session.

Dewailly et al. (1994) observed elevated levels of dioxin-like PCBs in the blood of fishermen on the north shore of the Gulf of the St. Lawrence River who consume large amounts of seafood. Of the 185 study samples, the 10 samples with the highest total PCB levels were analyzed for dioxin-like PCBs. Samples from Red Cross blood donors in Ontario served as controls. Dioxin-like PCB levels were 20 times higher among the 10 highly exposed fishermen than among the controls (Table 5-13). Based on these results of the 10 highest samples, Dewailly et al. (1994) estimated that for the entire fishing population studied, dioxin-like PCB levels would be eight to ten times higher than the control group. Dewailly et al. (1994) also observed elevated levels of dioxin-like PCBs in the breast milk of Inuit women of Arctic Quebec. The principal source of protein for the Inuit people is fish and sea mammal consumption. Breast milk samples were collected from 109 Inuit women within the first 3 days after delivery and analyzed for di-ortho-dioxin-like PCBs during 1989 and 1990. Subsets of 35 and 40 randomly selected samples were analyzed for mono-ortho dioxin-like and non-ortho dioxin-like PCBs, respectively. Samples from 96 Caucasian women from Quebec served as controls. The levels of non-ortho dioxin-like PCBs for Inuit women ranged from 24.7 to 220.9 ppt.

These values were three to seven times higher than those observed in the control group. For mono-ortho and di-ortho dioxin-like PCBS, the levels among the Inuit women were three to ten times higher than in the control group.

Humphrey et al. (2000) reported on an elevation in the PCB concentrations in serum of humans consuming Great Lakes fish. They described a careful identification of "sport fish eaters" and "non-sport fish eaters," or controls, from 11 Lake Michigan shoreline communities during the years 1979 and 1982. Sport fish eaters were defined as those individuals who consumed 26 or more pounds of sport-caught fish annually, while non-sport fish eaters consumed less than 6 pounds of sport-caught fish annually. This cohort was revisited a second time in 1992 for a study of individuals over the age of 50. Blood sampling occurred in 1993-1995 for 101 fish-eaters and 78 controls. These samples were measured to 90 PCB congeners, including dioxin-like PCB congeners 77, 105, 118, 123, 157, 169, and 180. They found that sport fishers had significantly higher PCB concentrations as compared to controls. The mean concentration of total PCBs (sum of the 90 measured) in the fish-eaters was 14.26 ppb whole weight, while for the controls, the concentration was 4.56 ppb. They found that 22 of the congeners explained most of the concentration, and dioxin-like PCBs 105, 118, and 180 were among those 22. The whole weight concentrations (ppb) of these three PCBs in sport and control fishers were 2.00 (fishers) vs. 0.79 (control) for PCB 180; 0.26 vs. 0.02 ppb for PCB 105; and 0.83 vs. 0.06 for PCB 118.

5.4. LOCALIZED IMPACTS

Data have been collected that demonstrate that localized impacts may occur from emissions of dioxins from incinerators and other potential sources. "Localized impacts" are defined as measurements of CDD/CDFs in environmental (air, soil) or biotic (vegetation, animal tissue) samples near incinerators or other sources that show elevation above typical background levels for the area being studied. Therefore, "impacts," as used below, refer to elevation above background. These localized impacts may result in elevated exposure among some members of the population. Most of the data on localized impacts originate from studies conducted outside the United States, specifically from the European countries of England, Switzerland, Germany, Austria, The Netherlands, Belgium, and France. Data collected include concentrations of dioxins in air and soil, biota including

grass and cow's milk, as well as human blood and hair samples. This section reviews several of these studies, primarily discussing results in terms of TEQs from CDD/CDFs only. Following a review of the studies, the principal findings with regard to localized impacts are summarized.

Goldman et al. (2000) compared serum concentrations of CDD/CDFs among residents of 2 homes where contaminated home-produced eggs and beef were consumed to residents of a similar rural area that did not consume home-produced eggs and beef. The contaminated eggs and beef originated from a residence located near the site of a 1987 fire at a wood preservative plant. The chicken eggs had an I-TEQ_{DF} mean concentration of 10 pg I-TEQ_{DF}/g; beef fat contained 27 pg I-TEQ_{DF}/g. These concentrations are 10- to 100-fold higher than the results observed in samples of commercial foods. The soil near the home where contaminated eggs were observed contained CDD/CDF levels ranging from 30 to 40 pg I-TEQ_{DF}/g, and the soil CDD/CDF profile was similar to that observed in the eggs. Serum samples were collected from 9 individuals residing in homes where contaminated eggs and beef were consumed. I-TEQ_{DF} concentrations in serum were 26.7 ppt for the 4 individuals who had consumed eggs from the contaminated site over a 2-year period and 63.7 ppt for the 5 individuals who had consumed both eggs and beef from the contaminated site for up to 15 years, compared to 17.0 ppt for the comparison group.

Beck et al. (1990) sampled milk from a rural and an industrial area in Germany, and from dairies near a metals reclamation plant in Austria. Beck et al. (1990) observed average lipid-based concentration of 0.9 pg I-TEQ_{DF}/g in rural, background milk, 2.5 pg I-TEQ_{DF}/g in "industrial milk," and 9.6 pg I-TEQ_{DF}/g in the milk obtained from dairies near the metals reclamation plant. The dairy nearest the metals reclamation plant was located about a kilometer in the downwind direction and had the highest milk concentration (i.e., 14 pg I-TEQ_{DF}/g).

The Austrian metals reclamation plant described above has also been studied for impacts to air, soil, vegetation, and human blood by another research team (Riss et al., 1990; Riss, 1993). The plant was located in a rural Alpine river valley in Tyrol, Austria, in a mostly agriculture area. Although emissions data were unavailable, air concentrations measured near the incinerator were 1.2 to 2.3 pg I-TEQ_{DF}/m^3 (Riss, 1993). These data suggest very high emissions, because typical urban air concentrations are approximately

0.10 pg/m^3 in Europe as well as in the United States, and rural air concentrations are typically less than 0.05 pg I-TEQ_{DF}/m^3. (See Chapter 3.) Soil concentrations averaged 420 pg I-TEQ_{DF}/g at the site of the incinerator, 170 pg/g within 200 meters of plant, and 46 ppt about 2 km in the downwind direction (Riss et al., 1990). This compares with typical urban soil concentrations of approximately 10 to 20 pg I-TEQ_{DF}/g in both Europe and the United States and rural soil concentrations of less than 5 pg I-TEQ_{DF}/g. (See Chapter 3.)

A dairy farm was located between 1,400 and 2,100 meters from the same metals reclamation site in the downwind direction, and members of that farming family consumed milk from their own cows. Samples of the cows milk ranged from 20.1 to 69.5 pg I-TEQ_{DF}/g on a lipid basis. Given a general background level of milk in the low to sub ppt level on a lipid basis, it is clear that the milk showed elevated dioxin levels. (See Chapter 3.) Samples in the grass and hay from that farm were also elevated at 13 to 36 pg I-TEQ_{DF}/g dry weight. This compares to typical grass samples found in rural areas at the low to sub ppt levels (Reed et al., 1990; Kjeller et al., 1991; 1996). Blood samples from two farmers who consumed this milk were also elevated. Their blood CDD/CDF concentrations were 152 and 946 pg I-TEQ_{DF}/g on a lipid basis. Subsequent samples from three additional family members were also slightly elevated above typical levels at 41, 66, and 77 pg TEQ_{P}-WHO_{94}/g lipid.

The Austrian samples described above were taken in the late 1980s, before emission controls and other practices (i.e, removal of some plastics) were undertaken to reduce emissions from these plants. Riss (1993) reported on reductions in both cow's milk and fodder from this nearby farm in the early 1990s and speculated that they resulted from reductions in incinerator emissions. CDD/CDF concentrations in cows' milk dropped steadily from a high in 1987/88 samplings, averaging 49 pg I-TEQ_{DF}/g fat, to an average of 5 pg I-TEQ_{DF}/g fat in the 1992/93 sampling. Grass concentrations similarly dropped from 33 pg I-TEQ_{DF}/g dry weight to 4 pg I-TEQ_{DF}/g dry weight between the two sample dates. This trend demonstrates an important expectation with regard to environmental responses to reductions in emissions from tall industrial stacks. Specifically, vegetation appears to respond immediately to reduced air concentrations, and if dairy cows are being fed with vegetation that has reduced concentrations, cow's milk should similarly respond in a rapid manner. Fries and Paustenbach (1990) stated that a

steady state is reached in cow's milk with a constant dietary input of dioxins after about 30 to 60 days. Therefore, reductions in emissions will result in both a reduction in vegetation and cow's milk concentrations almost simultaneously.

Another study was conducted in Austria by Moche and Thanner (1997). The study evaluated ambient air patterns and CDD/CDF concentrations in a vicinity of steel production plants in Leoben/Donawitz. Samples were collected from sites in the immediate vicinity of the production plants, in an area that was expected to be impacted by the production plants, and in an area that was shielded by mountains in the northwest. Sampling occurred over four periods to address the potential influence of the summer and winter fluctuations in CDD/CDF concentration. The CDD/CDF concentrations in these samples were compared to previous data collected in the three Austrian conurbations Graz, Linz, and Wien. The previous data suggested average summer levels of CDD/CDFs in the range of 20 to 40 fg I-TEQ_{DF}/Nm^3 and winter levels in the range of 50 to 220 fg I-TEQ_{DF}/Nm^3. The data collected at Leoben/Donawitz indicated higher ambient air levels of CDD/CDF concentrations. Only the levels in the area shielded by mountains fall within the levels of the previously reported data. In addition, the CDD/CDF profiles of the Leoben/Donawitz sites indicated a high contribution of the lower chlorinated CDFs (tetra- through hexachlorinated CDFs as the most abundant). The patterns were in good agreement with emission profiles of metallurgical processes reported by Hagenmaier et al. (1994) (Moche and Thanner, 1997).

Liem et al. (1991) reported on the analysis of over 200 samples of cow's milk that were taken in various regions in The Netherlands, including some that were near municipal solid waste incinerators and metals reclamations plants, and some identified as background sites. Background levels ranged from 0.7 to 2.5 pg I-TEQ_{DF}/g lipid. The highest levels were found approximately 2 km from the largest municipal solid waste incinerator identified at the time, with concentrations ranging from 2.8 to 12.6 pg I-TEQ_{DF}/g lipid. Higher than background levels were also found in samplings near other incinerators. The researchers did a principal component analysis on congener profiles in the milk samples to determine if there were any discernable differences among groupings of samples. Liem et al. (1991) observed a distinct pattern for samples around the metals reclamation plant compared to samples around municipal solid waste facilities. A higher CDF/CDD ratio was found around the metals reclamation plant (i.e., higher furan

concentrations were in the milk near the metals reclamation plant than near the municipal solid waste incinerator). Liem et al. (1991) speculated that metals reclamation plants process cables that contain PVC, and according to Christmann et al. (1989), furans are predominantly formed in the combustion of PVC. Subsequently, the higher levels of furans would be taken up into vegetation and then into cow's milk. Liem et al. (1991) also found distinct patterns in samples associated with other facilities, as characterized by the relative amounts of lower and higher chlorinated congeners. Two of the incinerators were closed in April of 1990, and a marked decrease in sample concentrations associated with these two incinerators was noted between the February and August 1990 sampling. This supports the expectation described above regarding the response of vegetation and milk to changes in nearby source emissions.

A limited sample from six cows in Switzerland showed similarly elevated CDD/CDFs in association with incinerators or manufacturing sites. Higher CDD/CDF concentrations were observed in milk samples that were within 1,000 meters of an incinerator (two samples) and those that were within 1,000 meters of a production site for various chlorinated samples (one sample) than samples from a background farm (one sample) and from local dairies that pooled milk from several farms (two samples) (Rappe et al., 1987). Insufficient information was available in this report to calculate I-TEQ_{DF} concentrations.

De Fre and Wevers (1998) evaluated paired CDD/CDF deposition and cow's milk data from several locations in Belgium to evaluate the relationship between deposition rates and milk levels, and the potential impact that elevated deposition rates may have on local milk supplies. CDD/CDF deposition ranged from approximately 2 ng I-TEQ_{DF}/m^2/year to 45 ng I-TEQ_{DF}/m^2/year, and CDD/CDF concentrations in milk fat ranged from approximately 1 pg I-TEQ_{DF}/g to 19 pg I-TEQ_{DF}/g. The correlation coefficient (R) for CDD/CDF deposition rates and milk fat concentrations was 0.69. The results of a regression analysis using these data indicated that milk fat concentrations of I-TEQ_{DF}s could be predicted from deposition rates using the equation $y = 0.3332x$, where y is the milk fat concentration of CDD/CDFs in units of pg TEQ_{DF}/g and x is the CDD/CDF deposition rate in units of ng TEQ_{DF}/m^2/y.

In France, the Ministry of Agriculture and Fisheries investigated CDD/CDF concentrations in cow's milk sampled from farms in a downwind direction within 11 km, but mostly within 5 km, of 26 industrial facilities (Defour et al., 1998). These industries

included: steel manufacturing, secondary lead and aluminum smelting, copper refining, chemical and oil refining industries, electricity production, and municipal waste incinerators. Of the 49 milk samples analyzed, 46 samples had CDD/CDF concentrations that were less than 3 pg I-TEQ_{DF}/g fat with an average of 1.53 pg I-TEQ_{DF}/g on milk fat basis. One milk sample collected from a site near a chemistry industry was found to contain 3 to 5 pg I-TEQ_{DF}/g fat, and two milk samples collected 250 m and 1 km downwind of incinerators had concentrations higher than 5 pg I-TEQ_{DF}/g fat. The average concentration in milk and diary products in France assessed through a 1996 survey conducted by the Ministry of Agriculture and Fisheries was 1.33 pg I-TEQ_{DF}/g fat (Defour et al., 1998).

Abraham et al. (1998) reported on the levels of CDD/CDFs in the human milk of 10 mothers who lived within a radius of 8 km of Ilsenburg, Germany. The town was identified as an area highly contaminated with CDD/CDFs reportedly resulting from emissions from a copper plant. At the time of sample collection (i.e., 1997) the plant had been closed for approximately 6 years, Abraham et al. (1998) compared the findings to the results of a previous study of human milk levels conducted in 1990/1991 when the plant was still in operation. The 1990/1991 human milk samples contained a mean I-TEQ_{DF} of 59 ppt, lipid based (n = 9). The 1997 human milk samples contained a mean I-TEQ_{DF} of 41 ppt, lipid based (n = 10). Abraham et al. (1998) documents that this decrease in CDD/CDFs is lower than the decline reported in general background concentrations in human milk from Western Germany in recent years. These values are somewhat higher than the values reported in Chapter 4 for the general population of the United States.

An extensive study was undertaken in the Pontypool environment of South Wales (Ball et al., 1993; Ball et al., 1994a; Ball et al., 1994b; Ball et al., 1995). Evidence of the impact of emissions from waste incineration at Rechem International Ltd. (a chemical company) prompted extensive investigations into impacts from emissions of PCBs and CDD/CDFs to nearby and regional media including soil, grass, water, air, fruit/vegetables, cow's milk, duck meat, and eggs from chicken and ducks. The region has a combination of residential and industrial uses, with very little agricultural uses. The greatest impact was found at a residence adjacent to the site, located only about 100 meters away. The soil at Rechem International averaged 810 pg I-TEQ_{DF}/g (n = 4), while at this nearby

residence, the concentration averaged 66 pg I-TEQ_{DF}/g (n = 8). Other areas evaluated ranged from 4 to 24 pg I-TEQ_{DF}/g. Data were not available on CDD/CDF emissions, but air measurements at this residence suggested high emission rates. For five air samples taken at the residence, air concentrations ranged from 1.6 to 14.8 pg I-TEQ_{DF}/m^3. This compares to air concentrations ranging from 0.02 to 0.68 pg I-TEQ_{DF}/m^3 taken from a site about 2,500 meters away in the same direction from the Rechem site. The researchers also compared these air concentrations to average air concentrations ranging from 0.21 to 0.67 pg I-TEQ_{DF}/m^3 in four other UK urban areas. Concentrations of CDDs/CDFs in grass were found to be elevated at the same residence, but described as more typical for other grass sampling sites. Perhaps most importantly, samples of duck and bantam eggs from this residence showed concentrations that exceeded other duck and bantam egg samples in the area by a factor of 10. Duck and bantam egg concentrations in the area, but not at this residence, were described as typical of background. Duck meat at the impacted residence was not described as elevated compared to duck meat from nearby settings. Sampling of sediments in a nearby reservoir did not indicate elevated concentrations of dioxins or PCBs. There was no sampling of human blood or tissue. However, a simple exposure exercise showed that consumption of duck eggs, duck meat, apples, inhalation, and incidental soil ingestion at this impacted residence would result a daily intake of 165 pg I-TEQ_{DF}/day, compared to a background intake from these pathways of 43.2 pg I-TEQ_{DF}/day (consumption rates described as typical derived from consumption data from the Ministry of Food and Fisheries in the UK).

Foxall et al. (1997) also reported geographical variations in environmental levels and human exposure to CDD/CDFs and PCBs of the above study. The data indicated a particular impact in a 200-meter wide strip of land around the boundary of the incineration plant owned by Rechem International Ltd. This location is predominantly downwind from the incinerator and there had been evidence suggesting that fugitive emissions from the plant contributed to the environmental impacts. Marked differences were noted between the CDD/CDF and PCB content of samples (i.e., air, soil, and foods) collected at the impacted site and those collected at rural background locations. Intakes of CDD/CDFs (pg I-TEQ_{DF}/day) and PCBs (μg/day) were estimated using mean daily food consumption rates, inhalation and soil ingestion rates of 20 m^3/day and 100 mg/day, respectively, and the median concentrations of CDD/CDFs and PCBs found in the samples. These estimates

indicated that exposure to CDD/CDFs and PCBs at the impacted site was much higher than for background levels and the main contributors to these higher levels were residues in bantam and duck eggs. The estimated intake of CDD/CDFs from ingestion of bantam or duck eggs at the impacted site were 204 pg I-TEQ_{DF}/day and 103 pg I-TEQ_{DF}/day, respectively; levels that are substantially higher than the average UK dietary intake of 88 pg I-TEQ_{DF}/day from all food sources. Based on a body mass of 60 kg, these egg intakes (i.e., 3.4 and 1.7 pg I-TEQ_{DF}/kg body mass/day) would represent 34 and 17 percent of the WHO (World Health Organization) TDI (Total Dietary Intake) value of 10 pg I-TEQ_{DF}/kg body mass. Similarly, the corresponding PCB intake of 7.3 and 6.3 μg/day would represent 73 and 63 percent, respectively, of an average dietary intake (10 μg/day) of PCBs.

Lovett et al. (1998) performed additional analysis of chicken, bantam, and duck eggs; and also duck meat collected from the vicinity of the Rechem incinerator and compared the results to PCB and CDD/F levels of comparable foodstuffs collected from rural areas in the same Welsh district. Poultry produced at the impacted residence displayed a congener profile with noticeable variations compared to those collected from nearby rural sites. A prominence of higher chlorinated congeners in the egg and duck meat samples for the residence located near the incinerator was observed. Analysis of 46 PCB congeners resulted in a median fresh mass total PCB concentration in duck eggs of 191 μg/kg (n = 2), 341 μg/kg in bantam eggs (n = 2), and 43 μg/kg in duck meat (n = 2) from samples collected in the impacted area. Observations from rural areas showed fresh mass based total PCB concentrations of 14 μg/kg for duck eggs (n = 6), 22 μg/kg for bantam eggs(n = 4), and 25 μg/kg for duck meat (n = 6).

A second location in the United Kingdom, the Derbyshire area in central England, has shown elevations in cow's milk and other animal tissues. Initially, samples of cow's milk were taken by the Ministry of Agriculture, Fisheries, and Food (MAFF) from individual farm tanks on 11 farms in 1990. When 2 of the samples showed high concentrations of 40 and 42 ng I-TEQ_{DF}/kg fat (the other 9 showed more typical concentrations in the 1.1 to 7.1 ng I-TEQ_{DF}/kg fat), the sampling was expanded to 30 farms. These original two farms, plus an additional farm, continued to show high concentrations in the milk. Testing continued in milk through 1994. Milk concentrations dropped at one farm, but overall concentrations appeared to remain high (i.e., 29 ng I-TEQ_{DF}/kg) for the most recently

reported sampling in July of 1994 (Harrison et al., 1996). As a result of these findings, MAFF tested animal tissue from the three farms. Calves from one of the three farms had extremely elevated levels of dioxins and furans, with concentrations ranging from 2.5 to 6.9 ng I-TEQ_{DF}/kg whole weight (i.e., not lipid basis) in muscle tissue (MAFF, 1992a). This compares, for example, with I-TEQ_{DF} concentrations approximately 0.20 ng I-TEQ_{DF}/kg in the United States beef supply (from the national study on beef back fat, assuming 19 percent fat in whole beef (Winters et al., 1996). Egg samples were taken from one of the three farms and a second "free range" supplier. The concentrations found were reported as 2.2 and 2.1 ng I-TEQ_{DF}/kg in whole eggs. A second sample from one of the farms taken a year later showed a lower concentration of 0.8 ng I-TEQ_{DF}/kg whole weight. These would appear to be elevated, considering that eggs found in a background setting in Mississippi (Cooper et al., 1995), had concentrations less than 0.10 ng I-TEQ_{DF}/kg whole weight.

MAFF (1992b) also sampled leafy herbage (grass, hay, etc.) from the three farms described above. Concentrations ranged from about 2 to 14 ng I-TEQ_{DF}/kg dry weight. This appears elevated, considering that samplings of background grass in England showed 0.89 ng I-TEQ_{DF}/kg dry weight, as reported in 1991 (Kjeller et al., 1991) and 0.57 ng I-TEQ/kg dry weight in 1996 (Kjeller et al., 1996). The evidence suggests that the impacts were due to nearby industrial emissions from a fuel plant and chemical waste incineration. Her Majesty's Inspectorate of Pollution (HMIP) conducted additional studies to evaluate this possibility. These included stack testing of the Coalite Fuels, Ltd. and the Coalite Chemicals, Ltd. (which were adjacent to one of the farms and near the other two), air dispersion modeling, and soil monitoring. No results were available to evaluate the stack testing, but the air dispersion modeling predicted that the three impacted farms would be in the sectors having the highest air concentrations. The soil sampling on the three farms showed concentrations ranging from 10 to 90 ppt. This can be considered elevated above typical rural background and in the range or even higher than typical urban concentrations. Specifically, this compares with typical urban soil concentrations of 10 to 20 pg I-TEQ_{DF}/g in both Europe and the United States, and rural soil concentrations typically less than 5 pg I-TEQ_{DF}/g. (See Chapter 3.) Also, these concentrations are similar to concentrations found near incinerators emitting very high concentrations of dioxins in Tyrol, Austria, as described above, and in Columbus, Ohio, as described below. The

National Rivers Authority sampled sediment upstream and downstream of the effluent discharge pipe of the Coalite Chemicals, Ltd site. Samples collected about 1.5 km downstream of the discharge site had CDD/CDF levels that were 1,000 times greater than background samples collected 1.5 km upstream of the discharge point (these studies reported in MAFF, 1992a).

Another interesting finding associated with the samplings of foods and environmental media in the Derbyshire area were the congener profiles. Compared to background milk samples, the samples from the three impacted farms had proportionally higher concentrations of lower chlorinated dioxins, particularly 2,3,7,8-TCDD and 1,2,3,6,7,8-HxCDD. The background samples of milk tended to be dominated by OCDD (MAFF, 1992b). Blood samples were also collected from residents of these three impacted farms and analyzed for CDD/CDFs (Startin et al., 1994). The I-TEQ_{DF} concentrations for the 10 individual blood samples ranged from 49 pg/g to 291 pg/g on a lipid basis. In contrast, the two control samples had I-TEQ_{DF} concentrations of 16 pg/g and 26 pg/g on a lipid basis. The Derbyshire samples were dominated by OCDD, followed by 1,2,3,4,6,7,8-HpCDD, 2,3,7,8-TCDD, and 1,2,3,6,7,8-HxCDD.

Sandalls et al. (1998) analyzed soil concentrations around the site of a chemical waste incinerator near Bolsover, Derbyshire, United Kingdom. At each of 46 sites, five surface soil samples were collected, at varying depths up to a depth of 5 centimeters, every 1 square meter. All 46 sample sites had total TCDD concentrations exceeding background concentrations. Higher concentrations of TCDD were observed at locations closer to the incinerator and there was a strong correlation between the TCDD concentration in a given quadrant and the amount of time that the wind was blowing in that direction. At four quadrants around the site, TCDD soil concentrations were reported as 603 ppt for the northeast (approximately 42 percent of the total deposition); 315 ppt for the southeast (22 percent of the total); 269 ppt for the southwest (19 percent of the total); and 244 ppt (17 percent of the total) for the northwest. The results of the spatial distribution of CDD/CDFs implicated the incinerator as the likely source, and the correlation between deposition and wind direction suggested that these compounds reached the ground via the atmosphere. Also, 42 of the 46 sample sites showed similar CDD/CDF congener ratios to the flue gas of the waste incinerator. Soil concentrations were well in excess of background concentrations, up to 5 kilometers around the site.

Ohta et al. (1997) studied levels of CDD/CDF and non-ortho coplanar PCBs in soil at a high cancer-rate area close to a batch-type municipal solid waste (MSW) incinerator in Japan. Sixty-one soil samples were collected around the MSW incinerator. Among them, 52 samples were radially collected within 2 km from the center of the MSW incinerator, and 9 samples were collected across the high cancer-rate area. High concentrations of CDD/CDFs and coplanar PCBs were observed in all the soil samples from the leeward side of the MSW incinerator. Total concentrations ranged from 5,303 to 32,167 pg/g; mean = 13,934 pg/g. On the other hand, all but one sample on the windward site showed high contamination. Among the 61 samples analyzed, the total concentration was greater than 2,000 pg/g in 45 of the 61 samples and the TEQ_{DFP}-WHO_{94} concentration was over 10 pg/g in 39 of the 61 samples. In addition, the levels of CDD/CDFs and coplanar PCBs at a distance of 0 to 1.1 km from the MSW incinerator was compared with that of the area 1.1 to 2.0 km from the MSW incinerator. The area closer to the incinerator contained a higher ratio of samples with contamination over 5,000 pg/g (63.2 percent) than in the area further away from the MSW incinerator (38.5 percent). Similarly, the area closer to the incinerator had a higher percentage of samples with CDD/CDF/PCB levels over 30 pg TEQ_{DFP}-WHO_{94}/g (26.3 percent) than the area further away from the incinerator (15.3 percent).

Miyata et al. (1998) collected blood samples from residents living within 2 km from a batch-type municipal solid waste incinerator in Japan where soil concentrations of CDD/CDFs and PCBs were shown to be elevated. Eighteen blood samples were collected from 13 men, aged 23 to 63 years old (average age = 45 years), and 5 women, aged 30 to 72 years old (average age = 46 years) in March 1996. The results indicated that the average lipid-based TEQ_{DFP}-WHO_{94} concentrations found in blood samples ranged from 34 pg/g to 200 pg/g with a mean of 81 pg/g for men, and from 22 pg/g to 463 pg/g with a mean of 149 pg/g for women. These mean TEQ_{DFP}-WHO_{94} values are higher than those reported for the general population of various countries (the mean value estimated in Chapter 4 of this document is 55 pg/g).

Local impacts around a waste-to-energy municipal solid waste incinerator in Columbus, Ohio, were undertaken by the Ohio Environmental Protection Agency, and the U.S. Environmental Protection Agency (Lorber et al., 1998). This incinerator operated between 1983 and 1994. A stack test was taken in 1992, and when the results were

extrapolated to typical operation of the incinerator, annual emissions were calculated at 985 g I-TEQ/yr. This is a very high emission rate, and compares to total emissions from several European countries. It is about one-tenth of the national emissions estimated for all United States sources. (See Volume 1.) Process modifications were undertaken in the winter of 1993/94. A stack test was conducted which indicated that annual emissions were reduced to 267 g I-TEQ_{DF}/yr. The U.S. EPA undertook a soil testing program in December of 1995. Results showed a definite impact to soils at the site of the incinerator, with an average concentration of 356 pg I-TEQ_{DF}/g (n = 4). Of the four samples collected, three of the samples averaged 458 pg I-TEQ_{DF}/g and the fourth was much lower at 50 g I-TEQ_{DF}/g. Just offsite in the downwind direction, a cluster of four samples within 1,000 meters also showed some elevation of CDD/CDFs with an average concentration of 49 pg I-TEQ_{DF}/g. Fourteen additional samples, generally within 2 miles of the site, averaged 10 pg I-TEQ_{DF}/g. Three soil samples at a background site 28 miles away in the upwind direction averaged 1 pg I-TEQ_{DF}/g. These latter two clusters of urban and background samples have concentrations that are typical of urban and background situations. The urban results suggests that, despite large emissions from this source, soil impacts above typical levels appeared to be restricted to within 1,000 meters of the incinerator.

The Ohio EPA conducted air monitoring in 1994 and 1995 (OEPA, 1994; Lorber et al., 1998). Monitoring in 1994 occurred after process modifications were undertaken to reduce dioxin emissions. A stack test conducted just prior to the air sampling showed reductions of 75 percent from the levels measured in 1992. Wind rose data were taken on an hourly basis during the 1994 sampling. This showed that two samples from a sampler located about 2 miles away were in the downwind direction during the 48-hour sampling period. Eight other samples from four samplers (which were between 1 and 2 miles from the incinerator) were clearly not in the downwind direction. The two downwind samples averaged 0.26 pg I-TEQ/m^3 CDD/CDFs, while the eight upwind samples averaged 0.05 pg I-TEQ_{DF}/m^3. The incinerator shut down in December 1994. Five samples taken in 1995 showed an average of 0.05 pg I-TEQ_{DF}/m^3 CDD/CDFs. This air sampling suggests the following: (1) the typical background urban air CDD/CDF concentration in Columbus is probably around 0.05 pg I-TEQ_{DF}/m^3; and (2) when the incinerator is emitting dioxins typical of the rate measured in the 1994 stack test (not the

1992 stack test), air concentrations about 2 miles away are higher, perhaps by a factor of 5. Other media, including vegetation, agricultural products, or human blood were not sampled.

Schecter and Papke (1998) examined CDD/CDFs and PCBs 77, 126, and 169 in blood sampled from 10 residents living near a PCB manufacturing facility in Alabama in 1997, and compared these concentrations to a pooled sample from a control group representing 100 adults. The results showed that, for the 10 residents, total lipid-based CDD/CDF concentrations ranged from 825 ppt to 6,422 ppt. The corresponding total CDD/CDF concentrations from the pooled control sample was 1,112 ppt. Total PCB concentrations ranged from 240 ppt to 5,216 ppt for the 10 nearby residents, compared to 1,112 ppt for the pooled control sample. PCB-77 was only detected in the blood of 5 of the 10 residents, ranging from 41 ppt to 713 ppt. PCB-126 concentrations ranged from 104 ppt to 4,050 ppt in residents, compared to 48 ppt found in the control sample. PCB-169 concentrations ranged from 136 ppt to 2,807 ppt for the 10 residents, compared to 35 ppt for the control sample. In terms of TEQ, the total I-TEQ_D and I-TEQ_F concentrations ranged from 16.3 ppt to 38.9 ppt, and from 6.7 ppt to 131 ppt, respectively, compared with 18.5 ppt and 8.3 ppt from the control blood. TEQ_P-WHO_{94}s ranged from 34 ppt to 360 ppt compared to 32 ppt for the control blood.

There were also studies conducted in Asia to address localized impacts. Luksemburg et al. (1997) reported, in a preliminary study, that high levels of CDD/CDFs were observed in soil and sediment samples collected inside and outside a sodium pentachlorophenate plant in Tianjin, China. The plant is situated in a wetland with rivers emptying into the nearby Pacific Ocean and close to several large housing developments. Human hair samples collected from barber shops in the housing developments near the plant were also collected and CDD/CDFs were detected in these samples. The I-TEQ_{DF} concentrations in soil ranged from 15 ppt at a site upstream of the plant to 740,000 ppt within the plant, and was 1,800 to 2,200 ppt at sites outside the plant. The I-TEQ_{DF} concentrations in sediment ranged from 150 ppt at a site 50 km away from the site to 110,000 ppt in a drainage canal located just southwest of the plant. Hair samples contained I-TEQ_{DF} concentrations ranging from 12 to 120 ppt. According to Luksemburg et al. (1997), "the isomer profiles of all the samples were consistent with the

pentachlorophenol sources." However, it should be noted that no background information on the test subjects (time of residence, health records, etc.) were collected in this study.

The major findings and conclusions based on this review of localized sources include:

- Localized impacts, meaning elevated concentrations of CDD/CDFs above background, have been found in the vicinity of some CDD/CDF sources.

- Localized impacts appear to be limited to an area within 5 km of an incinerator source, perhaps only within 2 to 3 km of the source, and in some cases, only within a few hundred meters of the source. One study noted elevations in grass, cow's milk, and human blood on a farm located 2 km from an incinerator presumed to be emitting high amounts of CDD/CDFs. Not all of the studies described in the literature discussed distance from the source, as the surveyed areas were simply identified as "industrial."

- Several studies continued environmental samplings after efforts were made to reduce emissions or after the sources were shut down. In these cases, reductions in CDD/CDF concentrations were noted for various media including, cow's milk, vegetation, and air. As discussed below, vegetation has been found to respond rapidly to reductions in air concentrations, and the time to reach steady state in cow's milk given a steady input of CDD/CDFs is also relatively short. In other cases, such as in the accumulation of CDD/CDFs in soils or in body fat, the benefits may not be as immediate. Soil and body fat are reservoirs in which the residence time of these compounds are measured on the order of years.

The available data reviewed above suggest that measurable impacts near incinerators only occur if the incinerator emits very high amounts of dioxins, in contrast to emissions that are known to be within regulatory limits. However, two key descriptors here, including "measurable impacts" and "very high amounts of emissions" cannot be rigorously defined. The data suggest that "measurable" impacts can be defined as

elevations in dioxin concentrations in environmental or biotic media on the order of 5-10 times higher than typical background. "Very high amounts" of releases is less well defined. The Columbus incinerator is the only incinerator reviewed above for which emission data were available, and the stack test of 1992 showed emissions that were about 200 times higher than the 1995 proposed regulatory limit for solid waste incinerators of 30 ng of total dioxins per m^3. By comparison of environmental media sampling, one could surmise that the metals reclamation plant in Tyrol, Austria, and the incinerators in the Derbyshire area of Central England, if not others noted above, were also emitting unusually high amounts of dioxins.

Also, it is important to understand that elevations in air, soil, vegetation, and animal products do not automatically translate to higher exposure levels. This document (and several other efforts worldwide) have concluded that the bulk of exposure to dioxins occurs via the diet, and specifically animal fats. Higher exposure to an individual would only result if an individual subsisted on animal food products from animals raised near incinerators (meaning also that the animal's diet was comprised of vegetation grown where the animal is raised), and perhaps only incinerators emitting high amounts of dioxins. As described above, there are limited human tissue data for individuals where localized environmental contamination has been demonstrated. In one study in Austria of a farming family consuming home-grown milk near the metals reclamation plant, both the milk and the blood of the family were shown to have elevated levels of dioxins. In the vicinity of a municipal solid waste incinerator in Japan where CDD/CDF and PCB concentrations in soil were elevated, nearby residents also had elevated blood levels of CDD/CDF/PCBs. In the U.S., there have been no studies to evaluate the prevalence of subsistence behavior near sources, in general, and near high emitting incinerators, in particular. Even if there is a sparsity of subsistence behaviors near sources in the U.S., it is reasonable to assume that animal fats produced near high emitting incinerators would likely have elevated CDD/CDF levels and be consumed. If incinerators are meeting regulation limits, they would not be high emitters, and the likelihood of localized impacts would be small.

In addition to the localized contamination resulting from incinerator emissions, as described above, there have been several incidents involving contamination of commercial food supplies from natural and accidental sources in various parts of the world. For

example, ball clay was found to be the source of elevated CDD/CDF levels in animal food products in the United States (Ferrario et al., 2000). Ball clay from a mine in Mississippi, which was used as an anti-caking agent in soy-based animal feeds, was found to be the source of contamination after poultry and catfish samples collected in the same region of the United States were found to have concentrations of CDD/CDFs that were significantly elevated above background concentrations. The incident, which occurred in 1998, involved less than 5 percent of the national poultry production. Subsequently, the use of ball clay in animal feeds was discontinued. In Germany, dairy products were found to be contaminated in 1998 (Malisch, 1998). The concentration of CDD/CDFs in milk was 1.38 pg I-TEQ_{DF}/g fat (N = 43) in 1998, compared to 0.62 pg I-TEQ_{DF}/g fat (N = 76) in 1997. After intense investigation, contaminated citrus pulp obtained from Brazil, which was used as a feed ingredient for dairy cows in certain regions of Germany in 1998, was found to be the source of contamination of the food supply. In 1999, similar contamination of the commercial food supply occurred in Belgium when 500 tons of animal feed was inadvertently contaminated with approximately 50 kg of PCBs and 1 g of dioxins in transformer oil (Van Larebeke et al., 2001). The feed was delivered to poultry farms (and to a lesser extent rabbit, cow, and pig breeding facilities), primarily in Belgium. This contaminated feed represented a "limited percentage" of the feed produced in Belgium, but was delivered to hundreds of farms in the country. The mean TEQ_{DFP}-WHO_{94} concentrations were 170 pg/g fat in poultry, 2.3 pg/g fat in eggs, and 2,320 pg/g fat in animal feed. Once discovered, animal products with excessive levels were destroyed, including approximately 2 million chickens.

5.5. CIGARETTE SMOKERS

As discussed in Volume 1, cigarette smoking has been found to be a source of CDD/CDFs. As a result, individuals who smoke cigarettes, and nonsmokers who are exposed to second-hand smoke, may experience higher levels of exposure to dioxin-like compounds than the general population. Matsueda et al. (1994) reported that the mean I-TEQ_{DF} content of a pack of U.S. cigarettes was 8.6 pg. This estimate is based on analytical data from seven brands of U.S. cigarettes. Assuming that a pack of cigarettes contains 20 cigarettes, the I-TEQ_{DF} content of a single cigarette would be 0.43 pg. This value represents about half of the I-TEQ_{DF} value reported for a mainstream cigarette smoke from a Swedish brand of cigarettes (Löfroth and Zebühr, 1992) and is about five times higher than the I-TEQ_{DF} level in mainstream smoke from German cigarettes (Ball et al., 1990). The daily intake of CDD/CDFs by smokers can be estimated by multiplying the CDD/CDF content of a single cigarette by the mean number of cigarettes smoked per day by current smokers. According to U.S. EPA (1992), 25.5 percent of the adult U.S. population were smokers in 1990. The average daily number of cigarettes smoked by this population was 19.1. Thus, mean CDD/CDF exposures via cigarette smoking are estimated to be 8.2 pg I-TEQ_{DF}/day for smokers. This level of exposure represents over 10 percent of the average daily background dose of CDD/CDFs from soil, air, water, and foods, as described in Chapter 4. The use of data on the total I-TEQ_{DF} content of a cigarette from Matsueda et al. (1994) results in uncertainties as to the estimate of exposure to smokers because the approach assumes that all of the dioxin in the unburned cigarette is inhaled. It is likely that some of the dioxins are released with the sidestream smoke rather than being inhaled. It is also possible that dioxins are destroyed and/or formed during the combustion process. Thus, it is unclear if these factors would lead to a net increase or decrease in the amount of dioxins inhaled. However, as described above, the I-TEQ_{DF} value reported by Matsueda et al. (1994) is less than that in mainstream (i.e., inhaled) smoke reported by Löfroth and Zebühr (1992) and greater than that of Ball et al. (1990) and provides the best estimate of CDD/CDFs in cigarettes to which smokers may be exposed.

Nonsmokers may also be exposed to CDD/CDFs from environmental tobacco smoke. Although the data on the frequency, magnitude, and duration of exposure to environmental tobacco smoke are limited, an idea of the magnitude of exposure to

CDD/CDFs can be gained by assuming that nonsmokers receive a fraction of the CDD/CDF TEQ received by smokers. Based on data for nicotine, the dose to nonsmokers exposed to environmental tobacco smoke is estimated to be 0.1 to 0.7 percent that of smokers (U.S. EPA, 1992). For 4-aminobiphenyl, nonsmokers exposed to environmental tobacco smoke were estimated to receive a dose that was 10 to 20 percent that of smokers (U.S. EPA, 1992). Assuming that nonsmokers receive 0.1 to 20 percent of the dose of CDD/CDFs from second-hand smoke that smokers receive, the estimated daily dose of CDD/CDFs for nonsmokers would range from 0.008 pg I-TEQ_{DF}/day to 1.6 pg I-TEQ_{DF}/day. It should be noted, however, that individual exposure to sidestream smoke is highly variable, depending on a person's proximity to smokers, how often they are near smokers, and the ventilation rate in these areas.

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Table 5-1. Concentrations of CDDs, CDFs, and Dioxin-Like PCBs in Blood (lipid based) of a Breast-Fed and a Formula-Fed Infant at the Age of 11 and 25 Months

Compound (conc. in pg/g fat)	Age (Months)			
	Breast-Fed Infant		Formula-Fed Infant	
	11	25	11	25
2,3,7,8-T4CDF	<2.7*	<2.5	<3.0	<2.5
2,3,7,8-T4CDD	3.7	4.1	<1.0	<1.0
1,2,3,7,8-P5CDF	<1.2	n.d. (1.4)	<1.2	n.d. (2.5)
2,3,4,7,8-P5CDF	23.1	29.7	1.5	<2.5
1,2,3,7,8-P5CDD	11.1	15.2	<1.0	n.d. (1.8)
1,2,3,4,7,8H6CDF	9.8	12.2	<2.2	<2.5
1,2,3,6,7,8-H6CDF	8.1	10.2	<1.0	<2.5
2,3,4,6,7,8-H6CDF	<3.4	<3.0	<2.3	<2.5
1,2,3,4,7,8-H6CDD	7.8	9.1	n.d (1.1)	n.d. (2.8)
1,2,3,6,7,8-H6CDD	43.0	51.7	2.5	<5.4
1,2,3,7,8,9-H6CDD	7.1	8.1	n.d. (1.2)	<4.5
1,2,3,4,6,7,8-H7CDF	13.1	n.a.	<5.8	<6.0
1,2,3,4,6,7,8-H7CDD	24.3	29.7	8.8	<10.0
OCDF	<5.0	n.a.	<5.0	n.a.
OCDD	148.7	204.0	79.3	70.0
TEQ_{DF}-WHO_{98} (<LD=0.5*LD)	29.2	36.8	2.4	2.3
PCB 77	23 (m)	20 (m)	26 (m)	20 (m)
PCB 126	287	n.a.	24	n.a.
PCB 169	270	183	7	11
TEQ_{P}-WHO_{98}	31.4	1.8	7	0.1

* for values reported as "<" a value (2.7, e.g.), ½ the concentration was used for TEQ calculations.
n.a. = not analyzed
n.d. = not detected (limit of detection)
(m) = maximum value, due to possible contribution of a contaminant

Source: Abraham et al. (1995).

Table 5-2. Concentrations of CDDs and CDFs in Adipose Tissue (lipid based) of Stillborn, Formula-Fed, and Breast-Fed Infants

Compound (conc. in pg/g fat)	Stillborn (n = 3)	Formula-Fed (n = 8)	Breast-Fed (n = 9)
2,3,7,8-TCDD	1.6	0.4	1.7
1,2,3,7,8-PCDD	3.4	1.1	4.9
1,2,3,4,7,8-HxCDD	2.5	1.0	4.0
1,2,3,6,7,8-HxCDD	8.8	4.0	19.9
1,2,3,7,8,9-HxCDD	1.3	0.7	3.7
1,2,3,4,6,7,8-HpCDD	12.9	5.0	25.2
OCDD	51.2	29.1	91.6
2,3,7,8-TCDF	1.4	1.9	1.1
1,2,3,7,8,-PCDF	0.2	1.0	0.5
2,3,4,7,8-PCDF	9.2	3.1	10.6
1,2,3,4,7,8-HxCDF	3.7	1.7	3.5
1,2,3,6,7,8-HxCDF	2.4	1.0	2.8
2,3,4,6,7,8-HxCDF	1.0	0.2	1.1
1,2,3,7,8,9-HxCDF	0.1	0.1	0.1
1,2,3,4,6,7,8-HpCDF	3.6	1.6	3.8
1,2,3,4,7,8,9-HpCDF	0.4	0.1	0.1
OCDF	2.1	1.8	1.6
TEQ_{DF}-WHO_{98}	11.9	4.3	15.9

Note: Average congener concentrations calculated assuming non-detects equal to ½ detection limit.

Source: Kreuzer et al. (1997).

Table 5-3. Parameters Used for Modeling the Impact of Nursing on Body Burden and Body Lipid Concentrations of TEQs from Infancy to Adulthood

Time After Birth	TEQ_{DFP}-WHO_{98} Concentration in Breast Milk Fat (pg/g)	Body Weight (kg)	Lipid Fraction	Half-life (yrs)	Administered Dose of Dioxin TEQ_{DFP}- WHO_{98}, pg/day[a]				
					Formula Only	6-week BF	6 Months BF	1 Year BF	2 Year BF
At birth	25	3.3	0.14	0.40	50	800	800	800	800
1 month	22.9	4.3	0.16	0.50	50	733	733	733	733
2 months	20.8	4.6	0.18	0.60	50	667 / 50	667	667	667
3 months	18.8	6.0	0.20	0.70	50	50	600	600	600
4 months	16.7	6.7	0.22	0.75	50	50	533	533	533
5 months	14.6	7.4	0.23	0.80	50	50	467	467	467
6 months	12.5	7.9	0.25	1.00	50	50	400	400	400
7 months	11.5	8.4	0.25	1.00	50	50	50	367	367
8 months	10.4	8.8	0.24	1.05	50	50	50	333	333
9 months	9.4	9.2	0.24	1.08	50	50	50	300	300
10 months	8.3	9.4	0.23	1.10	50	50	50	267	267
11 months	7.3	9.8	0.23	1.12	50	50	50	233	233
1 year	6.3	11.3	0.23	1.14	50	50	50	200	200
2 years	--	13.3	0.20	1.39	50	50	50	50	200
5 years	--	19.7	0.15	2.12	54	54	54	54	54
11 years	--	41.1	0.15	3.60	65	65	65	65	65
18 years	--	65.1	0.13	5.33	66	66	66	66	66
34 years	--	71.5	0.21	7.70	66	66	66	66	66
55 years	--	73.8	0.27	9.76	66	66	66	66	66

a Dose = TEQ_{DFP}-WHO_{98} concentration in milk fat (pg/g) x lipid fraction in milk (0.04) x ingestion rate of milk (800 g/day).

Table 5-4. Model Validation Data and Results (all concentrations in ppt TEQ_{DF}-WHO_{98} lipid basis)

Description	Observed Data				Model Predictions	
	Milk TEQ_{DF}-WHO_{98}/month	Milk TEQ_{DF}-WHO_{98}/month	Child TEQ_{DF}-WHO_{98}/month	Weeks Breast-Fed	Child TEQ_{DF}-WHO_{98} @ Selected k(t)*	Child TEQ_{DF}-WHO_{98} @ Long k(t)
1st Mother, 1st child	23.5 / 2	14.0 / 11	34.7 / 11	26	34	51
1st Mother, 2nd child	13.7 / 2	12.7 / 5	11.9 / 11	29	27	39
2nd Mother, 1st child	26.5 / 2	15.2 / 11	44.2 / 12	30	36	56
2nd Mother, 2nd child	18.3 / 2	13.1 / 6	18.8 / 12	32	27	41
3rd Mother, only child	13.7 / 2	NA	5.0 / 13	7	10	16
4th Mother, only child	12.7 / 2	13.0 / 6	26.5 / 12	30	21	32
Average, pg/g TEQ_{DF}-WHO_{98}			23.5		26	39

* Predicted child TEQ_{DF}-WHO_{98} at the time of measurement (between 11 and 13 months) using the more rapid dissipation rate, k(t), selected for this model in comparison to the slower k(t) (longer half-life of 7 years) shown in the last column.

Table 5-5. Results of PK Modeling for Formula Feeding and 4 Breast Feeding Scenarios

Description of Model Output	Formula	6-wk BF	6-mo BF	1-yr BF	2-yr BF
Peak concentration, pg TEQ_{DFP}-WHO_{98}/g lipid	13.0	34.1	44.3	44.3	44.3
Time after birth of peak	9 yr	6 wk	9 wk	9 wk	9 wk
AUC[1] after 1 year	2,168	5,989	12,129	13,645	13,645
AUC after 10 years	39,433	46,516	62,696	73,183	86,370
AUC after 70 years	27,5419	282,654	299,304	310,210	324,202
AUC (bf) / AUC (formula)[2] - 1 yr	---	2.8	5.6	6.3	6.3
AUC (bf) / AUC (formula) - 10 yr	---	1.2	1.6	1.9	2.2
AUC (bf) / AUC (formula) - 70 yr	---	1.03	1.09	1.13	1.18

[1] AUC = measure of accumulated exposure defined as, "area under the curve", equal to lipid-concentration, ppt TEQ_{DFP}-WHO_{98} * days. For example, a lifetime at 10 ppt TEQ_{DFP}-WHO_{98} lipid would yield an AUC of 10 ppt TEQ_{DFP}-WHO_{98} * 70 years * 365 d/yr = 255,500 ppt TEQ_{DFP}-WHO_{98}-day.

[2] AUC (bf) / AUC (formula) = ratio comparing the accumulated exposure difference between the breast-feeding scenario and the formula. A result of 6.0 means that the accumulated exposure for the breast-feeding scenario being evaluated is 6 times more than a formula only scenario.

Table 5-6. Sensitivity Analysis Testing of PK Model for Breast-Milk Impacts[3]

Description of Model Output	6-mo baseline	Dissipation Tests		Dose Tests		Extremes	
		Sc #1	Sc #2	Sc #3	Sc #4	Sc #5	Sc #6
Peak concentration, pg TEQ_{DFP}-WHO_{98}/g lipid	44.3	49.8	44.3	48.1	28.5	54.0	28.5
Time after birth of peak	9 wk	9 wk	9 wk	9 wk	9 wk	10 wk	9 wk
AUC[1] (sa) / AUC (6-mo)[2] - 1 yr	—	1.3	1.0	1.2	0.6	1.6	0.6
AUC (sa) / AUC (6-mo) - 10 yr	---	2.2	0.8	1.1	0.8	2.6	0.7
AUC (sa) / AUC (6-mo) - 70 yr	---	1.4	0.7	1.03	0.96	1.5	0.6

[1] AUC = measure of accumulated exposure defined as, "area under the curve", equal to lipid-concentration, ppt TEQ_{DFP}-WHO_{98} * days. For example, a lifetime at 10 ppt TEQ_{DFP}-WHO_{98} lipid would yield an AUC of 10 ppt TEQ_{DFP}-WHO_{98} * 70 years * 365 d/yr = 255,500 ppt TEQ_{DFP}-WHO_{98}-day.

[2] AUC (sa) / AUC (6-mo) = ratio comparing the accumulated exposure difference between the sensitivity analysis scenario and the 6-month breast-feeding baseline scenario. A result of 6.0 means that the accumulated exposure for the sensitivity analysis scenario being evaluated is 6 times more than the 6-month baseline scenario.

[3] Scenario definitions:

Sc #1: Use of the Pinsky and Lorber (1998) lipid-based function for dissipation rate
Sc #2: Use of the Kreuzer, et al. (1997) modeled dissipation rate
Sc #3: Assumption of mother's milk concentration not declining from 25 ppt TEQ_{DFP}-WHO_{98} lipid
Sc #4: Assumption of mother's milk concentration beginning at 15 ppt TEQ_{DFP}-WHO_{98}, declining to 7.5 ppt TEQ_{DFP}-WHO_{98} after 6 months.
Sc #5: Use of Pinsky and Lorber (1998) lipid-based function for dissipation rate and the assumption of mother's milk concentration not declining from 25 ppt TEQ_{DFP}-WHO_{98} lipid.
Sc #6: Use of Kreuzer, et al. (1997) modeled dissipation rate and the assumption of the mother's milk concentration beginning at 15 ppt TEQ_{DFP}-WHO_{98}, declining to 7.5 ppt TEQ_{DFP}-WHO_{98} after 6 months.

Table 5-7. Estimated CDD/CDF/PCB Exposures for Adult Subsistence Fishermen

Media	Conc. TEQ_{DFP}-WHO_{98}[a]	Contact Rate[b]	Daily Intake (pg/kg-day)[c]
Soil ingestion	11.6 ppt[e]	50 mg/day	8.2×10^{-3}
Soil dermal contact	11.6 ppt	12 g/day[f]	1.9×10^{-3}
Freshwater fish ingestion	2.2 ppt[g]	59 to 170 g/day	$1.9 \text{ to } 5.3 \times 10^{+0}$
Marine fish ingestion	0.51 ppt[g]	12.5 g/day	9.1×10^{-2}
Inhalation	0.12 pg/m^3	13.3 m^3/day	2.3×10^{-2}
Water ingestion	0.00056 ppq	1.4 L/day	1.1×10^{-5}
Milk ingestion	0.027 ppt	175 g/day	6.8×10^{-2}
Dairy ingestion	0.18 ppt	55 g/day	1.4×10^{-1}
Vegetable fat ingestion	0.093 ppt[e]	17 g/day	2.2×10^{-2}
	Total		$2.2 \text{ to } 5.7 \times 10^{+0}$ [d]

[a] Values from Table 3-64.

[b] Values for adult soil ingestion, inhalation, water ingestion, and subsistence fish ingestion from Exposure Factors Handbook (U.S. EPA, 1997). Contact rates for milk, dairy, and vegetable fats are based on data from USDA (1995).

[c] Daily intake (mg/kg-day) = [Contact rate (g/day; m^3/day; L/day; mg/day) x Conc. TEQ x Unit Conversion (soil unit conversion = 10^{-3}, all other media no unit conversion needed)/Body Weight (kg)] or Contact rate (g/kg-day) x Conc. TEQ x Unit Conversion.

[d] Approximately equivalent to 77 to 186 pg/day, assuming an adult body weight of 70 kg.

[e] Calculated by setting nondetects to zero.

[f] Calculated as the surface area of the body that contacts the soil (5,700 cm^2/day) x the rate that soil adheres to the skin (0.07 mg/cm^2) x the fraction of CDD/CDFs absorbed through the skin (0.03); exposure factors based on recommendations in U.S. EPA (1999) for an adult resident, which assumes that the lower legs, forearms, hands, and head are exposed to the soil.

[g] This concentration is a species-specific ingestion-weighted average value.

Table 5-8. Levels of Different PCB Congeners in Blood Samples from Three Groups of Men with Different Fish Consumption Habits

Congener (UIPAC)	Fish Intake					
	None		Moderate		High	
	Plasma (n = 9)	Lipid (n = 8)	Plasma (n = 14)	Lipid (n = 7	Plasma (n = 14)	Lipid (n = 11)
Non-ortho-PCBs						
77 (pg/g)[a]	0.04 (0.01-0.09)	15 (3-38)	0.1[b] (9.03-0.2)	41[b] (26-62)	0.2[b,c] (0.1-0.5)	50[b] (15-140)
126 (pg/g)	0.73 (0.3-1.2)	220 (100-450)	1.05 (0.6-2.4)	400[b] (210-650)	2.8[b,c] (1.2-4.9)	790[b,c] (380-1400)
169 (pg/g)	0.65 (1.3-1.5)	200 (100-340)	0.86 (0.4-1.7)	250 (170-360)	1.80[b,c] (0.3-3.6)	570[b,c] (210-1200)
Mono-ortho-PCBs						
105 (ng/g)	0.02 (0-0.03)	5 (0-13)	0.04 (0.02-0.07)	14[b] (9-20)	0.14[b,c] (0.04-0.3)	39[b,c] (18-77)
118 (ng/g)	0.12 (0.05-0.21)	41 (17-92)	0.21 (0.12-0.43)	76 (45-120)	0.58[b,c] (0.21-1.00)	160[b,c] (84-300)
156 (ng/g)[d]	0.13 (0.05-0.34)	40 (19-68)	0.14 (0.07-0.28)	44 (30-64)	0.3[b,c] (0.05-0.7)	90[b,c] (36-180)
157 (ng/g)[d]	0.02 (0.01-0.05	6.6 (2.8-11)	0.02 (0.01-0.05)	7.8 (5.4-11)	0.06[b,c] (0.01-0.14)	18[b,c] (7.4-39)
Di-ortho- and other PCBs						
180 (ng/g)[e]	1	400	1	400	2	600

Notes: Means and ranges indicated on plasma and lipid basis.

[a] Near the detection limit.
[b] $p < .05$, compared with group "none."
[c] $p < .05$, compared with group "moderate."
[d] Quantified, using single-response factors.
[e] CB-180 quantified from two fractions, concentrations thus estimated.

Source: Asplund et al. (1994).

Table 5-9. Mean TEQ Levels in Pooled Serum Samples

	$I\text{-}TEQ_{DF}$ (ppt, lipid basis)	$TEQ_P\text{-}WHO_{94}$ (ppt, lipid basis)
Cornwall		
Sports Fishers		
<38 years, lower	20.8	--
higher	22.2	3.6
38 years, lower	28.4	3.1
higher	31.4	9.5
> 50 years, higher	33.5	17.3
Nonfish Eaters		
<38 years	24.7	2.6
38-50 years	29.8	6.8
>50 years	36.8	9.7
Mississauga		
Sports Fishers		
<38 years	32.4	--
38-50 years	40.1	--
>50 years	41.2	--
Nonfish Eaters		
<38 years	34.0	--
38-50 years	29.1	--
>50 years	34.3	--

Source: Adapted from Cole et al. (1995).

Table 5-10. Mean CDD/CDF Levels in Serum of Consumers of Great Lakes Sport Fish (ppt, lipid adjusted)

	All Sport Fish Consumer Subjects (ppt) (n = 31)[a]	Lake Michigan Participants (ppt) (n = 9)	Lake Huron Participants (ppt) (n-11)	Lake Erie Participants (ppt) (n = 11)	Comparison Group[a] (ppt) (n = 70)
CDD Congeners					
2,3,7,8-TCDD	5.6	4.7	10.5	4.9	2.8
1,2,3,7,8-PeCDD	10.4	9.8	16	5.8	5.5
1,2,3,4,7,8-HxCDD	8.4	11.4	8.4	5.5	9.0
1,2,3,6,7,8-HxCDD	126	120	142	115	70.8
1,2,3,7,8,9-HxCDD	7.0	8.7	5.5	5.8	8.4
1,2,3,4,6,7,8-HpCDD	134	144	153	95.9	124
1,2,3,4,6,7,9-HpCDD		ND	ND		4.4
OCDD	777	783	918	623	971
Total	1,062	1,087	1,258	844	1,188
Total I-TEQ_D	27.5	25.8	36	20.7	15.5
CDF Congeners					
2,3,7,8-TeCDF	2.2	2.4	2.1		2.1
1,2,3,7,8-PeCDF	2.0	ND	1.7	ND	1.6
2,3,4,7,8-PeCDF	17.7	20.4	22.8	10.4	5.5
1,2,3,4,7,8-HxCDF	12.7	11.6	16.0	10.2	8.0
1,2,3,6,7,8-HxCDF	9.0	8.0	10.5	7.7	5.3
1,2,3,7,8,9-HxCDF	ND	ND	ND	ND	1.8
2,3,4,6,7,8-HxCDF	5.1	6.0	4.8	8.0	3.8
1,2,3,4,6,7,8-HpCDF	20.0	22.1	22.9	15.2	21.3
1,2,3,4,7,8,9-HpCDF	ND	ND	ND	ND	NA
OCDF		ND		ND	6.9
Total	58.2	70.8	79.3	48.3	87.3
Total I-TEQ_F	11.9	13.2	14.8	7.8	4.9

a One individual was excluded from the data summary due to unusually high occupational/environmental exposures.

b Comparison group is from a 1991 unpublished NCEH/CDC data set of a Jacksonville, Arkansas, population of 70 individuals.

Source: Anderson et al. (1998).

Table 5-11. Mean PCB Levels in Serum of Consumers of Great Lakes Sport Fish (ppt, lipid adjusted)

	All Sport Fish Consumer Subjects[a] (ppt) (n = 31)	Lake Michigan Participants (ppt) (n = 9)	Lake Huron Participants (ppt) (n-11)	Lake Erie Participants (ppt) (n = 11)	Comparison Group[b] (ppt) (n = 70)
Coplanar PCB Congeners					
77	14.6	16.5	14.2	13.3	12.6
81	13.5	17.4	13.2		8.6
126	148	261	187	28	18.4
169	80.8	113	84.2	48.4	17.9
Coplanar PCB Total	228	340	282	75.4	57.4
$I\text{-}TEQ_P\text{-}WHO_{94}$	17.4	26	23	4.8	1.8
Congener-Specific PCBs					
28	0.08	0.08	0.1	0.08	ND
52	0.01	ND	0.01	ND	ND
56	0.02	0.06	ND	ND	ND
58	0.04	0.08	0.04	0.01	ND
74	0.3	0.6	0.4	0.2	0.009
99	0.4	0.7	0.5	0.1	ND
101	ND	0.01	ND	ND	ND
1.5	0.1	0.2	0.1	0.02	0.4
118	0.4	0.8	0.5	0.08	0.03
130	0.1	0.2	0.1	0.02	NA
138	0.8	1.3	0.8	0.4	0.4
146	0.2	0.3	0.2	0.04	ND
153	1.1	1.7	1.1	0.6	0.4
156	0.02	0.04	0.02	ND	NA
157	0.1	0.2	0.1	0.08	NA
187	0.03	0.07	0.03	ND	ND
170	0.1	0.2	0.2	0.07	ND
172	0.02	0.05	0.03	ND	ND
177	0.04	0.09	0.06	ND	ND
178	0.07	0.13	0.08	0.03	ND
180	0.4	0.8	0.4	0.2	0.4
183	0.1	0.2	0.1	0.03	ND
187	0.3	0.4	0.3	0.08	0.04
189	ND	ND	ND	ND	NA
193	0.03	0.08	0.02	ND	NA
194	0.09	0.1	0.1	0.05	0.004
195	0.04	0.07	0.06	ND	ND
201	0.2	0.3	0.2	0.09	0.04
203/196	0.09	0.2	0.11	0.03	0.007
206	0.07	0.08	0.08	0.04	ND
209	0.02	0.03	0.04	ND	NA
Total	5.2	8.6	5.7	2.2	1.2

a One individual was excluded from the data summary due to unusually high occupational/environmental exposures.
b Comparison group from a 1996 unpublished data set of 41 non-Great Lake sport fish consumers analyzed by the Wisconsin State Laboratory of Hygiene.

Source: Anderson et al. (1998).

Table 5.12. Average PCB and CDD/F TEQ-WHO_{98} Concentrations (all concentrations in pg/g whole weight)

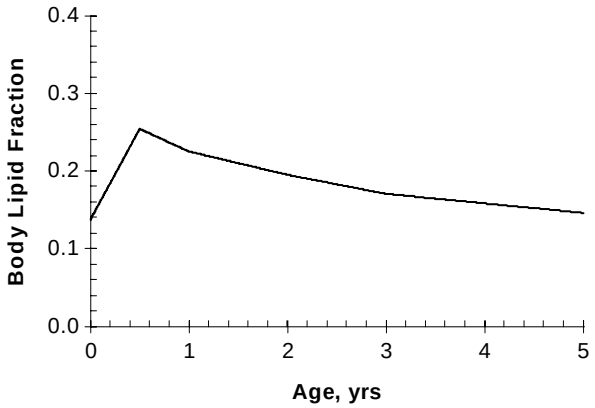
Main Water Body	Location	Species	$TEQ_P WHO_{98}$	TEQ_{DF}-WHO_{98}	TEQ_{DPF}-WHO_{98}
Lake Superior	Black Bay	Lake Trout (5)	9.4	0.68	14
	Jackfish Bay	Lake Trout (5)	13	5.3	2.5
	Peninsula Harbour	Lake Trout (5)	9.5	2.8	3.3
	Algoma Area	Lake Trout (5)	83	23	3.7
	Algoma-Agawa Bay	L. Whitefish (5)	4.5	5.4	0.83
	Goulais Bay	L. Whitefish (5)	4.1	1.8	2.3
Lake Huron	Manitoulin Island	L. Whitefish (5)	1.4	0	>1.4
	Nottawassaga River	Chinook (5)	14	0.94	15
	Nottawasaga River	Rainbow Trout (5)	6.9	0	>6.9
	Tobermory	L. Trout (5)	21	3.5	5.9
	Oliphant/Fishing Is.	L. Trout (5)	12	0.75	17
	Oliphant/Fishing Is.	L. Whitefish (5)	4.4	2.7	1.7
	Bruce Cty	Carp (5)	31	2.1	14
	Grand Bend	L. Trout (5)	22	0.76	29
Lake Erie	Western Basin	Ch. Catfish (5)	55	8.1	6.8
Niagara River	Niagara River Bar	Lake Trout (5)	79	22	3.5
	Niagara River Bar	Chinook (5)	52	12	4.4
	Niagara River Bar	Brown Trout (5)	21	4.6	4.5
	Niagara River	White Perch (5)	6.2	3.2	1.9
	Niagara River	Rainbow Trout (5)	22	4.8	4.6
	Niagara River	White Bass (4)	1.6	0	>1.6
Lake Ontario	Welland River	Carp (5)	11	0.13	86
	Hamilton Harbour	Carp (5)	25	1.9	13
	Hamilton Harbour	Ch. Catfish (5)	58	6.7	8.7
	Bronte Creek	Brown Trout (5)	56	8.3	6.7
	Port Credit	Lake Trout (4)	72	19	3.8
	Credit River	Brown Trout (5)	41	10	4.1
	Credit River	Chinook (5)	39	8.7	4.5
	Don River	White Sucker (5)	16	4.4	3.6
	Whitby Harbour	Carp (5)	27	40	0.66
	Whitby/Pickering	Chinook (5)	29	6.8	4.3
	Cobourg	L. Trout (5)	67	26	2.6
	Trent River	Chinook (5)	182	59	3.1
	Trent River - 4	L. Whitefish (5)	52	5.8	9.0
	Upper Bay of Quinte	Whitefish (5)	8.7	7.0	1.2
	L. Bay of Quinte	L. Trout (5)	110	29	3.8
	Cataraqui River	Carp (5)	57	4.7	12
Northern Areas	Mattagami River	White Sucker (5)	21	0	>21
	Cochrane	White Sucker (5)	21	0	>21

Source: Kolic et al. (2000).

Table 5-13. Comparison Between Mean PCB Levels in Fish-eating Populations and Controls

PCBs	Fishermen		Controls	
	Mean Concentration (ppt, lipid basis)	TEQ_P-WHO_{94} (ppt, lipid basis)	Mean Concentration (ppt, lipid basis)	TEQ_P-WHO_{94} (ppt, lipid basis)
126	1540	154	48	4.8
169	1010	10.1	29	0.29
118	568	56.8	25.4	2.54
170	539	53.9	27.7	2.77
180	1776	17.76	48.2	0.48
TOTAL TEQ_P-WHO_{94}	--	292.6	--	10.9

Source: Adapted from Dewailly et al. (1994).


Body Lipid Fraction
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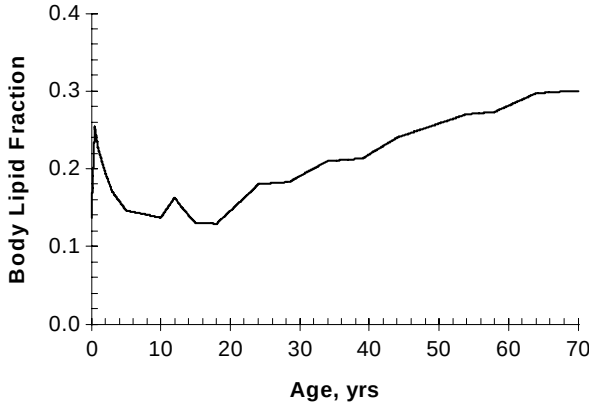
0.3
0.2
0.1
0.0
0
1
2
3
4
5
Age, yrs


Body Lipid Fraction
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0.2
0.1
0.0
0
10
20
30
40
50
60
70
Age, yrs

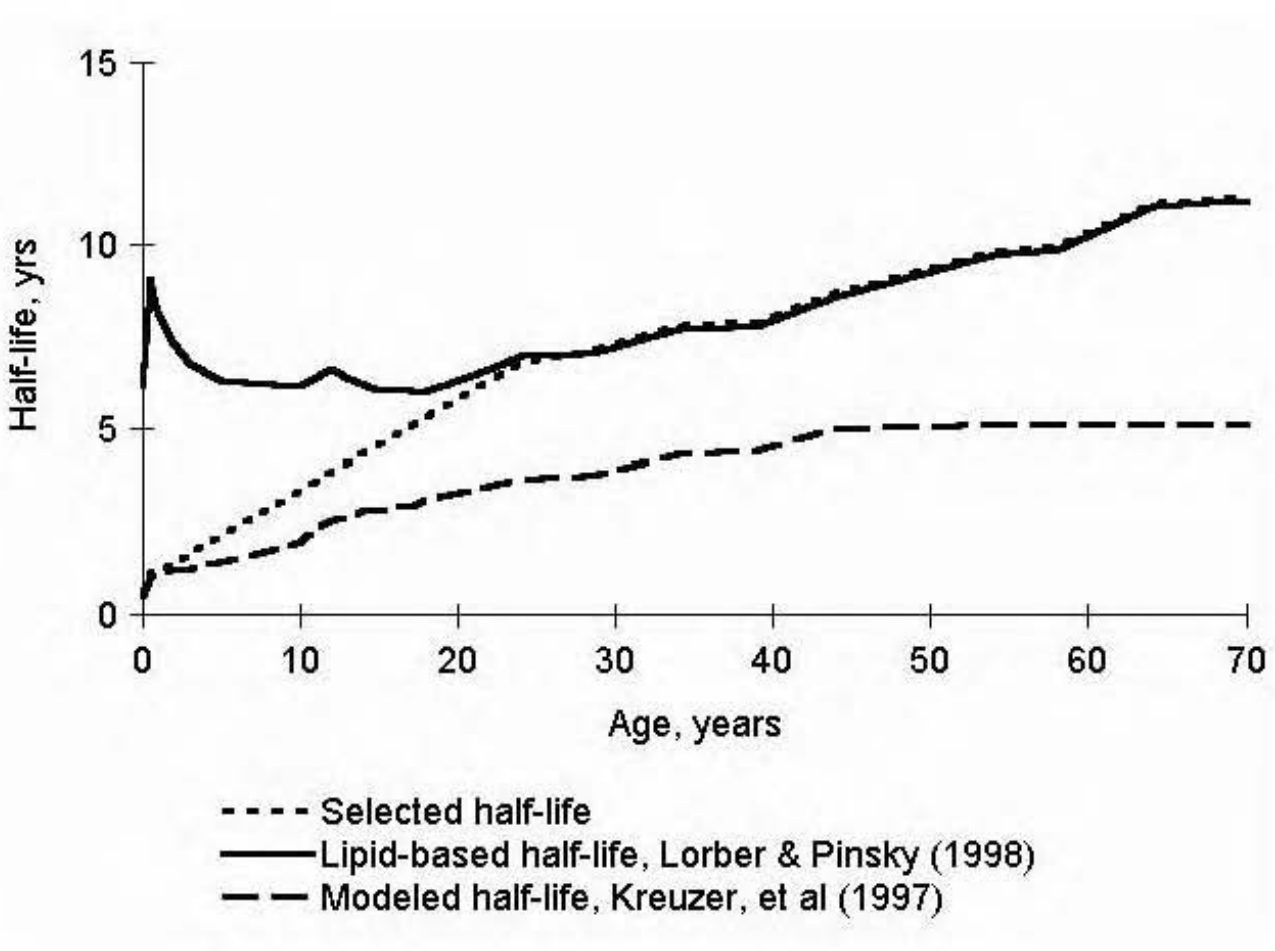
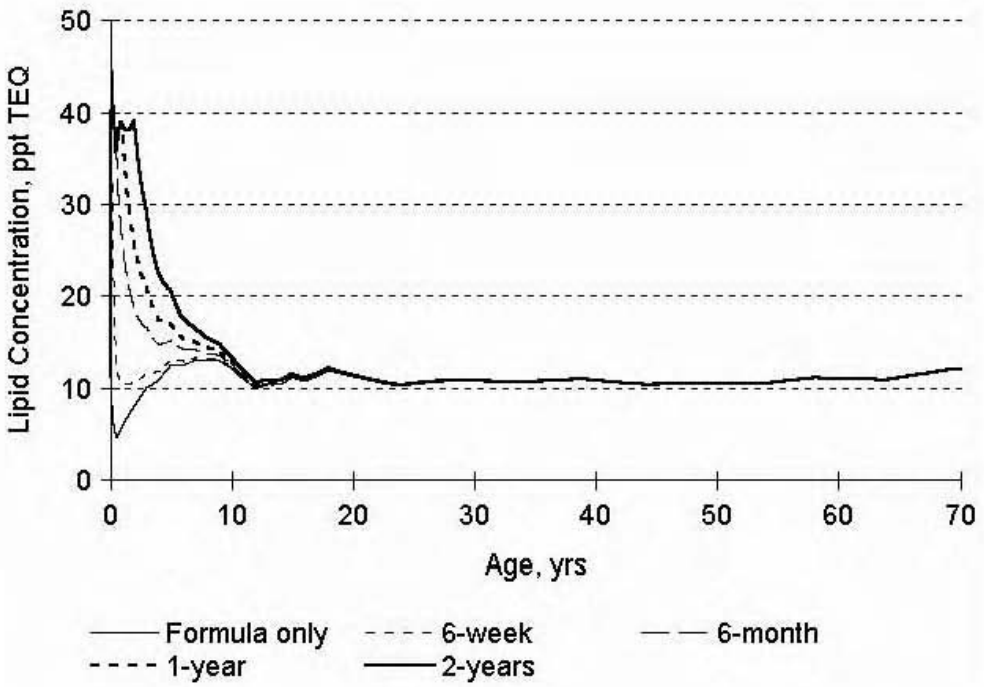


Figure 5-2. Comparison of the selected half-life of TEQs in the body with two options that were available in the literature for 2,3,7,8-TCDD.

(A)



(B)

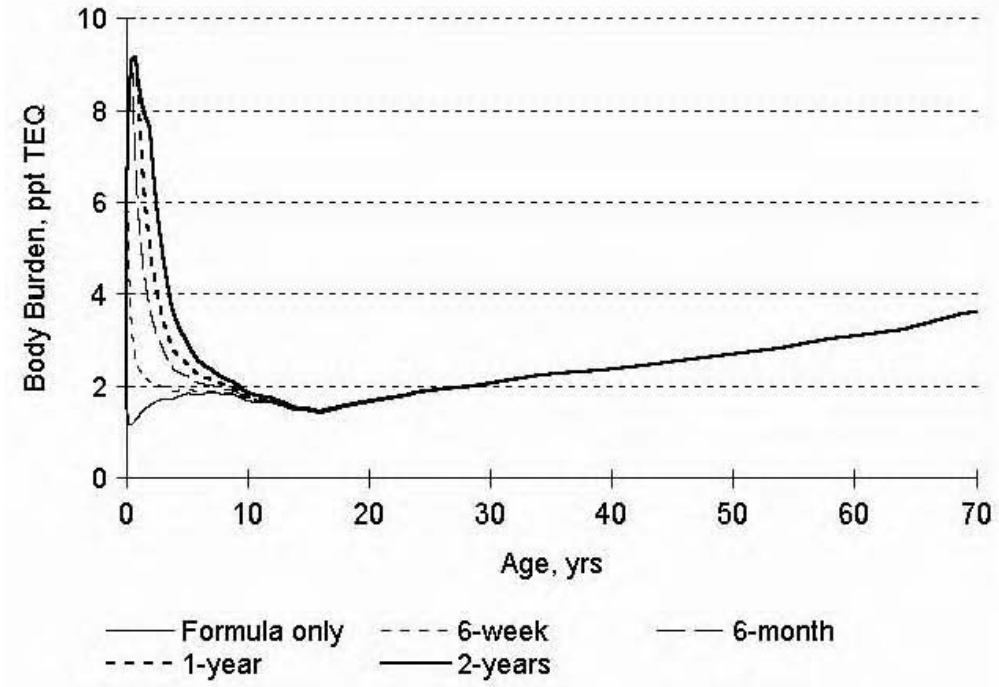
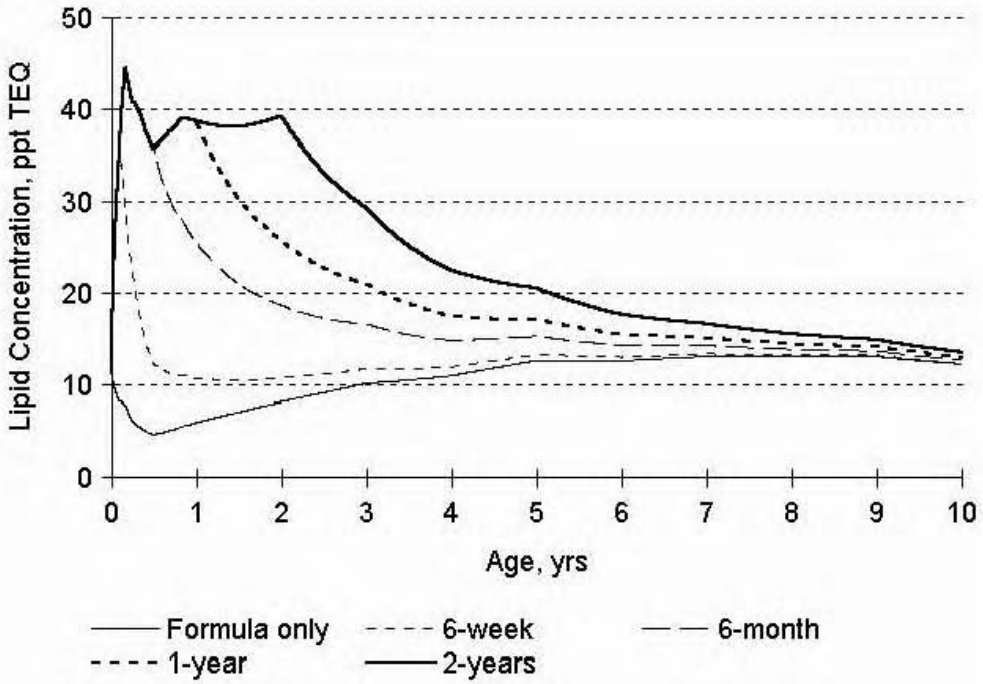


Figure 5-3. Demonstration of the model for evaluating impacts on lipid concentrations (A) and body burdens (B) of infants resulting from various nursing scenarios during a lifetime.

(A)



(B)

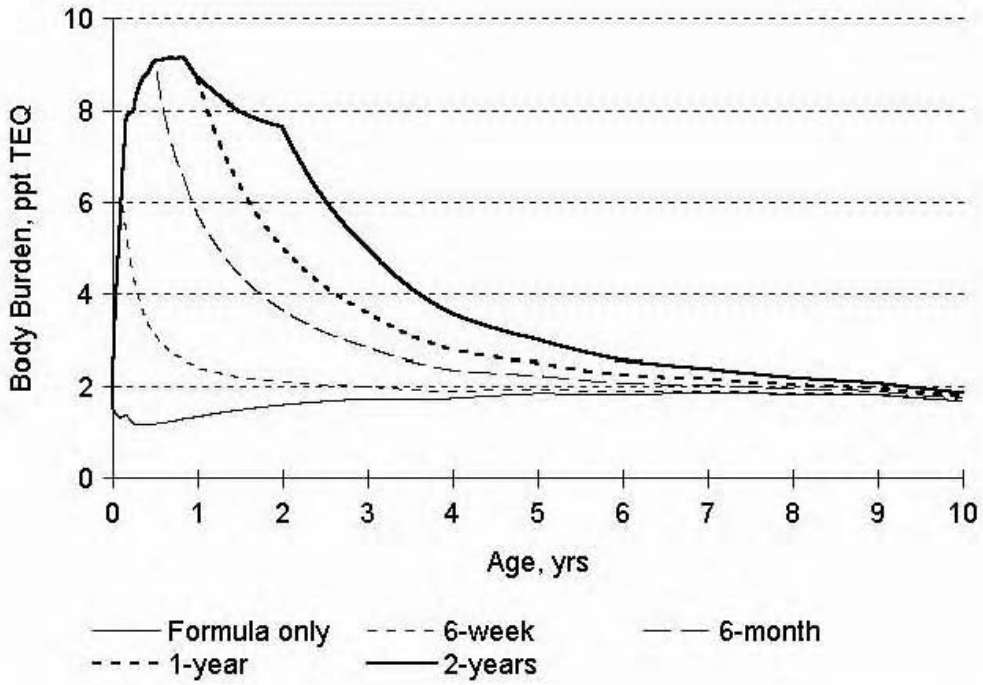
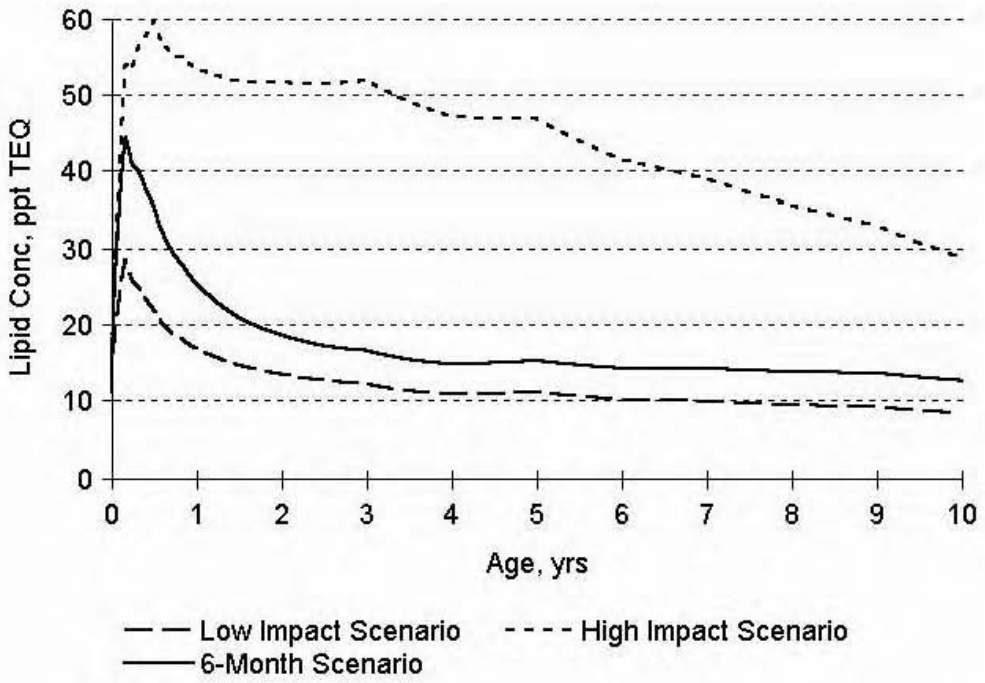


Figure 5-4. Demonstration of the model for evaluating impacts on lipid concentrations (A) and body burdens (B) of infants resulting from various nursing scenarios during the first 10 years of life.

(A)



(B)

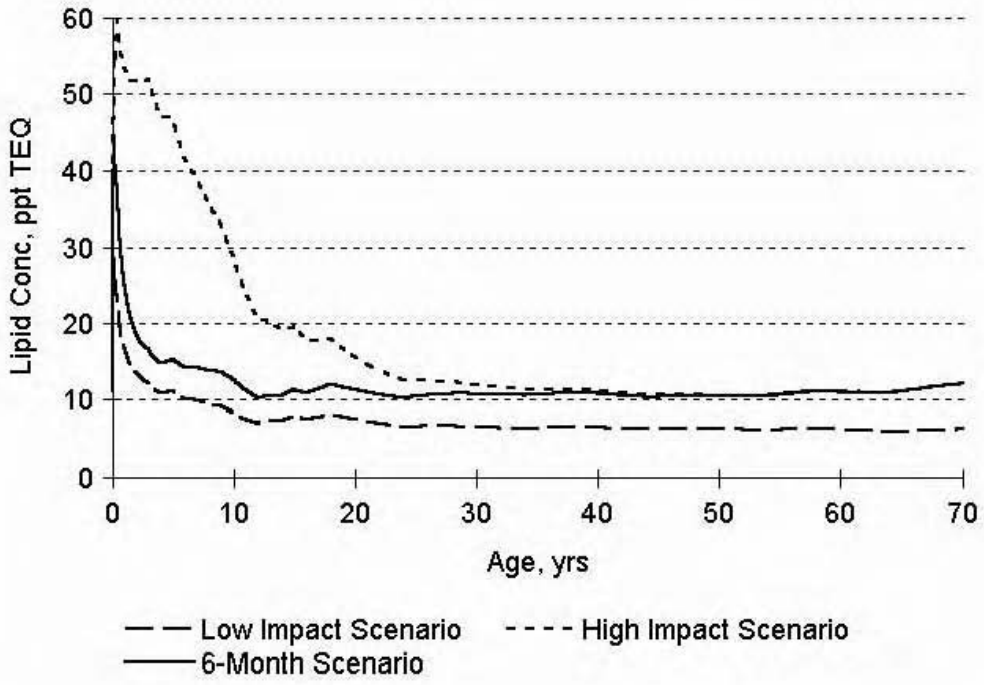


Figure 5-5. Results of sensitivity analysis showing the difference when making modeling assumptions that lead to a high impact to the infant (high impact scenario) and to a low impact to the infant (low impact scenario) as compared to the baseline scenario for a 6-month breast-feeding scenario (6-month scenario).

6. TEMPORAL TRENDS

6.1. INTRODUCTION

Small amounts of dioxin-like compounds may be formed during natural fires, suggesting that these compounds may have always been present in the environment. However, it is generally believed that greater amounts of these compounds have been produced and released into the environment in association with human industrial and combustion practices. As a result, environmental levels are likely to be higher in modern times than in earlier times. The trend of increasing levels may now be reversing (i.e., releases and environmental levels may be gradually decreasing), however, with changes in industrial practices. As discussed in Volume 1, the potential for environmental releases of dioxin-like compounds has been reduced as a result of the switch to unleaded automobile fuels and associated use of catalytic converters and reduction in halogenated scavenger fuel additives (remaining uses of leaded fuel include chain saws, logging machinery, and mowers), process changes at pulp and paper mills, improved emission controls for incinerators, and reductions in the manufacture and use of chlorinated phenolic intermediates and products.

This chapter describes trends in the levels of dioxin-like compounds that have been observed in various environmental media and foods, as well as evidence of downward trends in exposure to dioxin-like compounds in humans. The downward trend in human exposure is supported by a modeling exercise that reconstructs the most likely past doses of dioxin-like compounds contributing to observed body burdens. Reviews of several studies and the modeling exercise are followed by several observations with regard to temporal trends of dioxin-like compounds.

6.2. SEDIMENT CORE STUDIES OF TEMPORAL TRENDS

Questions regarding the contribution made by natural sources to the overall environmental burden of CDDs and CDFs can be partially addressed using the results from analyses of the temporal distribution of CDD/CDFs in sediment core samples. Sediment cores provide a historical record of contaminant inputs into the environment and have been used by several researchers to study temporal trends in CDD/CDF deposition. Studies at various sites in the United States and Europe suggest that environmental

concentrations of CDD/CDFs began to increase rapidly in the 1930s and peaked around the 1970s.

Czuczwa and Hites (1984) analyzed sediment core samples taken in Lake Huron by the University of Michigan's Great Lakes Research Station. Sedimentation rates within the core samples were determined using Cs-137 and Pb-210 techniques. Those rates were used as a basis for relating depth of core sample to time of deposition. CDD/CDFs were detected in the core samples with no appreciable degradation over time. The most abundant CDD/CDFs were OCDDs and HpCDD/CDFs. Analysis of sample depth showed that the concentration of CDD/CDFs increased steadily beginning in approximately 1940 and leveled off around 1960. Correlations were observed over time between the levels of CDDs and CDFs in the sediment cores and the total volume of synthetic chloro-aromatics produced by the petrochemical industry in the United States. However, coal consumption did not show a good correlation with CDD/CDF concentrations over time. Czuczwa and Hites (1984) concluded that the history of sedimentation rates of CDD/CDFs in core samples from Lake Huron reflected of atmospheric deposition from the combustion of synthetic chloro-aromatics.

In a similar study, Czuczwa et al. (1985a) reported on the temporal variability of CDD/CDFs in sediment core samples taken from a wilderness lake, located in an uninhabited and undeveloped island (Siskiwit Lake, Isle Royale) in Lake Superior. The only mechanism of contaminant input into the lake was believed to be atmospheric transport and deposition. The historical record of CDD/CDF concentration in the core samples showed that CDD/CDFs were virtually absent from the sediments until around 1940. All CDD/CDF homologue groups were detected in sediment samples near the surface, with HpCDDs and OCDDs accounting for the highest percentage of total CDD/CDFs. Comparisons were made between the congener profiles found in the lake sediments and congener profiles found in urban air particles. A correlation coefficient of 0.997 was observed, leading to the conclusion that CDD/CDFs entered the lake system from aerial transport and deposition.

Smith et al. (1992, 1993) analyzed sediment core layers from Green Lake, located near Syracuse, New York, to determine temporal trends in the deposition of CDDs and CDFs since the beginning of the industrial era (circa 1860). This deep lake (200-foot depth) is thought to be affected only by atmospheric deposition because no industrial

inputs are present and motorboats are not allowed. Relatively low concentrations of CDDs and CDFs (10 pg/g or less) were observed in sediments deposited from 1860 to 1930. However, concentrations increased rapidly thereafter, reaching a peak in the mid-1960s when total CDD concentrations exceeded 1,300 pg/g and total CDF concentrations exceeded 250 pg/kg. The concentrations of CDDs and CDFs have declined rapidly since the mid-1960s and, in 1986–1990, were measured at 750 pg/g as total CDD/CDF. In the most recent samples, HpCDD and OCDD dominated the mixture of CDD/CDFs. This observation is consistent with that of Czuczwa et al. (1985a). The authors speculated that the decline in CDD/CDF concentrations over time may be due to the switch to unleaded fuels for vehicles.

Sediment cores from the Hudson River were analyzed by Smith et al. (1995). The results indicated that the subsurface sediment layers, dated between 1950 and 1980, had the highest concentrations of CDD/CDFs. OCDD, HpCDF, and OCDF accounted for the highest percentage of total CDD/CDFs in these cores. Pearson et al. (1995) studied sediment cores collected from the Great Lakes (i.e., Lakes Superior, Michigan, and Ontario) and remote inland lakes. The researchers calculated CDD/CDF accumulation rates as the product of concentration (pg/g) and sedimentation rate (g/cm^2-yr). The results of this study indicated that CDD/CDF accumulation began in the 1930s–1940s and peaked in the early to mid-1970s. Lake Ontario (350 to 575 pg/cm^2-yr) and Lake Michigan (25 to 100 pg/cm^2-yr) were found to have higher CDD/CDF accumulation rates than Lake Superior and the remote inland lakes (5 to 10 pg/cm^2-yr). CDD/CDF profiles for these lakes indicated that OCDD dominated. However, the homologue profile for Lake Ontario differed from the other lakes, leading the authors to speculate that different nonatmospheric sources were responsible for the CDD/CDFs found in this lake. MacDonald et al. (1992) observed similar temporal results in Canada. MacDonald et al. (1992) observed that OCDD and PCB-77 concentrations in sediments collected from the Strait of Georgia, British Columbia, began to increase in about 1940, reaching a maximum in about 1970. However, 2,3,7,8-TCDF concentrations did not begin to increase until about 1965 as a result of discharges of chlorine bleach effluent from local pulp mills.

Lebeuf et al. (1995) observed decreasing dioxin-like PCB (i.e., PCBs 77, 126, and 169) trends in sediments from the Lower Estuary and Gulf of St. Lawrence, Canada. Two sediment cores were collected from sites approximately 50 km apart and sliced into 25

samples. PCB concentrations were found to increase with increasing depth. These results indicate that recent inputs to this water body have decreased substantially (Lebeuf et al., 1995).

Rappe et al. (1997) analyzed sediment core samples from five lakes in southern Mississippi. The sediment cores were collected from five man-made recreational lakes with no known industrial point source of CDD/CDFs and low atmospheric deposition rates. Cores were subdivided into sections to evaluate temporal trends in deposition of CDD/CDFs. No observable trend for levels of CDDs, homologues, or I-TEQs correlating to the age of the strata could be identified.

Recently, EPA/DOE conducted a time-trend study of dioxin-like compounds in sediment cores (Cleverly et al., 1996; Versar, 1996). Cores from 11 lakes/reservoirs were collected, sectioned, and dated using ^{137}Cs and ^{210}Pb dating techniques, and analyzed for CDD/CDFs and PCBs. The lakes were located in various geographic locations throughout the United States (10 within the continental United States and 1 in Arctic/Alaska) and were selected to represent background conditions (i.e., no known CDD/CDF sources). For several of the lakes, dated samples were available for time periods ranging from the 1700s to the present. The results of the study indicated that CDD/CDF and PCB inputs to U.S. lakes have increased over time, with significant increases occurring after the 1930s. This is consistent with the findings of other researchers. In general, a minimum of one order of magnitude increase in concentration occurred from the pre- to post-1930s timeframe. With few exceptions, this observation was consistent for all 2,3,7,8-substituted CDD/CDF congeners, CDD/CDF homologue groups, and PCBs. The observed temporal trends were consistent across lakes (except the Arctic/Alaska lake), especially for lakes within the same geographic region. For some lakes, a downward trend appeared to exist for the most recent periods. The point of inflection for this downward trend varied across lakes, but appeared to occur between the 1950s and 1970s. Figure 6-1 depicts the changes in concentration over time for Beaver Lake, Washington. The data also indicate that the CDD/CDF and PCB profiles in these lakes were similar across all periods and across all lakes. This may suggest that the relative congener-specific inputs from the atmosphere have remained consistent over time and are similar across all geographic regions. Relationships also were observed between CDD/CDF and PCB trends and indicators of anthropogenic activities (i.e., PCP production, leaded gasoline sales, carbon monoxide

emissions, and PCB releases) that may be associated with production of CDD/CDFs or PCBs. However, it should be noted that correlations between these variables do not necessarily reflect causal relationships.

Several studies have also evaluated sediment cores from European lakes. Czuczwa et al. (1985b) studied temporal trends in three Swiss lakes (Lakes Zurich, Lugano, and Baldegg). No CDD/CDFs were detected in the sediments prior to 1945, but increasing levels were observed in subsequent time periods. The most abundant congeners found in the uppermost sediment samples were OCDD, HpCDD/CDFs, and OCDF. Using sedimentation rates and CDD/CDF surface sediment concentrations, the estimated accumulation rates were 300 pg/cm^2-yr for Lake Zurich, 270 pg/cm^2-yr for Lake Lugano, and 190 pg/cm^2-yr for Lake Baldegg. The authors noted that the similarities in congener profiles and fluxes of CDD/CDF in Switzerland and the United States may be indicative of similar sources of CDD/CDFs. Similar trends were noted by Beurskens et al. (1993, 1994). These researchers evaluated sediment cores from Lake Ketelmeer, a sedimentation area of the Rhine River in The Netherlands. CDD/CDF concentrations were shown to increase after the 1940s and peak between 1960 and 1980. Similar results were obtained for coplanar PCBs.

Sediment cores from two lakes in the Black Forest region of Germany were analyzed for temporal trends in CDD/CDF deposition by Schramm et al. (1994). CDD/CDFs were found to have increased by a factor of 13 since the 1930s. Recently, Hagenmaier and Walczok (1996) evaluated CDD/CDF levels in dated sediment core samples collected from Lake Constance, Germany. Cores were collected in December 1995 and April 1996. Based on a preliminary dating scheme, the results indicated that the I-TEQ$_{DF}$ concentrations for these samples began increasing around 1940, reached their peak around 1970 to 1975, and then began decreasing. The homologue profiles for the 1940s sediments were similar to those in recent deposition samples.

Using dated sediment core analyses, Alcock et al. (1997a) reported that CDD/CDF concentrations in a remote lake in Scotland began increasing in the 1860s and 1870s and peaked in the 1950s and 1960s. According to Alcock et al. (1997a), concentrations appear to have decreased in recent years. Brzuzy and Hites (1995) reported on changes over time in the CDD/CDF homologue profile for Lake Windermere in the United Kingdom. CDFs accounted for a significant fraction of the total CDD/CDF concentration in sediment

core sections dated 1946–1950. In contrast, sections dated 1988-1992 had a significantly lower fraction of CDFs, and the profile was dominated by OCDD and HpCDD. These results provide evidence that the sources of CDD/CDF deposition have changed over time, with CDFs accounting for a much higher percentage of inputs during the earlier period.

Sediment core samples from the Baltic Proper, near Sweden, showed detectable levels of CDD/CDFs dating back as early as 1882 (Kjeller and Rappe, 1994). CDD/CDFs increased slowly in the sediment strata dated between 1882 (92 pg/g) and 1962 (233 pg/g) and then increased rapidly in the 1970s. Total CDD/CDFs were estimated to be 520 pg/g in 1970 and 1,803 pg/g in 1978. CDD/CDFs decreased to a concentration of 1,454 pg/g in the most recent layer, dated 1985. DeWit et al. (1990) also observed that CDD/CDF concentrations were higher in deeper sediment layers from the Baltic Sea. I-TEQ_{DF} concentrations in surface sediments (i.e., most recently deposited) were approximately 20 times higher than in sediments collected at depths of 22 to 28 cm.

Sediment cores were collected to a depth of 5–18 m at three locations near Osaka Bay, Japan, and analyzed for CDD/CDFs (Sakai et al., 1998). CDD/CDFs found at Yodo River, which is influenced by urban activities, increased slowly from 1980, reached a peak in 1993, and then dropped to a lower concentration before stabilizing. Comparison between the southern and northern parts of Lake Biwa, representing areas more and less affected by human activities, respectively, showed that CDD/CDF concentrations at the southern part of Lake Biwa began increasing around 1955 and increased dramatically in 1964, reaching a peak in 1973. At the northern part of Lake Biwa, CDD/CDF concentrations increased dramatically in the late 1960s and continued to increase until the 1980s, when they leveled off. Homologue profiles for the sediment core sampled from the northern part of Lake Biwa showed that OCDD was the dominant congener since 1842, followed by TCDD after 1935. The concentrations of OCDD and TCDD continued to increase after 1935. The sources of these two congeners were suspected to be herbicides, preservatives, and municipal solid waste incinerators (Sakai et al., 1998).

CDD/CDFs have also been detected in remote Arctic sediment core samples, but at very low concentrations (Tan et al., 1993; Vartiainen et al., 1995). Tan et al. (1993) analyzed a sediment core collected from Wonder Lake, Alaska. With the exception of 1,2,3,4,6,7,8-HpCDF and OCDF, which had concentrations of 13 and 15 pg/g,

respectively, in all sediment sections dated between 1590 and 1790, CDD/CDF concentrations were less than 8 pg/g. The authors suggest that these results support *de novo* synthesis of CDD/CDFs. Vartiainen et al. (1995) found total CDD/CDF levels of 2.29 pg/g in sediments dated 1890 and 55 pg/g in sediments dated 1994. OCDD dominated in these samples, followed by the hepta- and hexa-chlorinated congeners.

The results of these sediment core studies provide evidence that deposition of dioxin-like compounds began increasing dramatically after the 1930s and continued throughout the 1960s. Decreases appear to have occurred only during the most recent periods. In all of these studies, the higher chlorinated compounds dominated the homologue profiles. These observations are consistent among cores collected in various locations throughout the United States and Europe. CDD/CDFs have been observed both in relatively remote lakes, as well as in lakes close to industrialized areas. This suggests that atmospheric transport and deposition may be an important mechanism of entry into these lakes.

6.3. TEMPORAL TRENDS IN SOIL, VEGETATION, AND AIR

Temporal trends in CDD/CDF and PCB deposition have also been studied in other types of environmental media including soil, vegetation, and air samples. Kjeller et al. (1991) analyzed archived soil samples dated from 1846 to 1986 from semirural plots in the United Kingdom. Herbage samples dated from 1891 to 1988 that originated from a grassland area were also tested for CDD/CDFs (Kjeller et al., 1991, 1996). All CDD/CDF homologue groups were detected in soil and herbage samples from all time periods, and the CDD/CDF concentrations increased over time beginning at about 1900 (Kjeller et al., 1991). The concentrations of total CDDs in soil increased from 31 to 92 pg/g between 1893 and 1986. CDD/CDFs in the vegetation samples remained essentially constant between 1861 and 1945, increased to peak levels in the early 1960s, declined, and then reached a second peak in the late 1970s (Kjeller et al., 1996). CDD/CDFs were about 7 to 8 times higher in the 1960s to 1980s than in the sample from 1891 to 1900. In the most recent sample (1991 to 1993), total CDD/CDFs declined to levels similar to those observed in pre-1946 samples (Kjeller et al., 1996).

In a similar study, Alcock et al. (1997b) presented evidence that CDD/CDFs were present in UK soils before the widespread development of chloroaromatics (around

1930s). A previously unopened bottle of soil, collected in 1881 from Rothamsted Experimental Station as part of an agricultural experiment, was analyzed for CDD/CDFs. The soil sample contained 0.7 ppt I-TEQ_{DF}, with OCDD, 1,2,3,4,6,7,8-HpCDD, and 1,2,3,4,6,7,8-HpCDF as the dominant congeners. Great care was taken to avoid contamination with modern air and dust for the initial analysis, and the sample was subsequently exposed to laboratory air for 32 days to determine whether current air concentrations would alter the CDD/CDF concentrations detected in the archived soil. The results indicated that such exposure did not alter the soil concentration of CDD/CDF. Modern soil samples collected from the same field plot were found to contain 1.4 ppt I-TEQ_{DF}. The authors speculated that the increase was presumably a result of cumulative atmospheric deposition of CDD/CDFs. The results also indicated that although the soils from 1881 had lower concentrations of CDD/CDFs, they contained similar congener profiles of CDD/CDF as modern soil. This may indicate long-term persistence of CDD/CDFs in soil, and similarities in source inputs over time (Alcock et al., 1997b). Alcock et al. (1997a) also summarized temporal trends in sediments, archived vegetation, soil, food groups, and direct air measurements from the United Kingdom. They suggested that concentrations in UK media were the highest between the 1950s and the 1970s and were directly related to human activities. Since the 1970s, CDD/CDF concentrations have shown a consistent decline. According to Alcock et al. (1997b), current herbage concentrations are similar to pre-1946 levels, and ambient air monitoring data from London and Manchester indicate that CDD/CDF air concentration have steadily declined since the 1970s. Archived soil, herbage, and air samples collected in the United Kingdom between 1942 and 1992 were used to evaluate changes in PCB emissions over time (Harner et al., 1995). The concentrations of PCB congeners 28, 52, 138, and 153 in these samples rose from near zero in 1935 to a maximum in the late 1960s and then fell steadily to their present levels.

Hiester et al. (1995) observed a decrease of CDD/CDF concentrations in Germany's ambient air over a 6-year period. Ambient air samples were collected over 12 sampling intervals from four sites in the heavily industrialized Rhine-Ruhr region of Germany during 1987–1988 and 1993–1994, and analyzed for CDD/CDFs. Total I-TEQ_{DF}s for these sites ranged from 0.13 pg/m^3 to 0.33 pg/m^3 during 1987–1988, and from 0.04 pg/m^3 to 0.12 pg/m^3 during 1993–1994. Reductions in CDD/CDF I-TEQ_{DF}s at these sites ranged from 46

to 69 percent over the 6-year period (i.e, from 0.22 pg/m^3 to 0.13 pg/m^3 at Dortmund, and from 0.13 pg/m^3 to 0.04 pg/m^3 at Köln). These reductions were attributed to abatement actions taken since 1989 (Hiester et al., 1995).

6.4. TEMPORAL TRENDS IN WILDLIFE

Temporal trends in CDD/CDFs and PCBs have also been studied in wildlife, including fish and bird eggs. Hebert et al. (1994) analyzed pooled herring gull eggs for CDDs annually between 1981 and 1991. The eggs were collected from colonies in the Great Lakes and the Gulf of St. Lawrence River. Analyses results indicate that CDD levels declined between 1981 and 1984, but that CDD levels have remained relatively constant since 1984. DeWit et al. (1994) evaluated temporal trends in the levels of CDD/CDFs and coplanar PCBs in the biota of Sweden. Guillemot eggs were collected from the Island of St. Karlso in the Baltic Proper (Sweden) between 1969 and 1992, and pike samples were collected from Lake Storvindeln in Lapland, Sweden, between 1968 and 1992. During these time periods, the concentrations of CDD/CDFs and PCBs decreased in both species. Roos et al. (1998) confirmed that PCB concentrations decreased significantly in the Baltic Sea between 1989 and 1997 at an annual rate of 2–4 percent by analyzing samples from 54 juvenile grey seals caught off the Swedish coast. Roos et al. (1998) also found that the PCB concentrations in herring, cod, and guillemot eggs caught from the Baltic Sea during the period 1969–1996 decreased over time by 9–10 percent annually. Decreases in PCBs since the 1970s were also observed in fish from Finland (Korhonen et al., 1995). Pike samples from both inland lakes and coastal areas of Finland had significantly lower total PCB concentrations in 1994 (1.7 to 2.1 μg/g) than in 1971 (>7 to 10 μg/g).

U.S. EPA (1994a) reported a decline in PCB concentrations in lake trout from Lake Michigan since the late 1970s; however, PCB concentrations currently appear to be approaching equilibrium in the Great Lakes system. U.S. EPA (1994a) attributed the decline in tissue concentrations to reductions in pollutant loadings to the water column. The levels of PCBs in coho salmon also declined during the early 1980s, but have remained relatively constant since that time. According to U.S. EPA (1994a), the leveling off of PCB concentrations in the Great Lakes is related to "(1) historically contaminated sediments; (2) tributaries inputs resulting from point sources, spills, and runoff from both

urban and rural areas, and resuspension from contaminated sediments; and (3) atmospheric deposition of pollutants."

Hilbert et al. (1997) analyzed cod livers collected from Danish waters between 1973 and 1996 for total PCBs (Aroclor 1260). The results indicated that PCB levels in cod livers decreased during the past three decades. Total PCBs ranged from approximately 4 to 8 mg/kg (fresh weight) in 1973 at five locations in Danish waters to less than 1 mg/kg (fresh weight) in 1996 in those same waters.

Huestis et al. (1997) examined the temporal and age-related trends of CDD/CDFs and coplanar PCBs in Lake Ontario lake trout. Archived samples of 4-year-old lake trout, collected between 1977 and 1993 from the eastern basin of Lake Ontario at Main Duck Island (MDI), were analyzed for CDD/CDF/PCBs. Three- to 9-year-old trout were collected from the western end of the basin at Port Credit. The results of the temporal trends analysis indicated that CDD/CDF/PCB concentrations were at their highest levels in 1977 and lowest in 1987. The total TEQ_{DFP}-WHO_{94} was 583 ppt in 1977, compared to 124 ppt in 1993. The most important contributor to the total TEQ_{DFP}-WHO_{94} was PCB 126. This PCB congener contributed between 40 to 50 percent of the total TEQ_{DFP}-WHO_{94}, depending on the year examined. The contribution of 2,3,7,8-TCDD accounted for 15 to 20 percent of the total TEQ_{DFP}-WHO_{94}. CDD/CDF contaminant profiles for 1977, 1982, and 1991 suggest an increase of the proportion of 2,3,7,8-TCDF as the proportion of 2,3,7,8-TCDD decreases. The study also evaluated age-related effects of CDD/CDF/PCB concentrations. The results of the analyses of 3- to 9-year-old fish indicate that as the age of the fish increases, the level of contamination also increases.

Boumphrey et al. (1998) examined 10 gannet eggs taken from Ailsa Craig, a colony in the northern part of the Irish Sea, every 2 years from 1977 to 1992 to analyze temporal trends in total PCB and PCB congener concentrations. The results indicated that the average total PCB concentration was 6.08 μg/g in 1977 and 2.5 μg/g in 1992 with an annual rate of decline of approximately 0.25 μg/g. Individual PCB congeners declined at various rates, which resulted in different congener profiles between 1977 and 1992.

6.5. TEMPORAL TRENDS IN FOOD PRODUCTS

Recent studies have evaluated trends in concentrations of dioxin-like compounds in food by analyzing levels of PCBs and CDD/CDFs in food products from different time

periods. The United Kingdom's Ministry of Agriculture, Fisheries, and Food (MAFF) compared the levels of CDD/CDFs found in commercially available cows' milk in 1990 to the levels in samples collected in 1995 (MAFF, 1997a). The 1995 samples were collected from 12 locations in England and corresponded, where possible, to the 1990 sampling locations. Analysis of the 1995 samples was performed on a pool of 105 pints of full fat milk from each location. As shown in Table 6-1, the lipid-based I-TEQ_{DF} concentrations in 1990 ranged from 1.1 to 3.3 ppt, while the 1995 I-TEQ_{DF} levels decreased to between 0.67 and 1.4 ppt. Table 6-1 also reports PCB levels for the 1995 samples. Lipid-based TEQ_{P}-WHO_{94} levels ranged from 0.75 to 2.2 ppt. No PCB analysis for the 1990 cows' milk samples was presented.

Fürst and Wilmers (1995) compared the levels of CDD/CDFs found in German dairy products in 1990 to the levels in 120 dairy samples collected in 1994. Over the 4-year period, mean I-TEQ_{DF} concentration in milk fat decreased by almost 25 percent from 1.35 ppt to 1.02 ppt. Similar reductions were noted in human milk fat (Fürst and Wilmers, 1995).

To examine trends in CDD/CDF and PCB concentration in American food products, Winters et al. (1998) analyzed 14 preserved food samples from various decades of the 20th century for 7 dioxin-like coplanar PCBs and the 17 2,3,7,8-substituted dioxin and furan congeners. The authors compared the concentrations found in historical samples to the current dioxin concentrations observed in the national food surveys for beef (Winters et al., 1996a; 1996b), pork (Lorber et al., 1997), poultry (Ferrario et al., 1997), and milk (Lorber et al., 1998). As shown in Table 6-2, all 10 samples, dated from 1957 to 1982, had I-TEQ_{DF} concentrations higher than the current mean concentrations (when nondetects were set to one-half the limit of detection). Similarly, mean TEQ_{P}-WHO_{94} concentrations were higher than current mean concentrations for 12 of the 13 samples taken between 1945 and 1983. If these samples are indicative of past CDD/CDF concentrations, normalized I-TEQ_{DF} results suggest CDD/CDF levels 2 to 3 times higher, and PCB levels over 10 times higher during the 1950s, 1960s, and 1970s than current concentrations. As shown in Figures 6-2 and 6-3, I-TEQ_{DF} and TEQ_{P}-WHO_{94} concentrations in food products began to increase with the 1957 sample and continued to increase throughout the 1960s and 1970s. The peak concentration was observed in the 1968 poultry sample. This trend in CDD/CDF and PCB concentrations in food products is consistent with the

pattern observed in sediment cores, as discussed in Section 6.2 (Cleverly et al., 1996; Versar, 1996; Smith et al., 1992, 1993, 1995; Czuczwa et al., 1984, 1985a).

6.6. TEMPORAL TRENDS IN HUMAN EXPOSURE

Several studies have examined trends in the dietary intake of CDD/CDFs and PCBs. In 1995–1996, MAFF reported on its analysis of Total Diet Study samples collected in 1982 and 1992 from 24 locations in the United Kingdom (UK) (MAFF, 1995, 1996, 1997b). Of the 11 food groups examined, 10 groups represented the major dietary contribution to intake of dioxins and PCBs, and 1 group represented bread because it is a dietary staple. The results indicated that total dietary intake of PCBs and CDD/CDFs by consumers in the United Kingdom decreased dramatically between 1982 and 1992. Dietary intake of CDD/CDFs and PCBs for specific food items was estimated by multiplying the TEQ concentration of CDD/CDFs and PCBs in the food item (calculated by setting nondetects to the limit of detection) by the average daily intake for that food item, as estimated in the UK's National Food Consumption Survey. Total dietary intake was calculated by summing the dietary intakes for all food groups. The estimated upper bound dietary intakes of CDD/CDFs and PCBs by the average adult UK consumer in 1982 and 1992 are presented in Table 6-3. The total dietary intake of CDD/CDFs was estimated to be 240-pg/day I-TEQ_{DF} in 1982 and 69-pg/day I-TEQ_{DF} in 1992. The total dietary intake of PCBs decreased from 156-pg/day TEQ_{P}-WHO_{94} in 1982 to 46-pg/day in 1992 (MAFF, 1997b). Harrison et al. (1998) also reported on composite human milk samples collected as part of the MAFF study. Lipid-based CDD/CDF I-TEQ levels in Birmingham, England, were 37 ppt in 1987–1988 and 21 ppt in 1993–1994. I-TEQ levels were 29 ppt in Glasglow in 1987–1988 and 21 ppt in 1993–1994.

Liem et al. (1997) analyzed duplicate portions of 24-hour diet samples collected in The Netherlands in 1978, 1984 to 1985, and 1994. This study was conducted to estimate the dietary intake of CDD/CDFs and PCBs in the Dutch population 18 years of age and older to evaluate trends in dietary exposures. Dietary intake was estimated by combining the results of the chemical analyses of foods with data on consumption rates from the Dutch National Food Consumption Survey. Liem et al. (1997) reported a significant reduction of CDDs and CDFs in the diet over the three time periods. The mean daily dietary intake of CDD/CDF decreased from 4.2 pg/kg I-TEQ_{DF} in 1978 to 1.8 pg/kg I-

TEQ_{DF} in 1984–1985 and 0.5 pg/kg I-TEQ_{DF} in 1994. When PCBs were included in the TEQ calculation, the daily dietary intake was 11 pg/kg TEQ_{DFP}-WHO_{94} in 1978, 4.2 pg/kg TEQ_{DFP}-WHO_{94} in 1984–1985, and 1.4 pg/kg TEQ_{DFP}-WHO_{94} in 1994. The percentage decrease in 1994 samples was consistent for all the measured CDD/CDF/PCBs. The results of this study suggest that a reduction in dietary ingestion of CDD/CDFs and PCBs occurred in The Netherlands beginning in the late 1970s.

In a study similar to the United Kingdom's MAFF (1995, 1996, 1997b) study, FÜrst and Wilmers (1997) found that CDD/CDF dietary levels also dropped in Germany in recent years. Several hundred food samples were randomly collected and analyzed for CDD/CDFs during 1989 and 1995. Fish products showed the greatest decline in CDD/CDF food concentrations over this period. Significant decreases also were noted for meats. Samples of more than 300 dairy products were collected in 1990 and 1994 from several dairies in North Rhine and Westphalia and analyzed for CDD/CDFs. The results indicate that from 1990 to 1994, CDD/CDF levels in cows' milk decreased approximately 25 percent. To test whether the reduction of CDD/CDF concentrations in food had a positive effect on human exposure, dietary intake of CDD/CDFs was estimated using the results of the food sample analysis described above and standard food consumption data. This analysis indicated that in the past few years, CDD/CDF intake by humans decreased by approximately 50 percent. The current average daily intake is estimated to be 69.6 pg I-TEQ_{DF} compared to a daily average intake of 127.3 pg I-TEQ_{DF} in 1990. This decrease in daily intake was also reflected in a decrease in breastmilk concentrations (Fürst and Wilmers, 1997). A study of more than 1,000 individual breastmilk samples from the North Rhine-Westphalia region showed a decrease from 34 ppt I-TEQ_{DF} in milk fat in 1989 to 14.2 ppt I-TEQ_{DF} in milk fat in 1996. This represents a 60 percent reduction since 1989.

6.7. TEMPORAL TRENDS IN HUMAN BODY BURDENS OF DIOXIN-LIKE COMPOUNDS IN THE UNITED STATES

Long-term, nationally representative environmental monitoring for dioxin-like compounds has not been conducted. However, this section reviews various dioxin body burden monitoring studies which have been conducted in the United States in past decades. Studies which sampled either blood or adipose tissue were compiled; studies on

other matrices such as breast milk were not included. Also, this compilation only included dioxin and furan congeners; dioxin-like PCBs were not included. Other characteristics of studies included in this compilation are:

1. All or a toxicologically significant subset of the 17 dioxin-like dioxins and furans were measured and individual-specific or overall study average concentrations of these congeners were available (this was needed in order to calculate TEQ_{DF} - WHO_{98} concentrations).
2. All results were reported on a lipid-basis.
3. Although not possible for all studies, data were obtained which had reported detection limits so that average congener concentrations could be derived assuming non-detects (NDs) equal one-half detection limit (½ DL). When detection limits were not supplied, NDs were assumed to equal zero. In only one study from the 1970s (Kang et al., 1991; U.S. EPA, 1990), NDs were reported as zero and detection limits were not supplied. In this case, it made no difference in the calculation of TEQ_{DF} -WHO_{98} concentrations.
4. All measurements were on background populations. The first study described below included Vietnam Veterans, non-Vietnam Veterans, and civilians. All three groups were included in this analysis as the concentrations in the three were indistinguishable - the civilian population had, in fact, the highest concentrations. Another reason to include all three populations was that this was the only study available with the full suite of congener concentrations in the 1970s. Two other studies (Schecter et al., 1989; Schecter et al., 1993) were comprised of blood samples taken from Vietnam Veterans only. In both of these, small subsets of individuals appeared to have elevated concentrations of 2,3,7,8-TCDD and TEQ. Congener-specific averages, not including these individuals, could be developed with the information in the articles, so these amended profiles were included in this compilation.
5. Only studies which sampled adult populations were included; data on children or infants were not included. Studies on "average adult populations" which included demographic information were comprised of approximately the same number of males and females and the average age was usually in the 40s. Studies on

Vietnam Veterans were all male populations and the maximum age was in the 40s, and one study that sampled breast adipose tissue was on females alone.

Twelve studies were found for this compilation. A summary of the results from these studies is shown in Table 6-4. Table 6-5 provides the congener-specific average concentrations from each of the years in this compilation. Figure 6-4 shows the TEQ concentrations collected from these studies as a function of year. Figure 6-5 shows the age trend for three studies. This trend refers to the common finding for surveys in the 1980s and 1990s that older individuals had higher dioxin concentrations as compared to younger individuals. Following now are study-by-study summaries.

Study 1: Dioxins and Dibenzofurans in adipose tissue of US Vietnam veterans and controls

This study was undertaken by the U.S. Department of Veterans Affairs and the U.S. EPA (Kang et al. 1991; U.S. EPA, 1990). They used EPA's National Human Adipose Tissue Survey (NHATS) Repository to collect samples. In the repository at the time of the study were approximately 8,000 tissue samples, with up to a 1000 a year collected annually starting in 1970. The target population for NHATS was all non-institutionalized persons in the US. Due to the invasive nature of adipose tissue sampling, the population was actually derived from individuals who died from external causes (90%) and surgical patients (10%). From that repository, they were able to identify samples from 494 males who potentially served in Vietnam, those born between 1936 and 1954. These 494 samples were taken between 1972 and 1981. Searching through military records, they were able to identify 134 veterans from this potential population of 494, 40 of whom served in Vietnam. They selected all of these 40, as well as 80 of the remaining 94 veterans who had not served in Vietnam (these 80 selected randomly from the population of 94). They matched each of the 40 Veterans with 2 civilians in terms of age and sex from the potential population of 494. The final population of this study was, therefore, 200 individuals: 40 Veterans serving in Vietnam, 80 non-Vietnam Veterans and 80 civilians. Five samples were discarded as inappropriate (not enough lipid, records of individuals not certain with regard to military status, etc.), for a final sample count of 195.

While a comprehensive set of data, this was not a good background representation because the oldest individual was no older than 45 years old (the last year sampled, 1981, minus the earliest birth date, 1936), and they were all males. Still, it was the only data set from these years which measured all the 17 CDD/CDF congeners, and results suggest that these individuals were not influenced by unique high exposures.

The results from these three sample sets were indistinguishable - TEQ_{DF} -WHO_{98} concentrations were 71.9, 65.4, and 72.0 pg/g lipid for the Vietnam Veterans, the non-Vietnam Veterans, and the civilians, respectively. The 2,3,7,8-TCDD concentrations followed the same trend, with concentrations of 13.4, 12.5, and 15.8 pg/d lipid for the same three groups. For this reason, these study populations were merged for further analysis here. These full study summaries can be considered to represent the years 1972 to 1981, for this limited male population. It would be desirable to compile concentrations by sampling year, to see if there was a temporal trend in the data. However, the full sample-specific study results in U.S. EPA (1990) did not indicate the year in which each of the samples were taken. This information was retrieved from EPA's files by personal communication (personal communication, J. Remmers, Office of Prevention, Pesticides, and Toxic Substances, U.S. EPA, to M. Lorber, Office of Research and Development, U.S. EPA, 2000), which allowed for the year-by-year compilations shown in Table 6-4. Only 178 of the 195 samples could be identified by year of sample collection.

As seen in Table 6-4, there appears to be a clear trend, with concentrations (in ppt) declining from the 80s to the 50s between 1972 and 1981. The 5 samples averaging 129 ppt TEQ in 1976 appear to be anomalous. There were other samples with concentrations above 100 ppt, such as a sample at 151 ppt TEQ_{DF} -WHO_{98} from 1981, at 166 ppt TEQ_{DF} -WHO_{98} from 1978, and at 179 ppt TEQ_{DF} -WHO_{98} from 1973, but 4 of 5 samples in 1976 ranged from 99 to 215 ppt TEQ_{DF} -WHO_{98}. There is no reason to believe that the high average in 1976 is indicative of any exposure for that year.

Data from 1976 notwithstanding, these data are the earliest that could be found and seem to clearly suggest a declining trend of TEQs throughout the 1970s, starting as high as in the 80s ppt TEQ lipid during the early 1970s, and declining to the 50s ppt TEQ lipid by the late 1970s.

Study 2. Control samples taken to compare to individuals exposed to a PCB transformer fire in a building in upstate New York

Schecter et al. (1986) sampled intra-abdominal and subcutaneous adipose tissue in five individuals in Binghamton, during 1983 and 1984 (these samples were assumed to be taken in 1983 for tabular and figure display). One individual had been exposed to fumes from a PCB transformer fire in an office building, but that individual is not included here. Two of the remaining 4 individuals had died from unknown causes - two types of adipose tissue were sampled and averaged for purposes here. Subcutaneous adipose tissue samples were taken from an additional two controls. No information was available as to the age and sex of these four individuals. Schecter et al. (1986) reported the concentrations of 14 of 17 of the CDD/CDF congeners; 1,2,3,7,8-PCDF; 2,3,4,6,7,8-HxCDF; and 1,2,3,7,8,9-HxCDF were not reported. The average of the four control samples was 34 ppt TEQ_{DF} -WHO_{98} lipid.

Study 3. Background population of St. Louis, Missouri

Graham et al. (1986) reported on the analysis of adipose tissues from autopsy patients who had died suddenly or violently out of the hospital during 1985. It was unclear as to whether to include the results from this study in this compilation, since only these 6 CDD/CDF congeners were measured: 2,3,7,8-TCDD; 1,2,3,7,8-PCDD; 1,2,3,6,7,8-HxCDD; 1,2,3,4,6,7,8-HpCDD; OCDD; and 2,3,4,7,8-PCDF. However, a comparison between these results and the results from the previous two studies suggests that these six congeners comprise over 90% of total TEQ_{DF} -WHO_{98}. For this reason, TEQ_{DF} -WHO_{98} concentrations were calculated and included in this compilation. Graham et al. (1986) also listed age and sex in the tabular summary of results. Of the 35 samples, 16 were male and 19 were female, and the age range was from 21 to 88 years, with an average age of 43. The average (congener limited) TEQ_{DF} -WHO_{98} concentration from this population was 47 ppt lipid. Figure 6-5a shows the results from this study, with concentrations displayed as a function of age. There is a clear age trend, with concentrations ranging from less than 20 ppt TEQ_{DF} -WHO_{98} lipid for the youngest sampled individual to over 100 ppt TEQ_{DF} -WHO_{98} lipid for the oldest sampled individual. The highest sample was about 140 ppt TEQ_{DF} -WHO_{98} lipid for a 60 year-old individual.

Study 4: Four background individuals from Atlanta, Georgia

Patterson et al. (1994) reported on the analysis of mono- and di-ortho substituted polychlorinated biphenyls, dioxins, and furans in serum and adipose tissue samples collected in Atlanta. The results included from this study for the present purposes were adipose tissue samples from four individuals who had died suddenly. These four included 2 men and 2 women, ages 19, 25, 35, and 55 years. Patterson et al. (1994) reported on 13 of 17 congeners, not evaluating 2 hexa- and 1 hepta-furan congeners. As above, the reported results comprised the bulk of the TEQ. Therefore, these data were included in the current compilation. The average TEQ concentration from this small set was 31 ppt TEQ_{DF} -WHO_{98} lipid.

Study 5: NHATS 1987

The National Human Adipose Tissue Survey of 1987, FY87 NHATS, was undertaken, in part, for comparison with a very similarly designed survey in 1982, FY82 NHATS. For both surveys, composite samples of adipose tissue from individuals characteristic of average background conditions were analyzed for the full suite of dioxin and furan congeners. FY82 NHATS was not included in this temporal trend compilation because there appears to have been unexplained high findings of 1,2,3,7,8-PCDD. Table 6-6 compares average congener concentrations of selected dioxin congeners from FY82 NHATS and FY87 NHATS for the 15-44 year age group. As seen in Table 6-6, all dioxin congeners had reasonably comparable concentrations, except 1,2,3,7,8-PCDD. The finding of 125.0 ppt for 1,2,3,7,8-PCDD is much higher than results for that congener for any of the studies found here, even the highest ones in the 1970s. The overall average 1,2,3,7,8-PCDD concentration for FY82 NHATS at 73.6 is itself significantly higher than ever found anywhere. For that reason, FY82 NHATS was not included in this compilation.

Results from 38 of the 48 composite samples from NHATS '87 were used. These were results for the adult population, described in the age groups: 15-44 and >45 years. The 10 composites representing the <15 year age group were not included. The 38 samples represented 666 individuals (the 48 samples represent 865 individuals). According to the 1980 census, these two age groups comprised 46 and 31% of the population, respectively. Average congener concentrations for these age groups presented in U.S. EPA (1991) were weighted to calculate the adult average concentrations

shown in Table 6-5. Again, not all congeners were reported, but those that were reported comprised over 90% of TEQ concentrations, as suggested by other studies which had results for all congeners. The overall adult average concentration was 37 ppt TEQ_{DF} - WHO_{98} lipid. Like other studies, there appears to be an age trend, with the older set having an average of 53 ppt TEQ_{DF} -WHO_{98}, while the younger age range had an average that was almost half that at 28 ppt TEQ_{DF} -WHO_{98}.

Study 6. Vietnam Veterans in Massachusetts in 1988

Schecter et al. (1989) reported on a study in which blood was taken from 28 Vietnam Veterans from the state of Massachusetts. The year in which the sampling occurred was not provided. Therefore, it is assumed to have occurred one year prior to the year of study publication. Of the 28 individuals sampled, it appeared as though 2 individuals had been exposed to Agent Orange in Vietnam or to another source of 2,3,7,8-TCDD. The concentration of this congener in their blood was 34 and 29 ppt lipid, and the TEQ_{DF} -WHO_{98} concentrations were 54 and 62 ppt lipid. The other congeners in the blood of these two individuals did not appear elevated. For the other 26 individuals, the average 2,3,7,8-TCDD concentration was 4.8 ppt and the average TEQ_{DF} -WHO_{98} concentration was 29.6 ppt lipid.

Study 7: San Francisco and Los Angeles residents in the late 1980s

This study was undertaken by the California Air Resources Board for the purpose of determining a preliminary estimate of the body burden levels of CDD/CDFs in the California population, so that future efforts evaluating the impact of specific air sources could use the knowledge gained, both in terms of survey design, implementation, and analysis, as well as the background levels found (Kramer et al., 1989). A total of 57 adipose tissue samples, from an initial target population of 60, were taken from surgical patients who were in surgery for reasons other than cancer. Samples were selected based on the following stratification variables: 1) age - three age groups of 12-34, 35-49, and >50 years were sampled, 2) location - San Francisco and Los Angeles were targeted, 3) sex - half of the samples were sought from each sex. The average age of the respondents was about 50 years. The average concentration found was 31 ppt TEQ_{DF} -WHO_{98} lipid. Figure 6-5b shows the results as a function of age. Again, a trend is suggested showing higher

concentrations with age. However, the trend is not nearly as well defined as in the Missouri study. Concentrations ranged from <10 ppt TEQ_{DF} -WHO_{98} lipid for the youngest individuals sampled (about 21 years old) to approximately 80 ppt TEQ_{DF} -WHO_{98} lipid for an individual over 60 years old.

Study 8: Pooled blood sample from blood bank donors in upstate New York

In a survey article describing various sampling efforts in the United States and around the world, Schecter (1991) presented the results of a pooled blood sample comprised of the blood from 100 individuals. This same profile was identified in Schecter et al. (1991) as the control population for an AIDS study, and having originated from a Syracuse Red Cross Blood Bank. Schecter et al. (1991) claims that this control population contained samples collected from approximately an equal number of males and females. No additional demographic information was available for these individuals. The average concentration reported was somewhat higher at 50 ppt TEQ_{DF} -WHO_{98} lipid, compared to other values presented for the 1980s in this compilation.

Study 9: Fifty Michigan Vietnam Veterans

Blood samples from 50 Michigan Vietnam Veterans were collected by Schecter et al. (1993) in 1991. The purpose of this collection was to compare impacts of exposure to Agent Orange in these veterans to levels of dioxin in Vietnamese exposed to Agent Orange. The average age of the 50 veterans at the time of sampling was 48 years, with a range of 41 to 66 years. Levels of 2,3,7,8-TCDD and other dioxins were elevated in 6 of these 50 Vietnam veterans. The average TEQ_{DF} -WHO_{98} concentration in these 6 veterans was 85 ppt lipid. The average TEQ_{DF} -WHO_{98} concentration in the other 44 veterans was much lower at 29.1 ppt lipid. The difference in 2,3,7,8-TCDD concentration was more striking: 46 ppt in the 6 veterans versus 4.1 ppt in the other 44 veterans. The average of the 44 veterans was used for this compilation.

Study 10: Pooled blood sample from Binghamton

Schecter et al. (1997) reported on the result of a pooled blood sample representing 100 adult men and women. The samples were collected at a Binghamton hospital laboratory from specimens ready to be discarded after having been used for routine

medical purposes. The average TEQ concentration from this pooled sample was 32 ppt TEQ_{DF} -WHO_{98} lipid.

Study 11: Blood samples from 6 study sites around the country

This is the extensive compilation prepared by the Centers for Disease Control (CDC, 2000) that forms the basis of this Reassessment's representation of current background body burdens in the United States. Details on this compilation are provided in Chapter 4, Section 4.3.2 and are not included here. Briefly, these were background populations from site-specific studies. Sites and populations were: Manchester, Missouri (n = 61); Times Beach, Missouri (n = 67); Jacksonville, Arkansas (n = 57); Oregon (n = 9); Wisconsin (n = 93); and North Carolina (n = 29). The average TEQ_{DF} -WHO_{98} concentration is 20 ppt lipid. The age of the individuals sampled were available for 214 individuals located in Missouri, Arkansas, and North Carolina. The average age was 45 years, with a range of 20-70 years. The concentrations of these individuals are graphed in Figure 6-5c. While an age trend is evident, it does appear as though that the trend is much less marked, as compared to earlier years.

Study 12. Breast adipose tissue in San Francisco

Petreas et al. (2000) presented a summary of results of analyses of breast tissue samples taken from women undergoing breast surgery during 1998. These 45 individuals comprised the control group in a breast cancer case-control study in the San Francisco Bay area. Specific results from each individual were not available in Petreas et al. (2000), but were supplied by personal communication (personal communication from M. Petreas, Hazardous Material Laboratory, California EPA, to M. Lorber, Office of Research and Development, U.S. EPA, 2000). The average age of these women was 45 years, with a range of 28-67 years. The average TEQ_{DF} -WHO_{98} concentration was 25 ppt lipid.

Two important trends that can be ascertained from these data are:

1) While certainly not a statistically collected set of data, these studies suggest a downward trend in average adult body burdens of CDD/CDFs from the 1970s through the 1990s. The adult concentrations appear to be in the range of 70 - 90 ppt TEQ_{DF} -WHO_{98} in the early 1970s; in the range of 30 - 50 ppt TEQ_{DF} -WHO_{98} in

the 1980s; below 30 ppt in the 1990s; and perhaps approximately 20 ppt by the year 2000.

2) An age trend that has been identified by others in the literature is displayed is discussed here and displayed in Figure 6-5. Specifically, older individuals appear to have higher body burdens as compared to younger individuals. Based on an examination of three studies in the 1980s (NHATS FY87 and the two studies graphed in Figure 6-5), and one from the 1990s (Figure 6-5c), one might speculate that the age trend is less pronounced through the 1990s. This is probably due to a dose trend discussed earlier in Section 6.7 (i.e., that doses to CDD/CDFs, as exemplified by 2,3,7,8-TCDD, were possibly higher in the 1960s and 70s, declining to current background levels). With lower exposures through the 1990s, older individuals could be in a period of depuration - body burdens are actually declining as they age. For example, individuals who were in their 30s and 40s in the 1970s and 80s may have had concentrations above 40 ppt TEQ_{DF} -WHO_{98}, but may have had concentrations less than 30 ppt in the 1990s, as lower background doses could not sustain the higher body burdens.

6.8. ADDITIONAL EVIDENCE OF TEMPORAL TRENDS IN BODY BURDENS

Schecter (1991) analyzed liver tissues estimated to be 100 to 400 years old recovered from the frozen bodies of two Native American (Eskimo) women. The women died in their igloo in Point Barrow, Alaska, when they were trapped and frozen by an ice overflow. Oil was used for cooking and heating, and ventilation was poor. One woman had soot-laden lungs. The results indicated that dioxin levels were much lower in these ancient tissues than in livers of people currently living in industrial areas. Tong et al. (1990), as cited in Schecter (1991), found a lipid-based total I-TEQ_{DF} level of 0.24 ppt in one of the ancient liver samples. I-TEQ levels (i.e., CDD, CDF, and total) were nondetectable in the other ancient sample. Analysis of two liver samples from modern times showed lipid-based total I-TEQ_{DF} levels of 13.3 ppt (Ryan et al., 1986, as cited in Schecter, 1991).

Recently, Päpke et al. (1997) analyzed 180 whole blood samples collected in Germany in 1996 for CDD/CDFs. The samples were taken only from individuals who had no known exposure to CDD/CDFs (i.e., their only exposure would be through food

ingestion). The results of this study were compared to a similar study conducted in 1994. The results indicated that concentrations declined from 19.1 ppt I-TEQ_{DF} in blood lipids in 1994 to 16.5 ppt I-TEQ_{DF} in blood lipids in 1996. These results suggest human exposure to CDD/CDFs have decreased over the past several years.

Wittsiepe et al. (1998) measured CDD/CDFs in 507 blood samples collected in Germany between 1991 and 1996. The samples were intended to represent the general population (i.e., the individuals were not exposed to dioxin-like compounds as a result of occupational or accidental contacts). The results indicated that blood levels of CDD/CDFs declined significantly between 1991 and 1996, with the more recent concentrations representing approximately one-half the earlier concentrations. The mean lipid-based total CDD/CDF concentrations were 71.8 pg/g in 1991 and 334.4 pg/g in 1996 (Table 6-7).

Liem et al. (1996) detected downward trends in the levels of CDD/CDFs in human breastmilk between 1987–1988 and 1992–1993. Breastmilk samples were collected from women in 11 countries as part of a World Health Organization (WHO)-coordinated exposure study. Protocols were developed to ensure that the samples collected during the two periods were comparable. The protocols included criteria for selection of donors, sampling areas, etc. The samples were analyzed for the 17 CDD/CDF congeners, as well as 6 marker PCBs (IUPAC numbers 28, 51, 101, 138, 153, and 180). The results indicated that CDD/CDF levels are decreasing in some countries (Table 6-8). Liem et al. (1996) estimated an overall annual CDD/CDF decrease of 7.2 percent, based on the data from those countries.

In a similar study, Schecter et al. (1997) assessed CDD/CDF concentrations in blood and breastmilk samples collected in Germany and the United States during two time periods. More than 100 blood samples were collected in Germany during the years 1989 and 1994 from "persons for whom there was concern about dioxin exposure but abnormal dioxin blood levels were not found." American blood samples were collected in 1984–1989 (male veterans with no dioxin abnormalities) and 1996. The German milk samples were collected in Westphalia in 1991 and 1995, and American samples were two pooled samples from 1988 (Binghamton, NY, and Los Angeles, CA), five individual analyses from the period 1995-1996 (Binghamton, NY), and one pooled sample from 1997 (Binghamton, NY). The results of the study indicated that from 1989 to 1994, the CDD/CDF concentrations in German blood declined from 43 ppt I-TEQ_{DF} to 19 ppt I-TEQ_{DF}.

CDD/CDF concentrations in United States blood samples declined from 28 ppt I-TEQ_{DF} in 1984–1989 to 25 ppt I-TEQ_{DF} in 1996. The results of the German breastmilk analyses indicated a decline from 23 ppt I-TEQ_{DF} in 1991 to 16 ppt I-TEQ_{DF} in 1995. American milk samples showed a reduction from 17 ppt I-TEQ_{DF} in 1988 to 9 ppt I-TEQ_{DF} in 1995–1997.

Kiviranta et al. (1998) measured the concentrations of the 17 toxic CDD/CDF congeners and 6 PCB congeners (IUPAC 28, 52, 101, 138, 153, and 180) in human milk samples from primiparae mothers in Finland. Samples were collected from women in both rural and urban areas between 1992 and 1994 and compared to data from 1987 (Table 6-9). Total lipid-based CDD/CDF concentrations declined from 339 ppt (n = 37) to 217 ppt (n = 28) in rural areas between 1987 and 1992–1994; urban concentrations were similar: 375 ppt (n = 47) and 381 ppt (n = 14) for the two sample periods, respectively. I-TEQ_{DF} values decreased from 20.1 ppt to 13.6 ppt in rural areas, and 26.3 ppt to 19.9 ppt for urban areas between 1987 and 1992–1994. Total lipid-based PCB concentrations declined from 396 ng/g (n = 37) to 198 ng/g (n = 28) in rural areas, and from 496 ng/g (n = 47) to 296 ng/g (n = 14) in urban areas for the same two sample periods.

6.9. A MODELING EFFORT TO RECONSTRUCT PAST DOSES OF 2,3,7,8-TCDD

Previous sections in this chapter describe evidence supporting temporal trends in environmental concentrations and human exposure to CDD/CDF/PCBs. Levels of dioxin-like compounds appeared to increase in the environment starting from the 1930s through the 1960s, and loadings began to decline perhaps starting in the 1970s to the present. Recent evidence collected on animal food products in the United States (Winters et al., 1998), combined with body burden data, are the best evidence that human exposures to dioxins may have followed the same trends. (See Sections 6.5 and 6.6.) This section describes a third way of evaluating past exposures to dioxins. Pinsky and Lorber (1998) described an effort to statistically reconstruct the pattern of past human exposure to the most toxic dioxin congener, 2,3,7,8-TCDD (abbreviated TCDD), through use of a simple pharmacokinetic (PK) model that included a time-varying TCDD exposure dose. This section summarizes the procedure and presents some key results from this modeling exercise. The original reference (Pinsky and Lorber, 1998) should be obtained for further detail.

A first-order, one-compartment PK model was used to compute an individual's body lipids' TCDD concentration over time. Key inputs for that model include: (1) a time-varying dose of TCDD (expressed in units of pg/kg-day), (2) a fraction of dose absorbed into the body lipid compartment (assumed to be constant), (3) the volume of the body lipid compartment (assumed to be time varying), and (4) a rate of TCDD loss from the lipid compartment (modeled as a function of the percent of body fat). To calculate the rate of TCDD loss, a model was needed to predict how body lipid volumes vary over time, in addition to a model of how overall body weight varied over time.

In this modeling exercise, all inputs were fixed except the time-varying dose of TCDD. Using Bayesian statistical approaches, the dose was "calibrated" to best fit a set of data on TCDD concentration in body lipids. These data, shown in Table 6-10, were obtained from studies that focused on persons with no known direct exposure to dioxins and, as such, measured background exposure levels. In terms of this modeling exercise, the most important data from this set, were from the 1970s, suggesting that body lipid concentrations of TCDD were above 10 ppt during those years (VA/U.S. EPA, 1988). Current data from the 1980s into the 1990s show TCDD concentrations below 10 ppt (U.S. EPA, 1991; Michalek et al., 1998; Andrews et al., 1989).

The feature of the Bayesian approach that is most relevant to this calibration modeling exercise was the use of constraints on the input functions. In other words, much of the evidence described earlier in this chapter suggests an expected trend on the dose function that was being calibrated in this modeling exercise (i.e., that the TCDD dose may have increased from the 1930s to the 1970s and declined thereafter). An examination of the existing trend data suggests, specifically, the following for the current dose modeling purposes: (1) a peak in environmental levels appears to have occurred in the 1960s or 1970s, (2) early century levels are from 2 to >33 times lower than the peak, (3) late 1980s levels are from 1 to 20 times lower than the peak, and (4) late 1980s levels are higher than early century levels; in all cases, the ratio of peak to 1980s levels is lower than the ratio of peak to early century levels. Also, and importantly for this modeling exercise, the estimate of TCDD exposure dose based on the 1994 release of this dioxin reassessment document (U.S. EPA, 1994b) was 0.17 pg TCDD/kg-day. Using these trends, the following Bayesian "plausibility criteria" were established for calibration modeling purposes:

1. A range of 0.0 to 0.50 pg TCDD/kg-day for the exposure dose in 1990. The same plausible range was used for the 1900 dose.
2. Ranges of 2 to 200 for the ratio of peak to 1900 dose, and 1 to 100 for peak to 1990 dose.
3. Peak year set between 1945 and 1980.

Finally, to ensure a smooth exposure curve, a limit of 20 percent was set on the rate of decrease from the peak exposure level going forward or backward 1 year.

Pinsky and Lorber (1998) detailed how well the calibrated doses duplicated the measured body burdens shown in Table 6-10. In general, several slightly different calibrated dose functions fit the data equally well. An example of a family of similar dose curves is shown in Figure 6-6. In that figure, the dose appears to increase from the 1940s through the 1960s, then begins to drop through the 1970s, with a baseline level being reached by the 1980s. This qualitatively fits some of the trend data described previously. However, while the calibrated model fits the data reasonably well, it does not fit the data perfectly. Obviously, the lack of a perfect model fit beginning in the 1970s could be partially attributed to the lack of observed body concentrations of 2,3,7,8-TCDD. As seen in Figure 6-6, the dose curves appear to converge after the 1970s, when there were observed data, while the dose curves seem to diverge prior to 1970, when there were no data on which to base the calibration. Also, some data were inconsistent, particularly the National Human Adipose Tissue Study (NHATS) data from 1982 and 1987 (U.S. EPA, 1991). Specifically, in a comparison of the NHATS 1982 and 1987 data, the mean TCDD concentration increased considerably from 1982 to 1987 in the oldest age group (45+), but decreased considerably in the two younger age groups. Further, the NHATS 1982 data do not display the trend of increasing TCDD concentrations by age that is seen in most other studies done in the 1980s (mean was 6.9 pg/g in the 15–44 age group and 5.5 pg/g in the 45+ age group), while the age trend in NHATS 1987 data (mean of 4.4 pg/g in the 15–44 age group versus 9.4 pg/g in the 45+ age group) seems exaggerated. These trends are difficult to explain with the current modeling structure; subsequently, all models with a good data to model fit overpredicted the 1982 mean and underpredicted the 1987 mean in the highest age group. More data from prior to and during the 1970s would have provided a much more useful database from which to

calibrate the model; however, no other TCDD body concentration data could be found from those time periods.

Despite the lack of a perfect fit of the model to the data, several informative findings resulted from this exercise.

1. The model calibration exercise was regenerated using two changes to the initial Bayesian constraints on the shape of the exposure/dose curve. One change essentially dropped all constraints in order to test whether the imposition of the constraints restricted how well a calibrated dose curve could fit the data. It was found that a best-fit solution for exposure with no constraints provided only an insignificant improvement. The second change was to constrain the exposure dose, making it constant over time. Results showed that the temporally varying dose provided a significantly improved fit to the data, as compared to the constant dose. Further, the best-fit constant dose in this exercise was 0.35 pg TCDD/kg-day, compared with the current average adult dose of 0.17 pg TCDD/kg-day, as determined by the previous version of this dioxin reassessment (U.S. EPA, 1994b), and with the revised 0.09 pg TCDD/kg-day of this current reassessment. The result provides strong evidence that past doses were, in fact, higher than current doses.
2. The exposure/dose curves in Figure 6-6 suggest that dioxin exposure followed a sharp bell curve, with a precipitous drop to a flat baseline in dose before 1980. This drop is counterintuitive and probably more the result of the simplicity of the pharmacokinetic model than a real-world trend. However, it may be reasonable to treat some generalizations from these calibrated dose curves as reasonable hypotheses. For example, the late 1960s were estimated as years of peak TCDD exposure, an observation that coincides with peaks found in sediment core studies. The estimates derived suggest that TCDD exposures may have been 20 times higher during the 1960s than the 1980s. Over a 10-year peak period in the 1960s and early 1970s, daily exposures could have been as high as 1.5 to 2.0 pg/kg-day, possibly dropping to as low as 0.10 pg/kg-day and below into the 1980s. Without body burden data, it may be difficult to go much further with the model results.

3. In addition to an exposure dose, the results of this exercise also include temporal body burden levels, as described by body lipid concentrations of TCDD. An example of these results is shown in Figure 6-7. The "specimen year" on the x-axis refers simply to the year in which a cross-section of the population can be examined. For example, in 1986, young individuals have a body burden of about 2 pg/g lipid; whereas older individuals have a body burden exceeding 5 pg/g lipid. The modeled build-up of TCDD in an individual's body can be ascertained by following a curve corresponding to the individual's birth year, shown on the z-axis, and progressing to the left. This figure displays two important trends: (a) body burdens in general tend to be dropping (Schecter, 1991; U.S. EPA, 1991; MAFF, 1995), and (b) body burdens are higher in older individuals than younger individuals (Orban et al., 1994; Andrews et al., 1989; Van der Molen et al., 1996). As seen from specimen years after approximately 1970, body concentrations in individuals of all ages appear to be dropping. At the same time, the cross section of all birth-year populations after about 1970 suggests that concentrations are higher in older individuals. Interestingly, this trend may not have been present in the U.S. population in the mid-1970s and earlier. In the mid-1970s, peak body concentrations appear to have peaked for individuals in their 20s (roughly), with a constant body burden for older individuals. In the 1960s and earlier, differences in body burden do not appear to be a function of age.
4. This model also had a breastmilk feeding component. To search for the best-fit exposure/dose curve, it was arbitrarily assumed that half the population was breast fed and the other half was bottle fed. Therefore, the average concentration for all individuals was calculated as the midpoint of body lipid concentrations modeled with and without breast-feeding. Breast-fed infants were exposed to milk concentrations modeled to occur in 25-year-old females (where breastmilk lipid concentrations were assumed to equal body lipid concentrations). Infants were assumed to be breast fed for 4 months, and their consumption of breastmilk lipids was 26 g/day. Bottle-fed infants were assumed to be exposed to the general exposure dose, which as can be expected, turned out to be much lower than the breast-feeding dose. Model predictions were compared to a limited subset of the available body burden data, specifically to the under-15 age groups for the two

NHATS data sets, where the mean concentrations were 4.2 pg/g lipid (NHATS 1987) and 2.0 pg/g lipid (NHATS 1982). For the under-15 age group in 1982, the predicted mean concentrations in one possible solution were 3.8 pg/g in breast-fed children versus 0.3 pg/g in bottle-fed children; in 1987, the expected means in this age group were 1.8 pg/g for breast-fed and 0.2 pg/g for bottle-fed individuals. Assuming a 50 percent breast-fed rate, predictions yielded averages of 2.0 pg/g and 1.0 pg/g for the 1982 and 1987 NHATS, respectively. Two observations could be made. First, the modeling exercise shows the impact of breast-feeding since modeled predictions of bottle-fed body concentrations were much lower than breast-fed body concentrations (i.e., 0.3 and 0.2 pg/g lipid for bottle fed versus 3.8 and 1.8 pg/g lipid for breast fed). Therefore, if the low body burden found for bottle-fed infants reflects reality, then the NHATS data showing 4.2 and 2.0 pg/mL also show the influence of breast-feeding on the body burden of children. Second, both the model and the data show a drop in the body concentrations of the under-15 age group between 1987 and 1982, suggesting a trend toward declining exposures through the 1980s.

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Table 6-1. Lipid Based Concentrations of CDD/CDFs and PCBs in Samples of Pooled Retail Milk Purchased in the United Kingdom During 1990 and 1995

Location	Concentrations (ppt) TEQ (lipid)			
	CDD/CDFs (1990)[a]	CDD/CDFs (1995)	PCBs (1995)	CDD/CDF/PCBs[b] (1995/1996)
Bristol	2.0	0.92	2.2	3.1
Cambridge	1.4	0.84	1.5	2.3
Carlisle	1.1–1.4	0.67	0.75	1.4
Central London	1.4–3.3	0.99	1.7	2.7
Commuter London[c]	1.7–2.1	0.88	1.7	2.6
Crewe	—	1.4	2.1	3.5
Exeter	1.1–3.3	1.3	1.7	2.9
Northallerton	—	1.1	1.7	2.8
Norwich	—	1.1	2.1	3.2
Nottingham		1.1	2.3	3.5
Slough		0.80	1.6	2.4
Worchester	—	1.0	2.3	3.4

Note: I-TEF_{DF}s were used in calculating I-TEQ_{DF}s; TEF_P-WHO_{94}s were used in calculating TEQ_P-WHO_{94}s.

ppt = parts per trillion

a Some locations were sampled twice in 1990. Samples were also purchased from Beverley, Leeds, and Preston in 1990. Fat contents were not measured for the 1990 samples, and the whole milk concentrations were converted assuming 4 percent fat content, which is typical for UK whole milk.
b The combined concentrations of CDD/CDFs and PCBs were calculated before rounding.
c The individual pints forming this pool were purchased in outer London and the home counties.

Source: MAFF (1997a).

Table 6-2. CDD/F and PCB TEQ Concentrations and Percent Differences from Current TEQ Levels

Description	I-TEQ_{DF}, pg/g Lipid	TEQ_{P}-WHO_{94}, pg/g Lipid	Percent of Current I-TEQ_{DF} Levels[a]	Percent of Current TEQ_{P}-WHO_{94} Levels[a]
1908 Beef ration	0.34 (0.15)	0.07 (0.07)	38 (42)	15 (15)
1945 Beef and pork	0.98 (0.75)	0.36 (0.36)	89 (197)	140 (146)
1957 Dried cream	2.05 (0.81)	3.56 (3.54)	244 (96)	827 (824)
1968 Bacon bar	3.01 (2.94)	1.05 (1.05)	231 (638)	1747 (2620)
1968 Deviled ham	3.73 (3.71)	0.61 (0.61)	287 (805)	1019 (1529)
1971 Beef	1.36 (0.02)	2.48 (1.98)	153 (7)	540 (540)
1971 Bacon wafer	1.75 (1.62)	1.98 (1.98)	135 (352)	3301 (4952)
1977 Raw chicken	1.29 (1.18)	2.72 (2.72)	202 (287)	970 (970)
1977 Cooked chicken	1.33 (1.20)	2.83 (2.83)	209 (292)	1009 (1009)
1979 Pork slices	1.46 (1.20)	0.04 (0.04)	112 (262)	72 (105)
1980 Beef steak	0.94 (0.73)	0.93 (0.93)	106 (207)	203 (203)
1982 Ham slice	1.36 (1.04)	0.07 (0.07)	105 (227)	119 (178)
1983 Beef in bbq	0.50 (0.03)	0.79 (0.79)	56 (8)	171 (171)
1983 Turkey with gravy	0.55 (0.23)	0.32 (0.31)	85 (57)	113 (113)

Note: (results assume ND = ½ LOD; results calculated at ND = 0 shown in parenthesis)

pg/g = picograms per gram

a Current CDD/CDF/PCB levels are the levels observed in national food surveys for beef (Winters et al., 1996a, 1996b), pork (Lorber et al., 1997), poultry (Ferrario et al., 1997), and milk (Lorber et al., 1998).

Source: Winters et al. (1998).

Table 6-3. Estimated Upper Bound Dietary Intakes of CDD/CDFs and PCBs by the Average UK Consumer in 1982 and 1992

Food Group	CDD/CDF Intake (mean) (pg I-TEQ_{DF}/person/day)[a]		PCB Intake (mean) (pg TEQ_P-WHO_{94}/ person/day)[b]	
	1982	1992	1982	1992
Bread	3	4	2	2
Other cereal products	14	17	13	3
Carcass meat	16	4	10	3
Offals (internal organs)	3	1	0.3	0.2
Meat products	15	3	8	3
Poultry	8	2	4	1
Fish	7	3	13	6
Oils and fats	38	6	40	8
Eggs	22	3	5	2
Milk	48	17	28	11
Milk products	66	9	34	7
TOTAL	240	69	156	46

Note: Estimated total dietary intakes were calculated before rounding.

a MAFF (1995).
b Adapted from MAFF (1997b).

Table 6-4. Summary of Studies with Body Burden Data of Dioxins and Furans

Year	Mean TEQ, pg/g lipid	N	Ages (years)	Study #; Reference; Location
1972 1973 1974 1975 1976 1977 1978 1979 1980 1981	87 89 70 68 129 69 69 67 55 54	7 14 14 14 5 17 17 22 42 26	18-45	1; Kang et al., 1991; U.S. EPA, 1990. Vietnam Veterans, non-Vietnam Veterans, and Civilians.
1983	34	4	NA	2; Schecter et al., 1986; Binghamton
1985	47	35	$\bar{X}$ = 43 (21-88)	3; Graham et al., 1986; St. Louis
1986	31	4	$\bar{X}$ = 34 (19-55)	4; Patterson et al., 1994; Atlanta
1987	overall: 37 15-44: 27.5 > 45: 53.4	666	NA	5; Orban et al., 1987; U.S. EPA,1991; NHATS '87
1988	30	26	NA	6; Schecter et al., 1989; Massachusetts
1988	37	57	$\bar{X}$~50 (12-88)	7; Stanley et al., 1989; San Francisco and Los Angeles
1989	50	100	NA	8; Schecter et al., 1991; Syracuse
1991	29	44	$\bar{X}$ = 48 (41-66)	9; Schecter et al., 1993; Michigan Vietnam veterans
1996	32	100	NA	10; Schecter et al., 1997; Binghamton
1996	20	316	$\bar{X}$ = 45 (20-70)	11; CDC, 2000; background populations from site-specific studies in MO, OR, WS, AK, and NC.
1998	25	45	$\bar{X}$ = 45 (28-67)	12; Petreas et al., 2000; San Francisco

Table 6-5. Average Congener Concentrations for Body Burden Studies of Dioxins and Furans (columns are study number and sampling year; all results in pg/g lipid)

Congener	1; 1972	1; 1973	1; 1974	1; 1975	1; 1976	1; 1977	1; 1978	1; 1979	1; 1980	1; 1981
2378-D	22.4	20.2	14.5	15.3	26.8	11.8	11.6	12.5	11.0	11.9
12378-D	22.1	24.4	20.1	18.8	38.4	18.1	18.1	18.2	14.1	16.0
123478-D	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]	NA[1]
123678-D	170.6	189.4	168.4	148.9	304.6	152.9	175.0	154.9	133.4	124.5
123789-D	18.5	24.7	18.1	17.1	36.2	16.5	18.6	17.1	14.6	12.8
1234678-D	277.0	448.1	250.5	221.5	588.2	246.1	308.8	265.7	214.8	178.4
OCDD	1273.4	1768.0	1291.4	939.4	2790.0	1154.7	1325.1	1294.1	1004.2	810.4
2378-F	3.8	3.2	2.3	1.6	4.2	1.1	1.3	1.2	1.9	1.3
12378-F	1.2	0.6	0.2	0.3	1.3	0.1	0.2	0.1	0.3	0.2
23478-F	30.9	25.9	19.5	23.8	32.8	24.4	25.3	25.0	18.0	15.6
123478-F	27.6	29.3	24.5	17.1	34.1	20.7	24.3	20.8	16.6	14.6
123678-F	11.0	13.9	11.1	8.7	17.0	11.1	11.5	10.9	8.6	7.5
234678-F	3.7	4.8	3.1	2.6	6.6	3.4	3.5	3.1	2.6	1.7
123789-F	0 (ND)	0.2	0 (ND)	<0.1	0 (ND)	0.1	0 (ND)	<0.1	<0.1	0.1
1234678-F	52.7	57.4	44.2	31.3	49.7	35.8	37.2	32.3	30.6	23.7
1234789-F	1.9	1.5	0.8	0.6	1.7	0.8	1.5	1.1	0.7	0.4
OCDF	3.7	5.9	4.2	3.7	2.9	2.8	1.9	1.8	1.6	1.8
WHO- TEQ	**87**	**89**	**70**	**68**	**129**	**69**	**69**	**67**	**55**	**54**

Table 6-5. Average Congener Concentrations for Body Burden Studies of Dioxins and Furans (columns are study number and sampling year; all results in pg/g lipid) (continued)

Congener	2; 1983	3; 1985	4; 1986	5; 1987	6; 1988	7; 1988	8; 1989	9; 1991	10; 1996	11; 1996	12; 1998
2378-D	6.7	8.4	4.4	6.4	4.8	6.2	5.2	4.1	4.2	2.1	3.9
12378-D	10.3	19.2	11.6	12.9	7.8	12.7	21.0	8.3	9.8	5.2	6.3
123478-D	NA	NA	5.1	NA	9.1	14.0	13.0	NA	10.6	6.2	NA
123678-D	55.9	107.5	94.2	90.7	64.1	70.1	84.0	76.2	67.9	73.1	57.6
123789-D	8.0	NA	16.9	13.3	13.3	12.8	15.0	10.9	10.7	7.1	NA
1234678-D	88.2	253.3	55.6	129.7	126.3	124.8	187.0	108.8	116.5	79.2	68.6
OCDD	579.5	1273.3	446	876.4	1054.6	700.7	1174.0	731.0	879.8	664.0	528.3
2378-F	1.3	NA	1.1	1.9	NA	2.7	3.1	2.1	ND (2.00)	0.7	NA
12378-F	NA	NA	NA	NA	NA	1.0	2.8	1.2	ND (1.9)	0.8	NA
23478-F	13.9	12.0	3.7	12.0	9.1	8.0	13.0	8.5	9.3	6.2	10.5
123478-F	13.4	NA	3.7	NA	13.1	8.8	15.0	10.5	14.0	6.5	5.9
123678-F	8.5	NA	5.8	7.0	7.3	5.4	14.0	5.5	7.9	5.3	4.1
234678-F	NA	NA	NA	NA	1.9	2.2	3.6	2.9	ND (4.1)	6.2	NA
123789-F	NA	NA	NA	NA	NA	0.6	ND (1.2)	2.7	4	0.7	NA
1234678-F	16.0	NA	12.0	NA	26.0	11.0	36.0	19.0	13.9	13.2	NA
1234789-F	9.1	NA	NA	NA	NA	60.1	ND (1.8)	3.2	4.9	1.3	NA
OCDF	5.8	NA	NA	NA	NA	1.2	4.2	9.9	ND (5.00)	2.1	NA
WHO- TEQ	**34**	**47**	**31**	**37**	**30**	**37**	**50**	**29**	**32**	**20**	**25**

[1] For these data, 123478-HxCDD and 123678-HxCDD were measured together and reported as, 123478/678-HsCDD.

Table 6-6. Comparison of the 15-44 Age Group Average Concentration of Selected Congeners from NHATS FY82 and NHATS FY87

Congener	NHATS FY82	NHATS FY87
2,3,7,8-TCDD	6.87	4.33
1,2,3,7,8-PCDD	125.0	9.48
1,2,3,4,6,7,8-HpCDD	114.0	99.8
OCDD	760.0	726.0

Source: U.S. EPA (1991).

Table 6-7. Trends in Blood CDD/CDF Levels in a German Population, 1991-1996

Year	1991	1992	1993	1994	1995	1996
Number of samples	95	157	17	74	69	95
Mean age (yrs)	44.7	42.4	40.5	46.5	45.2	37.7
Fat content (mg/g)	5.7	5.7	6.0	6.0	5.7	5.1
Mean total CDD/CDF concentration (pg/g)	718.4	703.2	534.5	376.7	431.6	373.1

Source: Wittsiepe et al. (1998).

Table 6-8. Comparison of Results from the First and Second Round of WHO-Coordinated Human Milk Study

Country	Area	CDDs and CDFs (pg I-TEQ$_{DF}$/g)				∑ [Marker PCBs] (ng/g)			
		1987/88[a]	n	1992/93	n	1987/88	n	1992/93	n
Austria	Vienna (urban)	17.1	54	10.7	13			381	13
	Tulln (rural)	18.6	51	10.9	21			303	21
Belgium	Brabant Wallou	33.7		20.8	8	558	12	275	8
	Liege	40.2		27.1	20	609	21	306	20
	Brussels	38.8		26.6	6			260	6
Canada	All Provinces 1981			28.6	200			212	200
	All Provinces 1982			14.5	100			112	100
	Maritimes	15.6	19	10.8	20			86	20
	Québec	18.1	34	13.4	20			137	20
	Ontario[b]	17.6	76	18.1	20			128	20
	Prairies	19.4	31	14.6	20			58	20
	British Columbia	23.0	23	15.7	20			70	20
Croatia	Kirk	12.0	14	8.4	10	500[c]	14	218	10
	Zagreb	11.8	41	13.5	13	450[c]	41	219	13
Denmark	Several Regions/Cities	17.8	42	15.2	48	830[c]	10	209	48
Finland	Helsinki	18.0	38	21.5	10	150	38	189	10
	Kuopio	15.5	31	12.0	24	203	31	133	24
Germany	Berlin	32.0	40	16.5	10			375	10
	North Rhine-Westphalia	31.6	79	20.7[e]		762	143		
Hungary	Budapest	9.1	100	8.5	20			61	20
	Scentes	11.3	50	7.8	10			45	10
Netherlands	Rural Area	37.4	13			416	10		
	Urban Area	39.6	13			392	10		
	All Regions	34.2	10	22.4	17	272	96	253	17
Norway[d]	Tromsø (coastal)	18.9	11	10.1	10	562[c]	10	273 (536[c])	10
	Hamar (rural)	15.0	10	9.3	10	507[c]	10	265 (4c83[c])	10
	Skien/Porsgrumm (ind)	19.4	10	12.5	10	533[c]	8	302 (468[c])	10
United Kingdom	Birmingham	37.0		17.9	20			129	20
	Glasgow	29.1		15.2	23			131	23

NOTE: Results are expressed on a fat basis. ∑ (marker PCBs) and I-TEQ$_{DF}$s are calculated assuming non-detect values are equal to zero.

a Calculated using Nordic TEF-model.
b Ontario-1988 denotes proportional mean of two pooled samples analyzed in the first round.
c Analyzed using packed column technique.
d To compare results between first and second round, samples from 1992/93 have been reanalyzed using (old) packed column technique (Becher and Skåre, personal communication).
e Dioxin levels in human milk samples from North Rhine-Westphalia collected in 1992 as reported by Fürst (1993).

Source: Liem et al. (1996).

Table 6-9. Comparison of CDD/CDF Concentrations in Human Milk from Finland in 1987 and 1992–1994

Selected Congeners	Conc. pg/g fat in 1992-1994		Conc. pg/g fat in 1987	
	Urban Area n = 14	Rural Area n = 28	Urban Area n = 47	Rural Area n = 37
2,3,7,8-TCDF	1.93 ± 0.74***	0.49 ± 0.44	2.98 ± 2.89	6.75 ± 4.29^{xxx}
2,3,7,8-TCDD	2.66 ± 1.46	1.71 ± 0.68	3.37 ± 1.85	2.50 ± 1.25^{x}
2,3,4,7,8-PeCDF	16.3 ± 7.0*	10.4 ± 4.65	20.1 ± 12.5	13.1 ± 5.41
1,2,3,7,8-PeCDD	6.22 ± 2.16*	4.36 ± 1.56	9.78 ± 4.87^{xxx}	7.53 ± 3.23^{xxx}
1,2,3,6,7,8-HxCDD	33.2 ± 8.94	26.9 ± 8.16	48.2 ± 15.8^{xxx}	41.5 ± 15.3^{xxx}
OCDD	230 ± 80.9***	126 ± 55.7	187 ± 83.6	171 ± 71.5^{xxx}
$\sum$CDD/CDF	381 ± 120***	217 ± 76.6	375 ± 132	339 ± 108^{xxx}
I-TEQ$_{DF}$	19.9 ± 7.42*	13.6 ± 4.57	26.3 ± 11.9	20.1 ± 6.54^{xxx}

Note:

Asterisks indicate a statistically significant difference between urban and rural areas in 1992–1994.
* $p < 0.01$
** $p < 0.005$
*** $p < 0.001$

x indicates a statistically significant difference between 1987 and 1992–1994 results
^{x} $p < 0.01$
^{xx} $p < 0.005$
^{xxx} $p < 0.001$

Source: Kiviranta et al. (1998).

Table 6-10. Mean Human Lipid TCDD Concentrations Reported in Various U.S. Studies

Study (Reference)	Age/Gender Group	Sample Size	Year	TCDD Mean, pg/g	Standard Error of the Mean
Andrews et al. (1989)	18-29, both	14	1986	4.0	0.95
	30-39, both	30	1986	5.9	0.65
	40-49, both	25	1986	5.5	0.71
	50-59, both	22	1986	8.0	0.76
	60-79, both	37	1986	9.5	0.59
Air Force (Michalek et al., 1997)	35-39, male	168	1987	3.8	0.23
	40-44, male	280	1987	4.0	0.18
	45-49, male	165	1987	4.6	0.23
	50-54, male	232	1987	4.7	0.20
	55-59, male	142	1987	4.8	0.25
	60-64, male	33	1987	5.0	0.52
	65-69, male	35	1987	6.2	0.51
NHATS 82 (U.S. EPA, 1991)	0-14, both	178	1982	4.2	0.69
	15-44, both	312	1982	6.9	0.87
	45+, both	273	1982	5.5	0.84
NHATS 87 (U.S. EPA, 1991)	0-14, both	146	1987	2.0	0.82
	15-44, both	318	1987	4.4	0.52
	45+, both	401	1987	9.4	0.41
VA/EPA (VA/U.S. EPA,1988)	20-36, male	27	1971–1973	19.8	1.2
	23-39, male	29	1974–1976	17.3	1.2
	26-42, male	57	1977–1979	11.6	1.2
	29-45, male	82	1980–1982	12.6	1.2

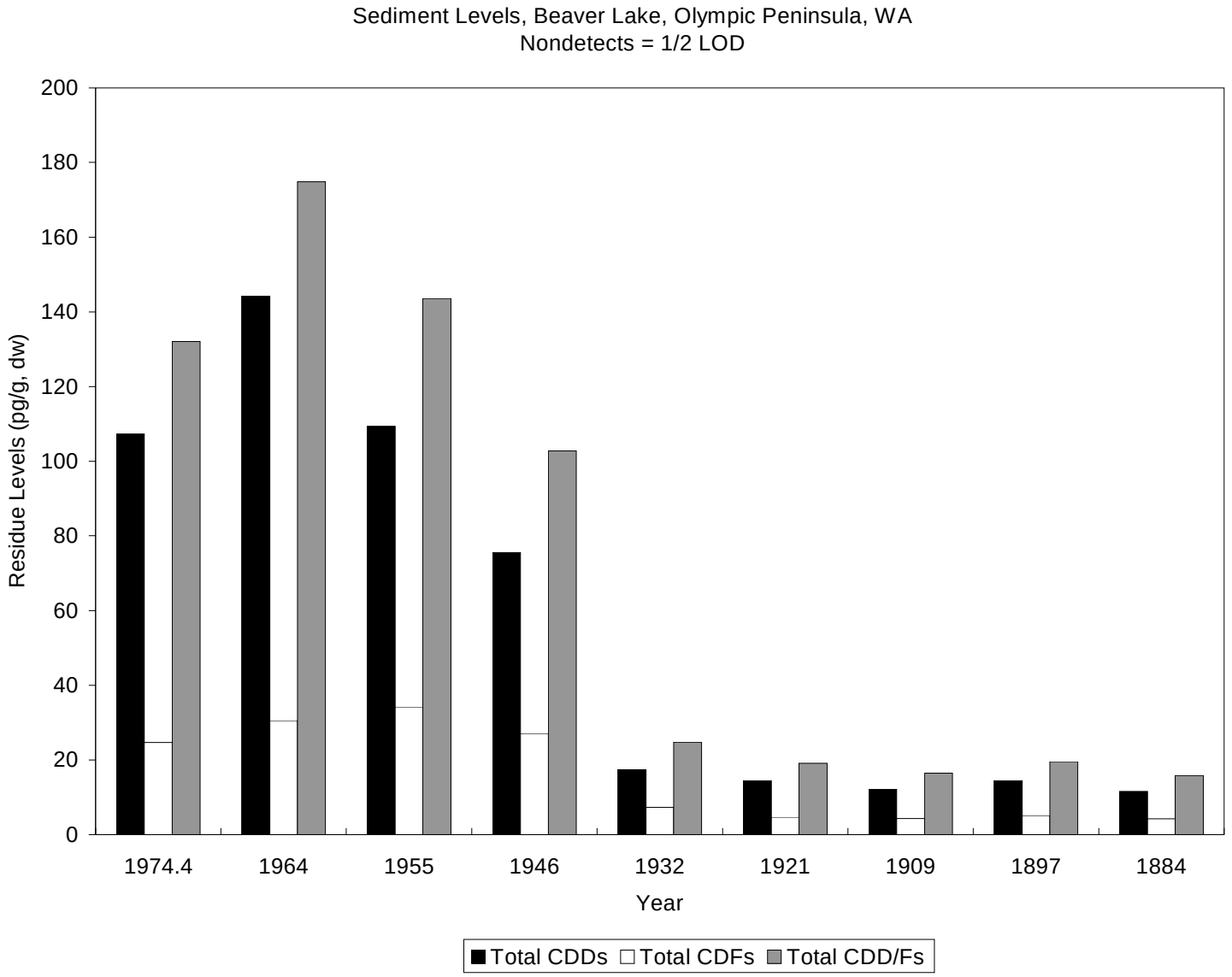


Figure 6-1. CDD/CDF Levels in Sediment, Beaver Lake, Washington

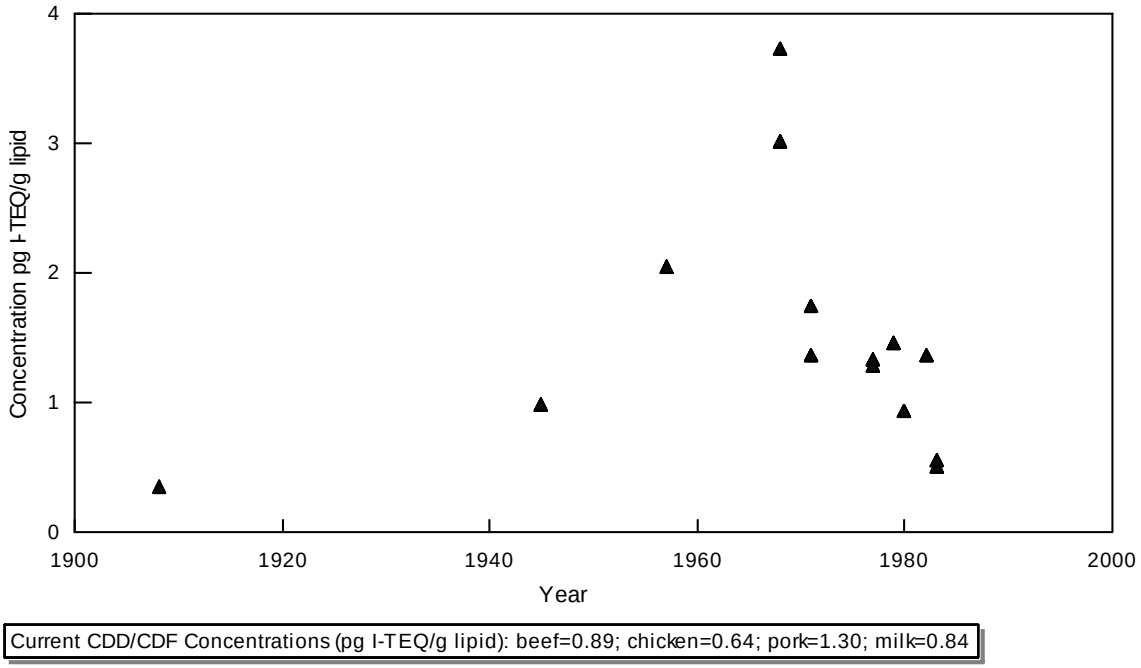


Figure 6-2. I-TEQ$_{DF}$ Concentrations of Historical Food Samples from the U.S. (results calculated at ND = ½ LOD)

Source: Adapted from Winters et al. (1998).

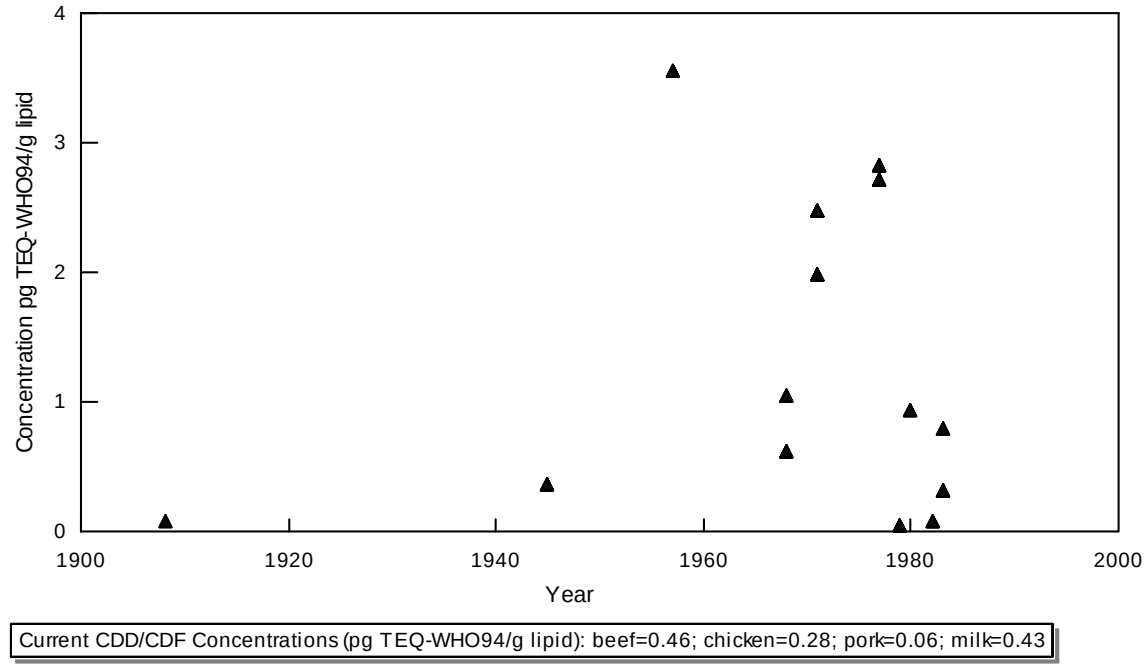


Figure 6-3. TEQ$_{P}$-WHO$_{94}$ Concentrations of Historical Food Samples from the U.S. (results calculated at ND = ½ LOD)

Source: Adapted from Winters et al. (1998).

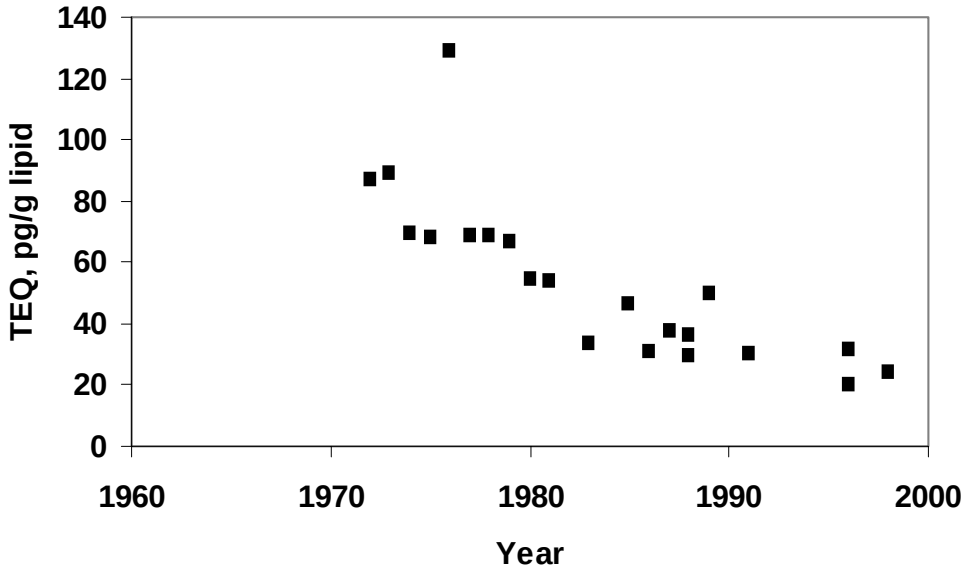
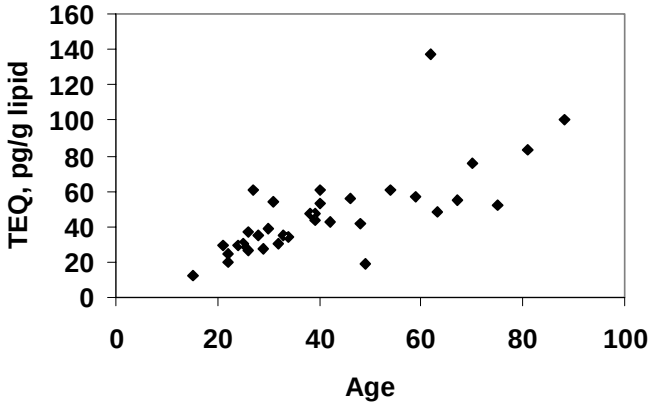
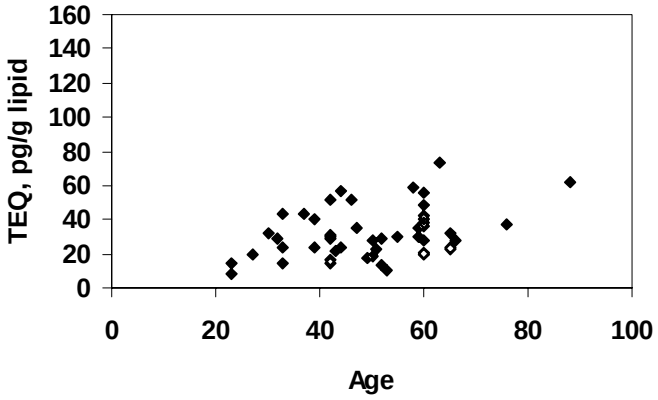


Figure 6-4. Average Adult Population TEQ_{DF} -WHO_{98} Concentrations as a Function of Year (all results in ppt lipid).

(a) Missouri, 1985 (n = 35), average = 47.0 ppt lipid (Graham et al., 1986)



(b) California, 1988 (n = 57), average = 31.0 ppt lipid (Orban et al., 1989)



(c) CDC data, 1995-1997 (n - 216), average = 18.3 pg/g lipid (CDC, 2000)

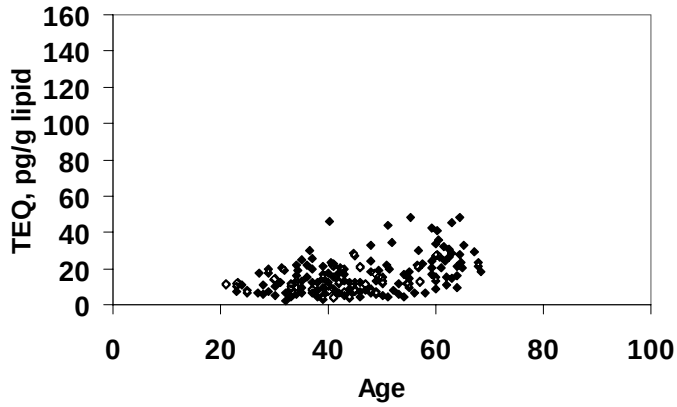


Figure 6-5. Age Trend Relationships for Three Studies.

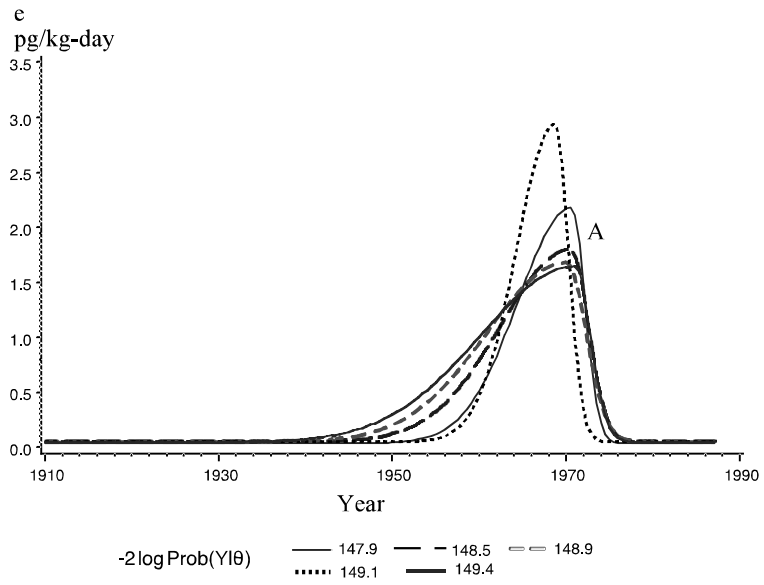


Figure 6-6. Examples of Temporal Exposure Curves for 2,3,7,8-TCDD, e(t) in Units of pg/kg-day.

Source: Pinsky and Lorber (1998).

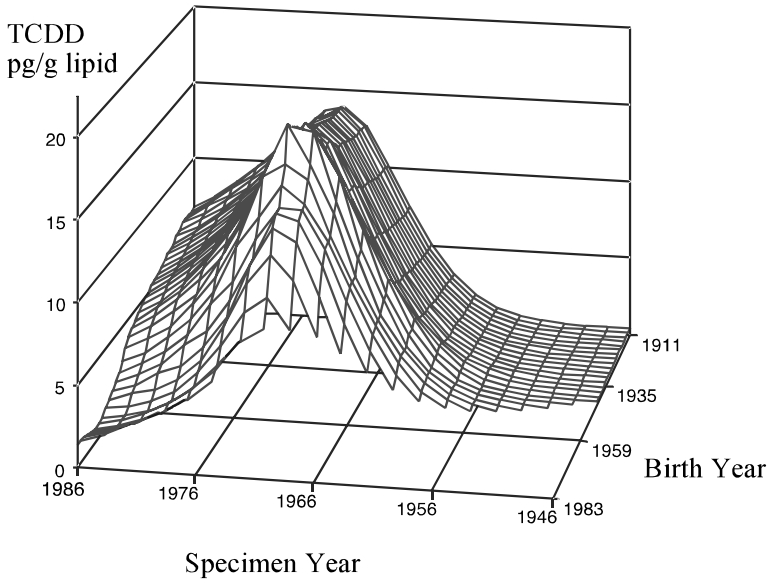


Figure 6-7. Predicted Mean TCDD Lipid Concentrations (pg/g) in Males by Birth Year and Specimen Year Derived Using e(t) Curve Labeled A in Figure 6-6

Source: Pinsky and Lorber (1998).

APPENDIX A. ENVIRONMENTAL CHEMISTRY

The tables in this appendix are discussed in Chapter 2. References listed at the end of each table are included in the reference list at the end of Chapter 2. Following are the tables included in this Appendix:

Table A-1. P-Chem Properties for the Dioxin, Furan, and PCB Congeners

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
Tetrachlorodibenzo-p-dioxins (MW = 321.98)												
1,2,3,4-TCDD 30746-58-8	3.88E-04-6.30E-04 [5.50E-04]	25 [25]	5,38,46,51,53 [53]	1.81E-08-4.80E-08 [4.80E-08]	25 [25]	9,33,53 [9,53]	1.99E-05-(3.70E-05) [1.99E-05]	5,51,53 [51]	(5.50)-(8.97) [6.60]	5,7,8,10, 26,29,53 [53]		
1,2,3,6-TCDD 71669-25-5									6.86	10		
1,2,3,7-TCDD 67028-18-6	2.80E-04-7.30E-04 [4.20E-04]	20-26 [20]	6,53 [6,53]	(7.50E-09)-(5.3E-08) [7.50E-09]	25 [25]	9,21,52,53 [21,53]	(7.57E-06)	9,53	(5.50)-(8.81) [6.90]	5,7,8,10, 26,53 [53]	4.26-6.55	45,53
1,2,3,8-TCDD 53555-02-5									6.48	10		
1,2,3,9-TCDD 71669-26-6									6.39	10		
1,2,4,6-TCDD 71669-27-7									6.10	10		
1,2,4,7-TCDD 71669-28-8									6.25	10		
1,2,4,8-TCDD 71669-29-9									6.25	10		
1,2,4,9-TCDD 71665-99-1									6.10	10		
1,2,6,7-TCDD 40581-90-6												
1,2,6,8-TCDD 67323-56-2									6.43	10		
1,2,6,9-TCDD 40581-91-7												

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,7,8-TCDD 34816-53-0									6.38	10		
1,2,7,9-TCDD 71669-23-3									6.86	10		
1,2,8,9-TCDD 62470-54-6												
1,3,6,8-TCDD 33423-92-6	1.68E-04-(6.0E-04) [3.2E-04]	20-25 [20]	6,7,38,53 [7,53]	(5.25E-09)-4.03E-06 [5.25E-09]	20-25 [25]	7,9,53 [9,53]	(5.92E-06)-6.81E-05 [6.95E-06]	5,7,53 [53]	(5.5)-(9.43) [7.10]	5,7,8,10, 26,53 [5,53]	2.05-(6.74)	53
1,3,6,9-TCDD 71669-24-4									6.25	10		
1,3,7,8-TCDD 50585-46-1				(6.3E-09)	25	9			6.30	10		
1,3,7,9-TCDD 62470-53-5									6.39-7.06 [6.39]	8,10 [10]		
1,4,6,9-TCDD 40581-93-9									6.38	10		
1,4,7,8-TCDD 40581-94-0									6.39	10		
2,3,7,8-TCDD 1746-01-6	7.91E-06-4.83E-04 [1.93E-05]	17-25 [25]	1,2,4,5,27, 36,50,53 [4,53]	7.40E-10-3.38E-08 [1.50E-09]	25 [25]	2,3,5,9,3 4,53 [9,53]	(2.07E-08)-(1.02E-04) [3.29E-05]	2,3,5,53 [53]	5.38-8.93 [6.80]	2,4,5,8,10, 50,53 [53]	3.06-8.50 [6.4-6.66]	32,47,48, 49,50,53,57 [50,57]
Congener Group Average	(3.3E-04)	25	20	(1.4E-08)	25	20	(1.7E-05)	20	(6.5)	20		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
Pentachlorodibenzo-p-dioxins (MW = 356.42)												
1,2,3,4,6-PeCDD 67028-19-7									6.30	10		
1,2,3,4,7-PeCDD 39227-61-7	9.55E-05-8.16E-03 [1.18E-04]	20-26 [20]	5,6,38,53 [6,53]	(6.60E-10)-7.5E-09 [6.60E-10]	25 [25]	5,9,53 [9,53]	(2.63E-06)	5,53	6.60-(10.05) [7.40]	5,7,8,10, 26,53 [53]	4.85-6.38	45,53
1,2,3,6,7-PeCDD 71925-15-0									6.74	10		
1,2,3,6,8-PeCDD 71925-16-1									6.53	10		
1,2,3,6,9-PeCDD 82291-34-7									6.24	10		
1,2,3,7,8-PeCDD 40321-76-4				(4.4E-10)-9.48E-10 [4.40E-10]	25 [25]	9,33 [9]			6.64	10		
1,2,3,7,9-PeCDD 71925-17-2									6.40	10		
1,2,3,8,9-PeCDD 71925-18-3												
1,2,4,6,7-PeCDD 82291-35-8												
1,2,4,6,8-PeCDD 71998-76-0												
1,2,4,6,9-PeCDD 82291-36-9									6.60	10		
1,2,4,7,8-PeCDD 58802-08-7				(5.8E-10)	25	9			6.20	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,4,7,9-PeCDD 82291-37-0												
1,2,4,8,9-PeCDD 82291-38-1												
Congener Group Average	(1.18E-04)	20	20	(5.6E-10)	25	20	(2.6E-06)	20	(6.6)	20		
Hexachlorodibenzo-p-dioxins (MW = 390.87)												
1,2,3,4,6,7-HxCDD 58200-66-1												
1,2,3,4,6,8-HxCDD 58200-67-2									6.85	10		
1,2,3,4,6,9-HxCDD 58200-68-3												
1,2,3,4,7,8-HxCDD 39227-28-6	4.00E-06-6.44E-06 [4.42E-06]	21-26 [25]	5,6,53 [6,53]	(3.8E-11)-1.01E-10 [3.8E-11]	25 [25]	5,9,33,53 [9,53]	(1.07E-05)-(4.46E-05) [1.07E-05]	5,19,53 [53]	7.79-10.44 [7.80]	7,8,26,53 [53]	5.02-(7.10)	45,53
1,2,3,6,7,8-HxCDD 57653-85-7				(3.6E-11)	25	9						
1,2,3,6,7,9-HxCDD 64461-98-9									7.59	10		
1,2,3,6,8,9-HxCDD 58200-69-4									7.59	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,3,7,8,9-HxCDD 19408-74-3				(4.9E-11)	25	9						
1,2,4,6,7,9-HxCDD 39227-62-8				(5.1E-11)	25	9			6.85	10		
1,2,4,6,8,9-HxCDD 58802-09-8									6.85	10		
Congener Group Average	(4.4E-06)	25	20	(4.4E-11)	25	20	(1.1E-05)	20	(7.3)	20		
Heptachlorodibenzo-p-dioxins (MW = 425.31)												
1,2,3,4,6,7,8-HpCDD 35822-46-9	2.3E-06-2.56E-06 [2.4E-06]	20-26 [20]	5,6,53 [6,53]	(5.6E-12)-(2.40E-10) [5.6E-12]	25 [25]	9,33,53 [9,53]	(1.31E-06)-(1.26E-05) [1.26E-05]	5,53 [53]	7.92-(11.98) [8.00]	7,8,10,26,53 [53]	5.47-(7.80)	53
1,2,3,4,6,7,9-HpCDD 58200-70-7												
Congener Group Average	(2.4E-06)	20	20	(5.6E-12)	25	20	(1.3E-05)	20	(8.0)	20		
Octachlorodibenzo-p-dioxin (MW = 460.76)												
1,2,3,4,6,7,8,9-OCDD 3268-87-9	7.4E-08-7.36E-06 [7.4E-08]	20-25 [25]	5,6,7,53 [5,53]	(8.25E-13)-6.54E-08 [8.25E-13]	20-25	7,9,33,53 [9,53]	(6.75E-06)	5,53	(7.5)-(13) [8.20]	5,7,8,26,29,53 [5,53]	5.92-(7.90)	53
Tetrachlorodibenzofurans (MW = 305.98)												
1,2,3,4-TCDF 30402-14-3				(3.1E-08)	25	21			6.17	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,3,6-TCDF 83704-21-6									6.15	10		
1,2,3,7-TCDF 83704-22-7				(3.2E-08)	25	21						
1,2,3,8-TCDF 62615-08-1				(2.1E-08)	25	21			6.15	10		
1,2,3,9-TCDF 83704-23-8									6.06	10		
1,2,4,6-TCDF 71998-73-7												
1,2,4,7-TCDF 83719-40-8												
1,2,4,8-TCDF 64126-87-0				(2.2E-08)	25	21			6.31	10		
1,2,4,9-TCDF 83704-24-9												
1,2,6,7-TCDF 83704-25-0				(2.0E-08)	25	21			6.25	10		
1,2,6,8-TCDF 83710-07-0												
1,2,6,9-TCDF 70648-18-9												
1,2,7,8-TCDF 58802-20-3				(1.8E-08)	25	21			6.23	10		
1,2,7,9-TCDF 83704-26-1				(2.5E-08)	25	21			6.25	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,8,9-TCDF 70648-22-5												
1,3,4,6-TCDF 83704-27-2									6.31	10		
1,3,4,7-TCDF 70648-16-7									6.23	10		
1,3,4,8-TCDF 92341-04-3									6.13	10		
1,3,4,9-TCDF 83704-28-3									5.89	10		
1,3,6,7-TCDF 57117-36-9				(2.8E-08)	25	21						
1,3,6,8-TCDF 71998-72-6				(2.7E-08)	25	21			6.37	10		
1,3,6,9-TCDF 83690-98-6												
1,3,7,8-TCDF 57117-35-8									6.34	10		
1,3,7,9-TCDF 64560-17-4				(1.9E-08)	25	21			6.34	10		
1,4,6,7-TCDF 66794-59-0				(2.6E-08)	25	21			6.15	10		
1,4,6,8-TCDF 82911-58-8												
1,4,6,9-TCDF 70648-19-0									5.60	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,4,7,8-TCDF 83704-29-4												
1,6,7,8-TCDF 83704-33-0									6.17	10		
2,3,4,6-TCDF 83704-30-7				(4.0E-08)	25	21			6.11	10		
2,3,4,7-TCDF 83704-31-8				(2.9E-08)	25	21			6.06	10		
2,3,4,8-TCDF 83704-32-9				(2.8E-08)	25	21						
2,3,6,7-TCDF 57117-39-2				(2.1E-08)	25	21			6.31	10		
2,3,6,8-TCDF 57117-37-0				(2.0E-08)	25	21			6.73	10		
2,3,7,8-TCDF 51207-31-9	4.19E-04	22.7	11	8.96E-09-(1.5E-08) [1.5E-08]	25 [25]	21,33,53 [21,53]	(1.44E-05)-(1.48E-05) [1.44E-05]	53,54 [53]	5.82-6.53 [6.1]	8,10,53 [53]	(5.20)-(7.50)	53
2,4,6,7-TCDF 57117-38-1				(3.3E-08)	25	21			6.25	10		
2,4,6,8-TCDF 58802-19-0				(2.0E-08)	25	21			6.17	10		
3,4,6,7-TCDF 57117-40-5												
Congener Group Average	(4.2E-04)	22.7	20	(2.5E-08)	25	20	(1.4E-05)	20	(6.2)	20		
Pentachlorodibenzofurans (MW = 340.42)												

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,3,4,6-PeCDF 83704-47-6				(2.7E-09)	25	21						
1,2,3,4,7-PeCDF 83704-48-7									6.53	10		
1,2,3,4,8-PeCDF 67517-48-0				(3.6E-09)	25	21			6.79	10		
1,2,3,4,9-PeCDF 83704-49-8												
1,2,3,6,7-PeCDF 57117-42-7				(2.2E-09)	25	21			6.26	10		
1,2,3,6,8-PeCDF 83704-51-2									6.33	10		
1,2,3,6,9-PeCDF 83704-52-3												
1,2,3,7,8-PeCDF 57117-41-6				(1.7E-09)-2.72E-09 [1.7E-09]	25	21,33 [21]			6.79	10		
1,2,3,7,9-PeCDF 83704-53-4												
1,2,3,8,9-PeCDF 83704-54-5												
1,2,4,6,7-PeCDF 83704-50-1				(3.5E-09)	25	21			6.27	10		
1,2,4,6,8-PeCDF 69698-57-3				(2.3E-09)	25	21			6.34	10		
1,2,4,6,9-PeCDF 70648-24-7									6.59	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,4,7,8-PeCDF 58802-15-6				(1.5E-09)	25	21			6.26	10		
1,2,4,7,9-PeCDF 71998-74-8				(2.6E-09)	25	21			6.19	10		
1,2,4,8,9-PeCDF 70648-23-6												
1,2,6,7,8-PeCDF 69433-00-7				(1.9E-09)	25	21			6.42	10		
1,2,6,7,9-PeCDF 70872-82-1									6.51	10		
1,3,4,6,7-PeCDF 83704-36-3				(2.7E-09)	25	21			6.19	10		
1,3,4,6,8-PeCDF 83704-55-6									6.24	10		
1,3,4,6,9-PeCDF 70648-15-6									6.34	10		
1,3,4,7,8-PeCDF 58802-16-7				(4.3E-09)	25	21						
1,3,4,7,9-PeCDF 70648-20-3									6.33	10		
1,3,6,7,8-PeCDF 70648-21-4												
1,4,6,7,8-PeCDF 83704-35-2									6.53	10		
2,3,4,6,7-PeCDF 57117-43-8				(2.4E-09)	25	21			6.47	10		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
2,3,4,6,8-PeCDF 67481-22-5				(1.9E-09)	25	21			6.59	10		
2,3,4,7,8-PeCDF 57117-31-4	2.36E-04	22.7	11	(2.63E-09)-3.29E-09 [2.63E-09]	25 [25]	21,33 [53]	(4.98E-06)	53	6.92-(7.82) [6.5]	10,53 [53]	5.59-(7.40)	53
Congener Group Average	(2.4E-04)	22.7	20	(2.7E-09)	25	20	(5.0E-06)	20	(6.4)	20		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
Hexachlorodibenzofurans (MW = 374.87)												
1,2,3,4,6,7-HxCDF 79060-60-9				(2.4E-10)	25	21						
1,2,3,4,6,8-HxCDF 69698-60-8				(2.2E-10)	25	21						
1,2,3,4,6,9-HxCDF 91538-83-9				(4.1E-10)	25	21						
1,2,3,4,7,8-HxCDF 70648-26-9	8.25E-06	22.7	11	(2.4E-10)-(6.7E-10) [2.4E-10]	25 [25]	21,52,53 [21,53]	(1.43E-05)	19	(7.0)	53	(7.40)	53
1,2,3,4,7,9-HxCDF 91538-84-0				(2.8E-10)	25	21						
1,2,3,4,8,9-HxCDF 92341-07-6												
1,2,3,6,7,8-HxCDF 57117-44-9	1.77E-05	22.7	11	(2.2E-10) - (6.68E-10) [2.2E-10]	25 [25]	21,53 [21,53]	(6.1E-06)-(7.31E-06) [7.31E-06]	19,53 [53]				
1,2,3,6,7,9-HxCDF 92341-06-5												
1,2,3,6,8,9-HxCDF 75198-38-8				(3.4E-10)	25	21						

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] ($atm\text{-}m^3/mol$)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,3,7,8,9-HxCDF 72918-21-9				(1.8E-10)	25	21						
1,2,4,6,7,8-HxCDF 67562-40-7				(2.6E-10)	25	21						
1,2,4,6,7,9-HxCDF 75627-02-0				(5.7E-10)	25	21						
1,2,4,6,8,9-HxCDF 69698-59-5				(1.8E-10)	25	21						
1,3,4,6,7,8-HxCDF 71998-75-9				(2.3E-10)	25	21						
1,3,4,6,7,9-HxCDF 92341-05-4												
2,3,4,6,7,8-HxCDF 60851-34-5				(2.0E-10)	25	21						
Congener Group Average	(1.3E-05)	22.7	20	(2.8E-10)	25	20	(1.1E-05)	20	(7.0)	20		
Heptachlorodibenzofurans (MW = 409.31)												
1,2,3,4,6,7,8-HpCDF 67562-39-4	1.35E-06	22.7	11	(3.5E-11)-1.33E-10 [3.5E-11]	25 [25]	21,33 [21,53]	(1.41E-05)-(5.3E-05) [1.41E-05]	19,53 [53]	7.92-(9.25) [7.4]	10,53 [53]	6.00-(7.90)	53

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
1,2,3,4,6,7,9-HpCDF 70648-25-8												
1,2,3,4,6,8,9-HpCDF 69698-58-4				(5.8E-11)	25	21						
1,2,3,4,7,8,9-HpCDF 55673-89-7				(4.7E-11)-1.07E-10 [4.7E-11]	25 [25]	21,33 [21,53]					5.00-(6.70)	53
Congener Group Average	(1.4E-06)	22.7	20	(4.7E-11)	25	20	(1.4E-05)	20	(7.4)	20		
Octachlorodibenzofurans (MW = 444.76)												
1,2,3,4,6,7,8,9-OCDF 39001-02-0	(1.16E-06)	25	11	(3.75E-12)	25	21	(1.88E-06)	19	(7.0)-(13) [8.0]	8,26,29,53 [53]	6.00-(7.40)	53
Tetrachloro-PCB (MW = 291.99)												
3,3',4,4'-TCB 32598-13-3	(5.5E-04)-(1.7E-01) [1.03E-03]	25	12,13,17,28,35,38,40,44,56 [56]	1.37E-07-4.47E-07 [4.47E-07]	25	13,18,56 [56]	1.70E-05-(1.0E-04) [1.70E-05]	13,35,39,56 [56]	5.62-6.77 [6.5]	8,15,31,55,56 [56]	(4.41)-(5.75)	56
3,4,4',5-TCB 70362-60-4 (81)	2.92E-03	25	17	(7.85E-07)	25	18	1.28E-04	41	(6.36)	15		
Pentachloro-PCB (MW = 326.44)												
2,3,3',4,4'-PeCB 32598-14-4	(1.9E-03)-(1.1E-02) [1.90E-03]	25	17,35,37,56 [35]	(8.28E-07)	25	18	(6.0E-05)-(9.93E-05) [9.93E-05]	16,35 [35]	(6.3)-(6.6) [6.0]	15,37,55,56 [56]		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] (atm-m^3/mol)	Ref.	Value[a]	Ref.	Value[a]	Ref.
2,3,4,4',5-PeCB 74472-37-0	(2.58E-03)- (1.1E-02) [2.58E-03]	20-25 [20]	17,35,37,41 [41]	(4.18E-07)- (1.43E-04) [4.18E-07]	20-25 [20]	18,41 [41]	6.90E-05- (1.4E-04) [6.90E-05]	16,35,41 [41]	(6.3)-(6.65) [6.65]	15,37 [15]		
2,3',4,4',5-PeCB 31508-00-6	(1.59E-03)- (1.1E-02) [1.59E-03]	20-25 [20]	17,35,37,41 [41]	(3.14E-07)- (1.38E-06) [3.14E-07]	20-25 [20]	18,41 [41]	8.50E-05- 4.0E-04 [8.50E-05]	16,35,41, 43 [41]	(6.2)-7.12 [7.12]	15,31,37, 55 [31]	(5.7)	42
3,3',4,4',5-PeCB 57465-28-8	(1.03E-03)	25	17	(2.19E-07)- (3.72E-07) [2.96E-07]	25	18 [18]	(5.4E-05)- (8.2E-05) [5.40E-05]	16,35 [35]	(6.26)- (6.89) [6.89]	15,37 [15]		
2',3,4,4',5-PeCB 65510-44-3	(1.64E-03)	25	17	(7.62E-07)- (9.95E-07) [8.78E-07]	25	18 [18]	(1.74E-04)- (2.62E-04) [1.74E-04]	16,35 [35]	(6.74)	15		
Hexachloro-PCB (MW = 360.88)												
2,3,3',4,4',5- HxCB 38380-08-4	(4.10E-04)- (2.4E-03) [4.10E-04]	20-25 [20]	17,37,41 [41]	(1.47E-07)	25	18	(2.2E-05) -8.7E-04 [8.70E-04]	16,35,43 [43]	(6.64)- (7.16) [7.16]	14,15,37 [14]		
2,3,3',4,4',5'- HxCB 69782-90-7	(3.61E-04)	25	17	(5.47E-08)- (1.08E-07) [5.47E-08]	25	18	(6.6E-05) -5.8E-04 [5.80E-04]	16,35,43 [43]	7.18-(7.20) [7.19]	14,15 [14]		
2,3',4,4',5,5'- HxCB 52663-72-6	(3.61E-04)- (2.44E-03) [3.61E-04]	25	17,37 [17]	(1.46E-07)- (1.95E-07) [1.95E-07]	25	18	(1.1E-04)- (1.2E-04) [1.10E-04]	16,35 [35]	(6.64)- (7.27) [7.09]	14,15,37 [14]		
3,3',4,4',5,5'- HxCB 32774-16-6	(3.61E-05)- (2.5E-03) [3.61E-05]	25	17,35,37 [17]	(8.1E-09)- (3.5E-07) [1.81E-07][d]	25	56	(1.6E-05)- (6.5E-05) [6.52E-05]	16,35,56 [35]	(6.64)-7.46 [7.46]	14,15,37, 56 [14]	(6.60)	56
Heptachloro-PCB (MW = 396.33)												
2,3,3',4,4',5,5'- HpCB 39635-31-9	(4.5E-05)- (5.3E-04) [6.26E-05]	25	17,35,37 [17]	(1.19E-08)- (1.73E-08) [1.31E-08]	25	18	(6.6E-05)	35	(7.0)-(7.71) [7.71]	15,37 [15]		

Table A-1 (continued)

Congener	Water Solubility			Vapor Pressure			Henry's Law Constant		Log K_{ow}		Log K_{oc}	
CAS No.	Value[a,c] (mg/l)	Temp. (°C)	Ref.	Value[a,b] (mm Hg)	Temp. (°C)	Ref.	Value[a] ($atm\text{-}m^3/mol$)	Ref.	Value[a]	Ref.	Value[a]	Ref.
2,2',3,3',4,4',5-HpCB 35065-30-6	(1.19E-04)-(5.21E-04) [2.27E-04]	20-25 [20]	17,35,37,41 [41]	(6.46E-09)-8.60E-09 [6.46E-09]	20-25 [25]	18,41 [41]	(1.50E-05)-(8.73E-05) [1.50E-05]	35,41 [41]	(7.03)-(7.27) [7.27]	15,37,42, 56 [15]	5.5-6.8	42,56
2,2',3,4,4',5,5'-HpCB 35069-29-3	(2.25E-04)-(4.40E-04) [4.40E-04]	20-25 [20]	17,35,37,41 [41]	3.39E-08-(2.72E-07) [2.72E-07]	20-25 [25]	18,41 [41]	(3.20E-05)-(1.07E-04) [3.20E-05]	35,41 [41]	(6.70)-(7.36) [7.36]	15,37,42, 56 [15]	5.1-7.4	42,56

Footnote References

[a] Values are presented as they appeared in the referenced article. Values in ( ) are either estimated or are calculated/extrapolated from experimental values.

[b] [R] is the ranking of the value from the cited reference.

[c] For several PCB congeners, subcooled liquid values were converted to solid values using the melting points presented in this table and the conversion methodology presented in Eitzer and Hites (1988) and Mackay et al. (1992).

[d] The selected vapor pressure value for PCB-169 is the midpoint of the range of calculated values.

$$\ln (P_{sc}/P_s) = 6.79 (T_m\text{-}T)/T$$

where: P_{sc} = subcooled value
P_s = solid value
T_m = melting point (°K)
T = ambient temperature (°K)

1. Marple et al. (1986a)
2. USEPA (1990)
3. Podoll et al. (1986)
4. Marple et al. (1986b)
5. Shiu et al. (1988)
6. Friesen et al. (1985)
7. Webster et al. (1985)
8. Burkhard and Kuehl (1986)
9. Rordorf (1987)
10. Sijm et al. (1989)
11. Friesen et al. (1990b)
12. Dickhut et al. (1986)
20. Average of all selected and single values within a congener group
21. Rordorf (1989)
22. Dulin et al. (1986)
23. Choudhry and Webster (1987)
24. Choudhry and Webster (1989)
25. Choudhry et al. (1990)
26. Sarna et al. (1984)
27. Adams and Blaine (1986)
28. Mackay et al. (1980)
29. Doucette and Andren (1988a)
30. Orth et al. (1989)
31. Rapaport and Eisenreich (1984)
39. Dunnivant et al. (1988)
40. Opperhuizen et al. (1988)
41. Murphy et al. (1987)
42. EPRI (1990)
43. Murphy et al. (1983)
44. Yalkowsky et al. (1983)
45. Webster et al. (1986)
46. Doucette and Andren (1988b)
47. Walters and Guiseppi-Elie (1988)
48. Jackson et al. (1986)
49. Puri et al. (1989)
50. Marple et al. (1987)

Table A-1 (continued)

13. Dunnivant and Elzerman (1988)
14. Risby et al. (1990)
15. Hawker and Connell (1988)
16. Sabljic and Gusten (1989)
17. Abramowitz and Yalkowsky (1990)
18. Foreman and Bidleman (1985)
19. Calculated by the VP/WS ratio technique
32. Lodge and Cook (1989)
33. Eitzer and Hites (1988)
34. Rordorf (1985)
35. Dunnivant et al. (1992)
36. Lodge (1989)
37. Patil (1991)
38. Nirmalakhandan and Speece (1989)
51. Santl et al. (1994)
52. Rordorf et al. (1990)
53. Mackay et al. (1992a)
54. Eitzer and Hites (1989)
55. Sacan and Inel (1995)
56. Mackay, et al. (1992b)
57. Walters et al. (1989)

Table A-2. Rankings for the P-Chem Property Literature

Reference Number	Ranking[a]					
	Water Solubility	Vapor Pressure	Henry's Constant	Log K_{ow}	Log K_{oc}	Photo Quantum Yield
1	2					
3		2	4			
4				1		
5	2		4	1		
6	2					
7	2	2	2	4		
8				4		
9		2 & 4				
10				1 & 2		
11	2					
12	1					
13	1	4	2			
14				3		
15				2 & 5		
16			5			
17	5					
18		2 & 4				
19			5			
20	5	5	5	5	5	
21		2 & 4				
22						2
23						2
24						2
25						2
26				5		
27	2					

Table A-2 (continued)

Reference Number	Ranking[a]					
	Water Solubility	Vapor Pressure	Henry's Constant	Log K_{ow}	Log K_{oc}	Photo Quantum Yield
1	2					
28	5					
29				5		
30						2
31				4		
32					1	
33		4				
34		4				
35	5		5			
36	2					
37	5			5		
38	5					
39			2			
40	2					
41	2	2	4			
42					4	
43			4			
44	5					
45					2	
46	2					
47					1	
48					1	
49					2	
50	1			1	1	
51	2		2			
52		4				

Table A-2 (continued)

Reference Number	Ranking[a]					
	Water Solubility	Vapor Pressure	Henry's Constant	Log K_{ow}	Log K_{oc}	Photo Quantum Yield
1	2					
54			4			
55				4		
57					1	

Footnote References

[a] P-chem properties with two ranks indicates that some of the values for the chemicals in the reference had been verified by another laboratory, and some values have not been verified yet. It also indicates that more than one methodology may have been used in the reference to determine the p-chem property.

1. Marple et al. (1986a)
3. Podoll et al. (1986)
4. Marple et al. (1986b)
5. Shiu et al. (1988)
6. Friesen et al. (1985)
7. Webster et al. (1985)
8. Burkhard and Kuehl (1986)
9. Rordorf (1987)
10. Sijm et al. (1989)
11. Friesen et al. (1990)
12. Dickhut et al. (1986)
13. Dunnivant and Elzerman (1988)
14. Risby et al. (1990)
15. Hawker and Connell (1988)
16. Sabljic and Gunsten (1989)
17. Abramowitz and Yalkowsky (1990)
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19. Calculated by the VP/WS ratio technique
20. Average of all literature values (measured and calculated) within a congener group.
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22. Dulin et al. (1986)
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29. Doucette and Andren (1988)
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32. Lodge and Cook (1989)
33. Eitzer and Hites (1988)
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39. Dunnivant et al. (1988)
40. Opperhuizen et al. (1988)
41. Murphy et al. (1987)
42. EPRI (199)
43. Murphy et al. (1983)
44. Yalkowsky et al. (1983)
45. Webster et al. (1986)
46. Doucette and Andren (1988)
47. Walters and Guiseppi-Elie (1988)
48. Jackson et al. (1986)
49. Puri et al. (1989)
50. Marple et al. (1987)
51. Santl et al. (1994)
52. Rordorf et al. (1990)
53. Mackay et al. (1992a)
54. Eitzer and Hites (1989)
55. Sacan and Inel (1995)
56. Mackay et al. (1992b)
57. Walters et al. (1989)

APPENDIX B. ENVIRONMENTAL CONCENTRATIONS

The tables in this appendix are discussed in Chapter 5. References listed at the end of each table are included in the reference list at the end of Chapter 4. Following are the tables included in this Appendix:

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
Tetrachlorodibenzo-p-dioxins (MW=321.98)									
2,3,7,8-TCDD	3	0	ND(0.01-0.02)	NA	Niagra Falls, NY	Urban	86-87	1	
	3	0	ND(0.01-0.02)	NA	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	ND(0.01)	NA	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.0095)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.05	0.01	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	2	ND-0.004	0.002	Wallingford, CT	Urban	88	5	
	NR	NR	ND(0.02)	NA	Rutland, VT	Urban	NR	6	
	NR	NR	ND(0.03)	NA	Durham, NC	Urban	NR	6	
	1	1	0.0004	0.0004	Stockholm, Sweden	Urban	89	7	
	2	2	0.02-0.06	0.04	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	0.02-0.08	0.05	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	0	ND(0.012-0.2)	NA	Akron, OH	Industrial	87	9	near incinerators
	2	0	ND(0.24-0.82)	NA	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.15)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	0	ND(0.058)	NA	Waldo, OH	Rural	87	9	background site
	3	0	ND(0.04-0.15)	NA	Albany, NY	Urban	87-88	10	
	1	0	ND(0.06)	NA	Binghamton, NY	Urban	88	10	
	2	0	ND(0.05-0.18)	NA	Utica, NY	Urban	88	10	
	2	0	ND(0.04-0.21)	NA	Niagara Falls, NY	Industrial	87	10	
	1	1	0.0004	0.0004	Stockholm	Urban	89	11	
	1	1	0.0007	0.0007	Stockholm	Suburban	89	11	
	1	1	0.0002	0.0002	Stockholm	Rural	89	11	
	1	1	0.0001	0.0001	Stockholm	Coastal	89	11	
	7	0	ND(0.004-0.023)	NA	Reseda, CA	Urban	87-89	12	mostly residential
	1	0	ND(0.030)	NA	Commerce, CA	Urban	87	12	near freeway

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
2,3,7,8-TCDD	6	0	ND(0.0026-0.048)	NA	North Long Beach, CA	Urban	87-89	12	mostly residential
(continued)	5	0	ND(0.0106-0.045)	NA	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	0	ND(0.0070-0.051)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	1	ND-0.034	0.017	Cal Transit, CA	Urban	88-89	12	near highway
	2	0	ND(0.022-0.039)	NA	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	1	ND-0.0086	0.0079	West Long Beach, CA	Urban	88-89	12	mostly residential area
	20	13	ND-0.003	0.00123	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	1	ND-0.001	0.000375	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	4	ND-0.026	0.0048	Franklin County, OH	Urban	95	14	
	3	0	ND	NA	Franklin County, OH	Background	95	14	
	2	2	0.012-0.026	0.019	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	0.0078	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.0001-0.003	0.00076	Various U.S. Sites	Rural	98-99	17	background
TCDDs	16	3	ND-0.18	0.04	Niagra Falls, NY	Urban	86-87	1	
	16	12	ND-10.12	0.99	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	7	NR	ND-0.54	0.20	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	27	20	ND-0.07	0.03	Wallingford, CT	Urban	88	5	
	1	1	0.05	0.05	Stockholm, Sweden	Urban	89	7	
	2	2	0.10-0.22	0.16	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	0.21-1.5	0.86	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	1	ND-0.18	0.12	Akron, OH	Industrial	87	9	near incinerators
	2	0	ND(0.24-0.82)	NA	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.15)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	0	ND(0.058)	NA	Waldo, OH	Rural	87	9	background Site
	3	0	ND(0.04-0.15)	NA	Albany, NY	Urban	87-88	10	
	1	0	ND(0.06)	NA	Binghamton, NY	Urban	88	10	

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	2	0	ND(0.05-0.18)	NA	Utica, NY	Urban	88	10	

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
TCDDs (continued)	2	0	ND(0.04-0.21)	NA	Niagara Falls, NY	Industrial	87	10	
	1	1	0.05	0.05	Stockholm	Urban	89	11	
	1	1	0.026	0.026	Stockholm	Suburban	89	11	
	1	1	0.031	0.031	Stockholm	Rural	89	11	
	1	1	0.0057	0.0057	Stockholm	Coastal	89	11	
	7	0	ND(0.0050-0.046)	NA	Reseda, CA	Urban	87-89	12	mostly residential
	1	0	ND(0.030)	NA	Commerce, CA	Urban	87	12	near freeway
	6	0	ND(0.0026-0.075)	NA	North Long Beach,CA	Urban	87-89	12	mostly residential
	5	0	ND(0.0106-0.093)	NA	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	0	ND(0.0090-0.051)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	1	ND-0.280	0.0788	Cak Transit, CA	Urban	88-89	12	near highway
	2	1	ND-0.0230	0.0170	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	1	ND-0.0402	0.0237	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.007-0.121	0.0457	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.007-0.032	0.017	Connecticut	Rural	93-94	13	near resource recovery facilities
	16	NR	NR	0.53	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
Pentachlorodibenzo-p-dioxins (MW=356.42)									
1,2,3,7,8-PeCDD	3	0	ND(0.01-0.02)	NA	Niagra Falls, NY	Urban	86-87	1	
	3	1	ND-0.49	0.17	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	ND(0.02)	NA	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.039)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.07	0.02	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	9	ND-0.02	0.006	Wallingford, CT	Urban	88	5	
	NR	NR	ND(0.03)	NA	Rutland, VT	Urban	NR	6	
	NR	NR	ND(0.01)	NA	Durham, NC	Urban	NR	6	
	1	1	0.006	0.006	Stockholm, Sweden	Urban	89	7	

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	2	1	ND-0.28	0.14	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,7,8-PeCDD	2	2	0.22-0.60	0.41	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
(continued)	3	0	ND(0.034-0.27)	NA	Akron, OH	Industrial	87	9	near incinerators
	2	0	ND(0.047-0.06)	NA	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.082)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	0	ND(0.033)	NA	Waldo, OH	Rural	87	9	background site
	1	1	0.006	0.006	Stockholm	Urban	89	11	
	1	1	0.0038	0.0038	Stockholm	Suburban	89	11	
	1	1	0.0014	0.0014	Stockholm	Rural	89	11	
	1	1	0.0007	0.0007	Stockholm	Coastal	89	11	
	1	1	0.0004	0.0004	Bloomington, IN	Urban	86	15	
	7	1	ND-0.14	0.0332	Reseda, CA	Urban	87-89	12	mostly residential
	1	1	0.120	0.120	Commerce, CA	Urban	87	12	near freeway
	6	0	ND(0.0060-0.095)	NA	North Long Beach, CA	Urban	87-89	12	mostly residential
	5	0	ND(0.048-0.93)	NA	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	0	ND(0.0062-0.058)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	0	ND(0.0126-0.081)	NA	Cal Transit, CA	Urban	88-89	12	near highway
	2	0	ND(0.0090-0.054)	NA	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	0	ND(0.043-0.088)	NA	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	19	ND-0.014	0.00633	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	3	ND-0.004	0.00213	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	8	ND-0.021	0.0103	Franklin County, OH	Urban	95	14	
	3	1	ND-0.01112	0.0052	Franklin County, OH	Background	95	14	
	2	2	0.042-0.082	0.0619	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	0.051	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00043-0.023	0.0043	Various U.S. Sites	Rural	98-99	17	background

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
PeCDDs	16	1	ND-0.05	0.02	Niagra Falls, NY	Urban	86-87	1	
	16	11	ND-11.16	1.04	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	7	NR	0.01-0.66	0.24	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	21	ND-0.15	0.05	Wallingford, CT	Urban	88	5	
	1	1	0.11	0.11	Stockholm, Sweden	Urban	89	7	
	2	2	0.07-1.3	0.68	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	2.4-5.0	3.70	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	1	ND-0.10	0.097	Akron, OH	Industrial	87	9	near incinerators
	2	0	ND(0.47-0.06)	NA	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.082)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	0	ND(0.033)	NA	Waldo, OH	Rural	87	9	background site
	3	0	ND(0.04-0.21)	NA	Albany, NY	Urban	87-88	10	
	1	0	ND(0.11)	NA	Binghamton, NY	Urban	88	10	
	2	0	ND(0.07-0.34)	NA	Utica, NY	Urban	88	10	
	2	0	ND(0.07-0.34)	NA	Niagara, NY	Industrial	87	10	
	1	1	0.110	0.110	Stockholm	Urban	89	11	
	1	1	0.079	0.079	Stockholm	Suburban	89	11	
	1	1	0.04	0.04	Stockholm	Rural	89	11	
	1	1	0.019	0.019	Stockholm	Coastal	89	11	
	7	2	ND-0.89	0.143	Reseda, CA	Urban	87-89	12	mostly residential
	1	1	0.57	0.57	Commerce, CA	Urban	87	12	near freeway
	6	2	ND-0.81	0.150	North Long Beach, CA	Urban	87-89	12	mostly residential
	5	0	ND(0.063-0.93)	NA	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	0	ND(0.0062-0.047)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	1	ND-0.18	0.0618	Cal Transit, CA	Urban	88-89	12	near highway
	2	1	ND-0.042	0.0345	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	2	0	ND(0.045-0.088)	NA	West Long Beach, CA	Urban	88-89	12	mostly residential
PeCDDs (continued)	20	19	ND-0.224	0.0801	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.009-0.043	0.0253	Connecticut	Rural	93-94	13	near resource recovery facilities
	16	NR	NR	0.57	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
Hexachlorodibenzo-p-dioxins (MW=390.87)									
1,2,3,4,7,8-HxCDD	3	0	ND(0.01-0.02)	NA	Niagra Falls, NY	Urban	86-87	1	
	3	3	0.04-0.64	0.24	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.01	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.076)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.08	0.03	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	8	ND-0.03	0.01	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.05	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.01	Durham, NC	Urban	NR	6	
	1	1	0.004	0.004	Stockholm, Sweden	Urban	89	7	
	2	0	ND(0.08-0.17)	NA	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	0.19-1.0	0.60	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	3	0.032-0.055	0.041	Akron, OH	Industrial	87	9	near incinerators
	2	0	ND(0.028-0.039)	NA	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.032)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.031	0.031	Waldo, OH	Rural	87	9	background site
	1	1	0.004	0.004	Stockholm	Urban	89	11	
	1	1	0.0028	0.0028	Stockholm	Suburban	89	11	
	1	1	0.0012	0.0012	Stockholm	Rural	89	11	
	1	1	0.0006	0.0006	Stockholm	Coastal	89	11	
	1	1	0.0023	0.0023	Bloomington, IN	Urban	86	15	
	7	3	ND-0.20	0.0588	Reseda, CA	Urban	87-89	12	mostly residential

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	1	1	0.12	0.12	Commerce, CA	Urban	87	12	near freeway
	6	1	ND-0.14	0.0402	North Long Beach, CA	Urban	87-89	12	mostly residential
1,2,3,4,7,8-HxCDD	5	1	ND-0.043	0.0406	San Bernadino, CA	Urban	87-89	12	mostly residential
(continued)	7	0	ND(0.012-0.10)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	0	ND(0.0078-0.074)	NA	Cal Transit, CA	Urban	88-89	12	near highway
	2	0	ND(0.015-0.025)	NA	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	0	ND(0.038-0.043)	NA	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.001-0.022	0.0088	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	3	ND-0.007	0.00338	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	8	ND-0.04	0.0142	Franklin County, OH	Urban	95	14	
	3	1	ND-0.0152	0.0079	Franklin County, OH	Background	95	14	
	2	2	0.053-0.109	0.081	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	0.096	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00058-0.027	0.0054	Various U.S. Sites	Rural	98-99	17	background
1,2,3,6,7,8-HxCDD	3	1	ND-0.03	0.02	Niagra Falls, NY	Urban	86-87	1	
	3	3	0.05-1.06	0.39	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.02	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.083)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.13	0.04	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	22	ND-0.06	0.02	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.07	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.01	Durham, NC	Urban	NR	6	
	1	1	0.008	0.008	Stockholm, Sweden	Urban	89	7	
	2	2	0.23-0.66	0.44	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	0.71-2.2	1.46	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	3	0.052-0.053	0.053	Akron, OH	Industrial	87	9	near incinerators

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	2	1	ND-0.078	0.046	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.032)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.025	0.025	Waldo, OH	Rural	87	9	background site
1,2,3,6,7,8-HxCDD (continued)	1	1	0.0076	0.0076	Stockholm	Urban	89	11	
	1	1	0.0062	0.0062	Stockholm	Suburban	89	11	
	1	1	0.0023	0.0023	Stockholm	Rural	89	11	
	1	1	0.0009	0.0009	Stockholm	Coastal	89	11	
	1	1	0.0029	0.0029	Bloomington, IN	Urban	86	15	
	7	3	ND-0.35	0.0801	Reseda, CA	Urban	87-89	12	mostly residential
	1	1	0.25	0.25	Commerce, CA	Urban	87	12	near freeway
	6	1	ND-0.39	0.0833	North Long Beach, CA	Urban	87-89	12	mostly residential
	5	1	ND-0.15	0.0586	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	0	ND(0.0070-0.097)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	1	ND-0.065	0.0383	Cal Transit, CA	Urban	88-89	12	near highway
	2	0	ND(0.015-0.025)	NA	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	0	ND(0.019-0.032)	NA	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.002-0.034	0.0145	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.002-0.010	0.005	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	12	ND-0.05	0.026	Franklin County, OH	Urban	95	14	
	3	1	ND-0.0191	0.0093	Franklin County, OH	Background	95	14	
	2	2	0.06-0.13	0.095	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	0.22	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.0011-0.044	0.0097	Various U.S. Sites	Rural	98-99	17	background
1,2,3,7,8,9-HxCDD	3	1	ND-0.03	0.02	Niagra Falls, NY	Urban	86-87	1	
	3	2	ND-0.11	0.06	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.02	Greenbay, WI	Urban	NR	2	

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	1	0	ND(0.086)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.25	0.08	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	18	ND-0.07	0.03	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.05	Rutland, VT	Urban	NR	6	
1,2,3,7,8,9-HxCDD	NR	NR	ND(0.01)	NA	Durham, NC	Urban	NR	6	
(continued)	1	0	ND(0.001)	NA	Stockholm, Sweden	Urban	89	7	
	2	0	ND(0.08-0.17)	NA	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	0.36-5.2	2.78	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	3	0.017-0.050	0.031	Akron, OH	Industrial	87	9	near incinerators
	2	1	ND-0.064	0.039	Columbus, OH	Industrial	87	9	near incinerators
	1	0	ND(0.032)	NA	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.025	0.025	Waldo, OH	Rural	87	9	background site
	1	1	0.0065	0.0065	Stockholm	Urban	89	11	
	1	1	0.0052	0.0052	Stockholm	Suburban	89	11	
	1	1	0.0018	0.0018	Stockholm	Rural	89	11	
	1	1	0.0013	0.0013	Stockholm	Coastal	89	11	
	1	1	0.0013	0.0013	Bloomington, IN	Urban	86	15	
	7	3	ND-0.35	0.1198	Reseda, CA	Urban	87-89	12	mostly residential
	1	1	0.27	0.27	Commerce, CA	Urban	87	12	near freeway
	6	1	ND-0.35	0.0758	North Long Beach, CA	Urban	87-89	12	mostly residential
	5	1	ND-0.10	0.0499	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	0	ND(0.009-0.12)	NA	El Toro, CA	Urban	87-88	12	mostly residential
	4	0	ND(0.023-0.074)	NA	Cal Transit, CA	Urban	88-89	12	near highway
	2	0	ND(0.015-0.019)	NA	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	0	ND(0.019-0.040)	NA	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.002-0.027	0.0123	Connecticut	Urban	93-94	13	near resource recovery facilities

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	4	3	ND-0.011	0.00463	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	11	ND-0.046	0.025	Franklin County, OH	Urban	95	14	
	3	1	ND-0.023	0.0135	Franklin County, OH	Background	95	14	
	2	2	0.06-0.11	0.09	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	0.18	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
1,2,3,7,8,9-HxCDD (continued)	53	53	0.00046-0.041	0.0093	Various U.S. Sites	Rural	98-99	17	background
HxCDDs	16	11	ND-0.23	0.08	Niagra Falls, NY	Urban	86-87	1	
	16	12	ND-12.16	1.69	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	7	NR	ND-2.17	0.72	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	27	ND-0.68	0.26	Wallingford, CT	Urban	88	5	
	1	1	0.10	0.10	Stockholm, Sweden	Urban	89	7	
	2	2	0.74-2.7	1.72	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	5.3-24	14.6	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	3	0.6-0.63	0.62	Akron, OH	Industrial	87	9	near incinerators
	2	2	0.43-0.78	0.60	Columbus, OH	Industrial	87	9	near incinerators
	1	1	0.15	0.15	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.33	0.33	Waldo, OH	Rural	87	9	background site
	3	1	ND(0.34)-0.13	0.125	Albany, NY	Urban	NR	10	
	1	0	ND(0.16)	NA	Binghamton, NY	Urban	NR	10	
	2	1	ND(0.55)-0.1	0.188	Utica, NY	Urban	NR	10	
	2	1	ND(0.11)-0.17	0.112	Niagara Falls, NY	Industrial	NR	10	
	1	1	0.096	0.096	Stockholm	Urban	89	11	
	1	1	0.082	0.082	Stockholm	Suburban	89	11	
	1	1	0.03	0.03	Stockholm	Rural	89	11	
	1	1	0.014	0.014	Stockholm	Coastal	89	11	
	7	7	0.062-3.0	0.988	Reseda, CA	Urban	87-89	12	mostly residential

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	1	1	2.00	2.00	Commerce, CA	Urban	87	12	near freeway
	6	4	ND-3.2	0.640	North Long Beach, CA	Urban	87-89	12	mostly residential
	5	2	ND-0.77	0.197	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	4	ND-0.11	0.0424	El Toro, CA	Urban	87-88	12	mostly residential
	4	2	ND-0.27	0.153	Cal Transit, CA	Urban	88-89	12	near highway
HxCDDs (continued)	2	1	ND-0.14	0.10	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	2	0.16-0.32	0.241	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.017-0.471	0.177	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.020-0.122	0.0615	Connecticut	Rural	93-94	13	near resource recovery facilities
	16	NR	NR	2.41	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
Heptachlorodibenzo-p-dioxins (MW=425.31)									
1,2,3,4,6,7,8-HpCDD	3	3	0.34-0.51	0.41	Niagra Falls, NY	Urban	86-87	1	
	3	2	ND-5.43	2.0	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.11	Greenbay, WI	Urban	NR	2	
	1	1	0.25	0.25	Los Angeles, CA	Urban	87	3	
	7	NR	0.02-1.07	0.48	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	23	ND-0.73	0.29	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.41	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.04	Durham, NC	Urban	NR	6	
	1	1	0.10	NA	Stockholm, Sweden	Urban	89	7	
	3	3	0.52-0.57	0.54	Akron, OH	Industrial	87	9	near incinerators
	2	2	0.26-0.52	0.39	Columbus, OH	Industrial	87	9	near incinerators
	1	1	0.32	0.32	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.24	0.24	Waldo, OH	Rural	87	9	background site
	1	1	0.1	0.1	Stockholm	Urban	89	11	
	1	1	0.091	0.091	Stockholm	Suburban	89	11	

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	1	1	0.027	0.027	Stockholm	Rural	89	11	
	1	1	0.012	0.012	Stockholm	Coastal	89	11	
	1	1	0.0051	0.0051	Bloomington, IN	Urban	86	15	
	7	7	0.11-8.40	2.44	Reseda, CA	Urban	87-89	12	mostly residential
	1	1	2.70	2.70	Commerce, CA	Urban	87	12	near freeway
	6	6	0.21-3.50	0.795	North Long Beach, CA	Urban	87-89	12	mostly residential
1,2,3,4,6,7,8-HpCDD	5	5	0.21-1.20	0.582	San Bernadino, CA	Urban	87-89	12	mostly residential
(continued)	7	4	ND-0.26	0.138	El Toro, CA	Urban	87-88	12	mostly residential
	4	4	0.41-0.87	0.540	Cal. Transit, CA	Urban	88-89	12	near highway
	2	2	0.19-0.22	0.205	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	2	0.30-0.40	0.351	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.019-0.314	0.140	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.016-0.159	0.0673	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	14	0.11-0.40	0.23	Franklin County, OH	Urban	95	14	
	3	3	0.197-0.265	0.2273	Franklin County, OH	Background	95	14	
	2	2	0.4-0.87	0.63	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	2.95	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.012-0.63	0.13	Various U.S. Sites	Rural	98-99	17	background
HpCDDs	16	14	ND-0.86	0.44	Niagra Falls, NY	Urban	86-87	1	
	15	15	0.24-9.78	2.60	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	7	NR	0.02-2.19	1.02	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	26	ND-1.48	0.61	Wallingford, CT	Urban	88	5	
	1	1	0.20	0.20	Stockholm, Sweden	Urban	89	7	
	2	2	0.6-3.4	2.0	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	5.3-15	10.2	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
	3	3	1.00-1.10	1.07	Akron, OH	Industrial	87	9	near incinerators

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	2	2	0.41-1.00	0.70	Columbus, OH	Industrial	87	9	near incinerators
	1	1	0.56	0.56	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.48	0.48	Waldo, OH	Rural	87	9	background site
	3	2	0.28-0.69	0.44	Albany, NY	Urban	NR	10	
	1	1	0.48	0.48	Binghamton, NY	Urban	NR	10	
	2	1	ND(0.77)-0.3	0.342	Utica, NY	Urban	NR	10	
	2	2	0.49-0.56	0.525	Niagara Falls, NY	Industrial	NR	10	
HpCDDs (continued)	1	1	0.2	0.2	Stockholm	Urban	89	11	
	1	1	0.19	0.19	Stockholm	Suburban	89	11	
	1	1	0.062	0.062	Stockholm	Rural	89	11	
	1	1	0.03	0.03	Stockholm	Coastal	89	11	
	7	7	0.24-8.90	4.94	Reseda, CA	Urban	87-89	12	mostly residential
	1	1	5.30	5.30	Commerce, CA	Urban	87	12	near freeway
	6	6	0.24-7.20	1.61	North Long Beach, CA	Urban	87-89	12	mostly residential
	5	5	0.43-1.60	1.06	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	4	ND-0.46	0.246	El Toro, CA	Urban	87-88	12	mostly residential
	4	4	0.66-1.96	1.07	Cal. Transit, CA	Urban	88-89	12	near highway
	2	2	0.46-0.48	0.467	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer
	2	2	0.70-0.78	0.739	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.039-0.628	0.279	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.033-0.317	0.136	Connecticut	Rural	93-94	13	near resource recovery facilities
	16	NR	NR	5.39	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
Octachlorodibenzo-p-dioxin (MW=460.76)									
1,2,3,4,6,7,8,9-OCDD	16	15	ND-5.79	1.14	Niagra Falls, NY	Urban	86-87	1	
	14	14	0.39-8.88	2.94	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.30	Greenbay, WI	Urban	NR	2	

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	1	1	1.9	1.9	Los Angeles, CA	Urban	87	3	
	7	NR	0.17-5.55	2.10	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	16	15	ND-29.5	5.53	Wallingford, CT	Urban	88	5	
	NR	NR	NR	1.10	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.13	Durham, NC	Urban	NR	6	
	1	1	0.23	0.23	Stockholm, Sweden	Urban	89	7	
	2	2	0.37-6.4	3.38	Hamburg, Germany	Urban	NR	8	urban air & inside traffic tunnel
	2	2	7.4-40	23.7	Hamburg, Germany	Urban	NR	8	downwind incinerator & industrial complex
1,2,3,4,6,7,8,9-OCDD (continued)	3	3	1.00-1.20	1.13	Akron, OH	Industrial	87	9	near incinerators
	2	2	0.51-1.10	0.80	Columbus, OH	Industrial	87	9	near incinerators
	1	1	0.96	0.96	Columbus, OH	Urban	87	9	next to interstate highway
	1	1	0.50	0.50	Waldo, OH	Rural	87	9	background site
	3	2	0.6-3.16	1.53	Albany, NY	Urban	NR	10	
	1	1	1.35	1.35	Binghamton, NY	Urban	NR	10	
	2	2	0.84-1.58	1.21	Utica, NY	Urban	NR	10	
	2	2	1.4-1.6	1.5	Niagara Falls, NY	Insdustrial	NR	10	
	1	1	0.23	0.23	Stockholm	Urban	89	11	
	1	1	0.23	0.23	Stockholm	Suburban	89	11	
	1	1	0.068	0.068	Stockholm	Rural	89	11	
	1	1	0.041	0.041	Stockholm	Coastal	89	11	
	6	6	0.43-17.0	5.36	Reseda, CA	Urban	87-89	12	mostly residential
	5	5	0.68-1.90	1.42	North Long Beach, CA	Urban	87-89	12	near freeway
	5	5	0.93-8.60	3.08	San Bernadino, CA	Urban	87-89	12	mostly residential
	7	6	ND-2.16	1.05	El Toro, CA	Urban	87-88	12	mostly residential
	4	4	1.80-3.73	2.37	Cal. Transit, CA	Urban	88-89	12	near highway
	2	2	0.48-1.60	1.04	Carson, CA	Industrial	88-89	12	on site at gas cooking equipment manufacturer

Table B-1. Environmental Levels of Dioxins in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	2	2	2.05-3.83	2.94	West Long Beach, CA	Urban	88-89	12	mostly residential
	20	20	0.072-0.839	0.436	Connecticut	Urban	93-94	13	near resource recovery facilities
	4	4	0.056-0.451	0.215	Connecticut	Rural	93-94	13	near resource recovery facilities
	14	14	0.431-1.56	0.952	Franklin County, OH	Urban	95	14	
	3	3	0.634-1.14	0.9037	Franklin County, OH	Background	95	14	
	2	2	1.17-2.36	1.77	Franklin County, OH	Industrial	95	14	near waste to energy facility
	16	NR	NR	9.55	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.058-1.7	0.44	Various U.S. Sites	Rural	98-99	17	background

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects;
NA = Not applicable;
ND = Non-detect;
NR = Not reported.

Sources:

1. Smith et al. (1989)
2. Harless et al. (1990)
3. Maisel and Hunt (1990)
4. Hunt and Maisel (1990)
5. CDEP (1988)
6. Harless et al. (1991)
7. Näf et al. (1990)
8. Rappe and Kjeller (1987)
9. Edgerton et al. (1989)
10. Smith et al. (1990)
11. Broman et al. (1991)
12. Hunt et al. (1990)
13. CDEP (1995)
14. OEPA (1995)
15. Eitzer and Hites (1989)
16. Hunt et al. (1997)
17. Cleverly et al. (2000)

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
Tetrachlorodibenzofurans (MW=305.98)									
2,3,7,8-TCDF	3	3	0.04-0.14	0.09	Niagra Falls, NY	Urban	86-87	1	
	3	3	0.28-3.81	1.47	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.03	Greenbay, WI	Urban	NR	2	
	1	1	0.02	0.02	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.20	0.08	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	22	ND-0.10	0.04	Wallingford, CT	Urban	88	5	
	NR	NR	ND(0.1)	NA	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.03	Durham, NC	Urban	NR	6	
	2	2	0.04-0.72	0.38	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	0.18-0.38	0.28	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.19-0.20	0.20	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.32-0.49	0.40	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.13)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.13	0.13	Waldo, OH	Rural	87	8	background site
	3	3	0.5-1.24	0.85	Albany, NY	Urban	87-89	9	
	1	1	0.18	0.18	Binghamton, NY	Urban	88	9	
	2	2	1.07-1.23	1.15	Utica, NY	Urban	88	9	
	2	0	ND(0.04-0.2)	NA	Niagra Falls, NY	Industrial	87	9	
	7	4	ND-0.046	0.0271	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.11	0.11	Commerce, CA	Urban	87	10	near freeway
	6	4	ND-0.039	0.0198	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	4	ND-0.091	0.0383	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	3	ND-0.027	0.0146	El Toro, CA	Urban	87-88	10	mostly residential
	4	2	ND-0.21	0.0687	Cal. Transit, CA	Urban	88-89	10	near highway
	2	1	ND-0.024	0.0137	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	2	0.019-0.48	0.250	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.002-0.024	0.0093	Connecticut	Urban	93-94	11	near resource recovery facilities

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	4	4	0.002-0.004	0.00325	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	12	ND-0.034	0.014	Franklin County, OH	Urban	95	12	
2,3,7,8,-TCDF	3	0	ND	NA	Franklin County, OH	Rural	95	12	
(continued)	2	2	0.032-0.069	0.051	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.033	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00021-0.0057	0.0017	Various U.S. Sites	Rural	98-99	17	background
TCDFs	16	10	ND-0.66	0.23	Niagra Falls, NY	Urban	86-87	1	
	16	16	0.18-17.4	3.25	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	7	NR	ND-2.29	0.86	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	26	ND-0.86	0.38	Wallingford, CT	Urban	88	5	
	1	1	0.33	0.33	Stockholm, Sweden	Urban	89	13	
	2	2	0.36-6.2	3.28	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	3.3-4.9	4.1	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.99-1.50	1.23	Akron, OH	Industrial	87	8	near incinerators
	2	2	1.90-3.80	2.85	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.13)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.89	0.89	Waldo, OH	Rural	87	8	background site
	3	3	2.08-5.46	3.64	Albany, NY	Urban	87-88	9	
	1	1	0.94	0.94	Binghamton, NY	Urban	88	9	
	2	2	5.87-8.81	7.34	Utica, NY	Urban	88	9	
	2	2	1.10-1.20	1.15	Niagra Falls, NY	Industrial	87	9	
	1	1	0.33	0.33	Stockholm	Urban	89	14	
	1	1	0.20	0.20	Stockholm	Urban	89	14	
	1	1	0.08	0.08	Stockholm	Urban	89	14	
	1	1	0.048	0.048	Stockholm	Urban	89	14	
	7	5	ND-1.10	0.275	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	1.40	1.40	Commerce, CA	Urban	87	10	near freeway
	6	4	ND-1.00	0.432	North Long Beach, CA	Urban	87-89	10	mostly residential

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	5	5	0.024-0.98	0.430	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	4	ND-0.32	0.147	El Toro, CA	Urban	87-88	10	mostly residential
	4	2	ND-0.87	0.418	Cal. Transit, CA	Urban	88-89	10	near freeway
	2	2	0.089-0.32	0.206	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
TCDFs (continued)	2	2	0.15-0.48	0.316	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.086-0.465	0.264	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.090-0.134	0.108	Connecticut	Rural	93-94	11	near resource recovery facilities
	16	NR	NR	1.57	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
1,2,3,7,8-PeCDF (MW=340.42)									
1,2,3,7,8-PeCDF	3	0	ND(0.01)	NA	Niagra Falls, NY	Urban	86-87	1	
	3	3	0.03-0.61	0.25	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.05	Greenbay, WI	Urban	NR	2	
	1	1	0.08	0.08	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.10	0.03	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	9	ND-0.02	0.01	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.03	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.01	Durham, NC	Urban	NR	6	
	3	3	0.026-0.033	0.029	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.032-0.057	0.044	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.036)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.021	0.021	Waldo, OH	Rural	87	8	background site
	7	1	ND-0.14	0.0327	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.092	0.0920	Commerce, CA	Urban	87	10	near freeway
	6	1	ND-0.13	0.0383	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	1	ND-1.90	0.399	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	2	ND-0.077	0.0349	El Toro, CA	Urban	87-89	10	mostly residential
	4	1	ND-0.053	0.0346	Cal Transit, CA	Urban	88-89	10	near highway
	2	0	ND(0.010-0.015)	NA	Carson, CA	Industrial	88-89	10	On site at gas cooking equipment manufacturer

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	2	1	ND-0.022	0.0161	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.003-0.019	0.00925	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.003-0.004	0.00325	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	12	ND-0.046	0.023	Franklin County, OH	Urban	95	12	
	3	1	ND-0.01354	0.0065	Franklin County, OH	Rural	95	12	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
1,2,3,7,8-PeCDF	2	2	0.08-0.16	0.12	Franklin County, OH	Industrial	95	12	near waste to energy facility
(continued)	16	NR	NR	0.052	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00033-0.0073	0.0019	Various U.S. Sites	Rural	98-99	17	background
2,3,4,7,8-PeCDF	3	0	ND(0.01-0.02)	NA	Niagra Falls, NY	Urban	86-87	1	
	3	2	ND-1.92	0.68	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.04	Greenbay, WI	Urban	NR	2	
	1	1	0.08	0.08	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.16	0.05	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	16	ND-0.04	0.02	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.20	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.01	Durham, NC	Urban	NR	6	
	1	1	0.02	0.02	Stockholm, Sweden	Urban	89	13	
	1	1	0.04	0.04	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	0.43-1.2	0.82	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.032-0.042	0.036	Akron, OH	Industrial	87	8	near incinerators
	2	1	ND-0.089	0.050	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.036)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	0	ND(0.033)	NA	Waldo, OH	Rural	87	8	background site
	1	1	0.018	0.018	Stockholm	Urban	89	14	
	1	1	0.0078	0.0078	Stockholm	Urban	89	14	
	1	1	0.0021	0.0021	Stockholm	Urban	89	14	
	1	1	0.0012	0.0012	Stockholm	Urban	89	14	
	7	1	ND-0.11	0.0295	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.0890	0.0890	Commerce, CA	Urban	87	10	near freeway
	6	1	ND-0.13	0.0393	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	1	ND-0.10	0.0379	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	2	ND-0.08	0.0363	El Toro, CA	Urban	87-88	10	mostly residential
	4	1	ND-0.15	0.0516	Cal. Transit, CA	Urban	88-89	10	near highway

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	2	0	ND(0.010-0.012)	NA	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	0	ND(0.010-0.012)	NA	West Long Beach, CA	Urban	88-89	10	mostly residential
2,3,4,7,8-PeCDF	20	20	0.003-0.038	0.0159	Connecticut	Urban	93-94	11	near resource recovery facilities
(continued)	4	4	0.004-0.006	0.00475	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	13	ND-0.055	0.025	Franklin County, OH	Urban	95	12	
	3	2	ND-0.01236	0.0095	Franklin County, OH	Rural	95	12	
	2	2	0.11-0.23	0.168	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.11	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00051-0.011	0.0032	Various U.S. Sites	Rural	98-99	17	background
PeCDFs	16	8	ND-0.41	0.12	Niagra Falls, NY	Urban	86-87	1	
	16	15	ND-12.4	2.08	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	7	NR	ND-1.77	0.57	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	28	0.04-0.71	0.29	Wallingford, CT	Urban	88	5	
	1	1	0.17	0.17	Stockholm, Sweden	Urban	89	13	
	2	2	0.51-4.1	2.30	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	5-10	7.5	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.53-0.66	0.59	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.69-1.30	1.00	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.036)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.50	0.50	Waldo, OH	Rural	87	8	background site
	3	3	1.24-3.26	1.96	Albany, NY	Urban	87-88	9	
	1	1	0.25	0.25	Binghamton, NY	Urban	88	9	
	2	2	2.71-3.61	3.16	Utica, NY	Urban	88	9	
	2	2	0.31-0.39	0.35	Niagra Falls, NY	Industrial	87	9	
	1	1	0.170	0.17	Stockholm	Urban	89	14	
	1	1	0.094	0.094	Stockholm	Urban	89	14	
	1	1	0.046	0.046	Stockholm	Urban	89	14	
	1	1	0.026	0.026	Stockholm	Urban	89	14	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	7	5	ND-1.90	0.402	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	1.00	1.00	Commerce, CA	Urban	87	10	near freeway
	6	4	ND-1.50	0.450	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	2	ND-2.70	0.582	San Bernadino, CA	Urban	87-89	10	mostly residential
PeCDFs (continued)	7	4	ND-0.57	0.247	El Toro, CA	Urban	87-88	10	mostly residential
	4	2	ND-1.60	0.524	Cal. Transit, CA	Urban	88-89	10	near highway
	2	2	0.25-0.28	0.265	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	2	0.23-0.24	0.235	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.057-0.451	0.199	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.057-0.078	0.0663	Connecticut	Rural	93-94	11	near resource recovery facilities
	16	NR	NR	1.43	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
Hexachlorodibenzofurans (MW=374.87)									
1,2,3,4,7,8-HxCDF	3	1	ND-0.06	0.02	Niagra Falls, NY	Urban	86-87	1	
	3	2	ND-0.22	0.11	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.03	Greenbay, WI	Urban	NR	2	
	1	1	0.15	0.15	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.41	0.11	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	21	ND-0.13	0.05	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.04	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.02	Durham, NC	Urban	NR	6	
	3	3	0.053-0.10	0.083	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.060-0.27	0.16	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.034)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.098	0.098	Waldo, OH	Rural	87	8	background site
	7	1	ND-0.27	0.0586	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.180	0.180	Commerce, CA	Urban	87	10	near freeway
	6	1	ND-0.25	0.0574	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	2	ND-0.18	0.0821	San Bernadino, CA	Urban	87-89	10	mostly residential

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	7	2	ND-0.15	0.0499	El Toro, CA	Urban	87-88	10	mostly residential
	4	0	ND(0.039-0.15)	NA	Cal. Transit, CA	Urban	88-89	10	near highway
	2	0	ND(0.038-0.054)	NA	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	0	ND(0.029-0.085)	NA	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.004-0.054	0.0198	Connecticut	Urban	93-94	11	near resource recovery facilities

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8-HxCDF	4	4	0.004-0.008	0.006	Connecticut	Rural	93-94	11	near resource recovery facilities
(continued)	14	13	ND-0.134	0.049	Franklin County, OH	Urban	95	12	
	3	1	ND-0.0261	0.0134	Franklin County, OH	Rural	95	12	
	2	2	0.123-0.286	0.205	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.15	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00071-0.016	0.0038	Various U.S. Sites	Rural	98-99	17	background
1,2,3,6,7,8-HxCDF	3	1	ND-0.02	0.01	Niagra Falls, NY	Urban	86-87	1	
	3	3	0.05-1.17	0.45	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.03	Greenbay, WI	Urban	NR	2	
	1	1	0.25	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.15	0.04	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	17	ND-0.07	0.03	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.03	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.02	Durham, NC	Urban	NR	6	
	1	1	0.008	0.008	Stockholm, Sweden	Urban	89	13	
	2	2	0.03-0.15	0.09	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	0.24-1.4	0.82	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.048-0.092	0.065	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.092-0.19	0.14	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.034)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.014	0.014	Waldo, OH	Rural	87	8	background site
	1	1	0.0078	0.0078	Stockholm	Urban	89	14	
	1	1	0.0059	0.0059	Stockholm	Urban	89	14	
	1	1	0.0024	0.0024	Stockholm	Urban	89	14	
	1	1	0.0014	0.0014	Stockholm	Urban	89	14	
	7	1	ND-0.80	0.130	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.41	0.410	Commerce, CA	Urban	87	10	near freeway
	6	1	ND-0.48	0.0931	North Long Beach, CA	Urban	87-89	10	mostly residential

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	5	1	ND-0.37	0.0977	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	2	ND-0.25	0.0689	El Toro, CA	Urban	87-88	10	mostly residential
1,2,3,6,7,8-HxCDF	4	0	ND(0.031-0.092)	NA	Cal. Transit, CA	Urban	88-89	10	near highway
(continued)	2	0	ND(0.030-0.036)	NA	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	0	ND(0.060-0.070)	NA	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.003-0.038	0.0161	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.003-0.007	0.005	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	14	0.0132-0.115	0.057	Franklin County, OH	Urban	95	12	
	3	1	ND-0.0243	0.0156	Franklin County, OH	Ruran	95	12	
	2	2	0.199-0.405	0.302	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.13	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00062-0.011	0.0035	Various U.S. Sites	Rural	98-99	17	background
1,2,3,7,8,9-HxCDF	3	0	ND(0.01-0.02)	NA	Niagra Falls, NY	Urban	86-87	1	
	3	1	ND-0.1	0.04	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.01	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.08)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.02	0.01	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	1	ND-0.003	0.003	Wallingford, CT	Urban	88	5	
	NR	NR	ND(0.03)	NA	Rutland, VT	Urban	NR	6	
	NR	NR	ND(0.01)	NA	Durham, NC	Urban	NR	6	
	1	1	0.0008	0.0008	Stockholm, Sweden	Urban	89	13	
	2	0	ND(0.01-0.05)	NA	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	1	ND-0.33	0.17	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.020-0.039	0.032	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.038-0.12	0.079	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.034)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.097	0.097	Waldo, OH	Rural	87	8	background site
	1	1	0.0008	0.0008	Stockholm	Urban	89	14	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	1	1	0.0006	0.0006	Stockholm	Urban	89	14	
	1	1	0.0003	0.0003	Stockholm	Urban	89	14	
	1	1	0.0004	0.0004	Stockholm	Urban	89	14	
	1	1	0.0001	0.0001	Bloomington, IN	Urban	86	15	
1,2,3,7,8,9-HxCDF	7	0	ND(0.0040-0.075)	NA	Reseda, CA	Urban	87-89	10	mostly residential
(continued)	1	0	ND(0.11)	NA	Commerce, CA	Urban	87	10	near freeway
	6	0	ND(0.010-0.043)	NA	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	0	ND(0.033-0.21)	NA	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	0	ND(0.015-0.083)	NA	El Toro, CA	Urban	87-88	10	mostly residential
	4	0	ND(0.0032-0.068)	NA	Cal. Transit, CA	Urban	88-89	10	near highway
	2	0	ND(0.0054-0.014)	NA	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	0	ND(0.040-0.086)	NA	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	19	ND-0.020	0.0072	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	3	ND-0.004	0.00213	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	1	ND-0.00528	0.003	Franklin County, OH	Urban	95	12	
	3	0	ND	NA	Franklin County, OH	Rural	95	12	
	2	0	ND	NA	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.21	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00018-0.0061	0.0014	Various U.S. Sites	Rural	98-99	17	background
2,3,4,6,7,8-HxCDF	3	1	ND-0.04	0.02	Niagra Falls, NY	Urban	86-87	1	
	3	2	ND-2.17	0.76	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	ND(0.01)	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.08)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.30	0.09	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	19	ND-0.10	0.04	Wallingford, CT	Urban	88	5	
	NR	NR	ND(0.03)	NA	Rutland, VT	Urban	NR	6	
	NR	NR	ND(0.01)	NA	Durham, NC	Urban	NR	6	
	1	1	0.005	0.005	Stockholm, Sweden	Urban	89	13	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	2	1	ND-0.05	0.03	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	0.21-0.8	0.50	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	0	ND(0.005-0.036)	NA	Akron, OH	Industrial	87	8	near incinerators
	2	0	ND(0.012-0.028)	NA	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.034)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	0	ND(.008)	NA	Waldo, OH	Rural	87	8	background site
2,3,4,6,7,8-HxCDF	1	1	0.0054	0.0054	Stockholm	Urban	89	14	
(continued)	1	1	0.0063	0.0063	Stockholm	Urban	89	14	
	1	1	0.002	0.002	Stockholm	Urban	89	14	
	1	1	0.0009	0.009	Stockholm	Urban	89	14	
	1	1	0.0016	0.0016	Bloomington, IN	Urban	86	15	
	7	1	ND-0.28	0.0551	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.180	0.180	Commerce, CA	Urban	87	10	near freeway
	6	1	ND-0.19	0.0474	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	1	ND-0.16	0.0584	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	0	ND(0.018-0.078)	NA	El Toro, CA	Urban	87-88	10	mostly residential
	4	0	ND(0.039-0.103)	NA	Cal. Transit, CA	Urban	88-89	10	near highway
	2	0	ND(0.014-0.021)	NA	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	0	ND(0.035-0.086)	NA	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.003-0.056	0.0215	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.004-0.009	0.00625	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	13	ND-0.08	0.0304	Franklin County, OH	Urban	95	12	
	3	1	ND-0.0174	0.0092	Franklin County, OH	Rural	95	12	
	2	2	0.122-0.255	0.189	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.078	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.00072-0.015	0.0044	Various U.S. Sites	Rural	98-99	17	background
HxCDFs	16	11	ND-0.58	0.14	Niagra Falls, NY	Urban	86-87	1	
	16	15	ND-10.2	1.96	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	7	NR	ND-2.15	0.58	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	28	0.03-1.57	0.49	Wallingford, CT	Urban	88	5	
	1	1	0.08	0.08	Stockholm, Sweden	Urban	89	13	
	2	2	0.18-1.1	0.64	Hamburg, Germany	Urban	87-88	7	urban air & inside traffic tunnel
	2	2	2.2-9.5	5.85	Hamburg, Germany	Industrial	88	7	downwind incinerator & industrial complex
	3	3	0.56-0.70	0.62	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.37-1.20	0.78	Columbus, OH	Industrial	87	8	near incinerators

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
HxCDFs (continued)	1	1	0.10	0.10	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.51	0.51	Waldo, OH	Rural	87	8	background site
	3	3	0.19-0.37	0.31	Albany, NY	Urban	87-88	9	
	1	0	ND(0.09)	NA	Binghamton, NY	Urban	88	9	
	2	1	ND(0.26)-0.46	0.295	Utica, NY	Urban	88	9	
	2	2	0.12-0.18	0.15	Niagra Falls, NY	Industrial	87	9	
	1	1	0.078	0.078	Stockholm	Urban	89	14	
	1	1	0.062	0.062	Stockholm	Urban	89	14	
	1	1	0.029	0.029	Stockholm	Urban	89	14	
	1	1	0.015	0.015	Stockholm	Urban	89	14	
	7	5	ND-2.00	0.415	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	1.1	1.10	Commerce, CA	Urban	87	10	near freeway
	6	4	ND-1.70	0.452	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	4	ND-0.90	0.606	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	4	ND-0.40	0.162	El Toro, CA	Urban	87-88	10	mostly residential
	4	3	ND-0.84	0.0341	Cal. Transit, CA	Urban	88-89	10	near highway
	2	2	0.19-0.27	0.0230	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	1	ND-0.35	0.200	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.038-0.426	0.181	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.041-0.078	0.055	Connecticut	Rural	93-94	11	near resource recovery facilities
	16	NR	NR	3.45	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
Heptachlorodibenzofurans (MW=409.31)									
1,2,3,4,6,7,8-HpCDF	3	1	ND-0.15	0.05	Niagra Falls, NY	Urban	86-87	1	
	3	3	0.26-5.43	2.08	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.08	Greenbay, WI	Urban	NR	2	
	1	0	ND(0.2)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.54	0.21	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	22	ND-0.80	0.26	Wallingford, CT	Urban	88	5	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	NR	NR	NR	0.12	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.02	Durham, NC	Urban	NR	6	
1,2,3,4,6,7,8-HpCDF	1	1	0.09	0.09	Stockholm, Sweden	Urban	89	13	
(continued)	3	3	0.22-0.25	0.24	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.20-0.47	0.34	Columbus, OH	Industrial	87	8	near incinerators
	1	1	0.087	0.087	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.22	0.22	Waldo, OH	Rural	87	8	background site
	1	1	0.087	0.087	Stockholm	Urban	89	14	
	1	1	0.055	0.055	Stockholm	Urban	89	14	
	1	1	0.028	0.028	Stockholm	Urban	89	14	
	1	1	0.011	0.011	Stockholm	Urban	89	14	
	1	1	0.0035	0.0035	Bloomington	Urban	86	15	
	7	3	ND-1.20	0.211	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.820	0.820	Commerce, CA	Urban	87	10	near freeway
	6	4	ND-1.10	0.276	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	3	ND-0.47	0.254	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	1	ND-0.13	0.0746	El Toro, CA	Urban	87-88	10	mostly residential
	4	3	ND-1.58	0.497	Cal. Transit, CA	Urban	88-89	10	near highway
	2	1	ND-0.20	0.110	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	1	ND-0.13	0.0733	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.012-0.164	0.0709	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.012-0.035	0.0228	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	13	ND-0.429	0.165	Franklin County, OH	Urban	95	12	
	3	2	ND-0.1	0.0612	Franklin County, OH	Rural	95	12	
	2	2	0.609-1.27	0.94	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.76	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.0037-0.064	0.02	Various U.S. Sites	Rural	98-99	17	background
1,2,3,4,7,8,9-HpCDF	NR	NR	NR	0.01	Greenbay, WI	Urban	NR	2	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
	1	0	ND(0.02)	NA	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.07	0.03	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	12	ND-0.30	0.03	Wallingford, CT	Urban	88	5	
	NR	NR	ND(0.01)	NA	Rutland, VT	Urban	NR	6	

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8,9-HpCDF	NR	NR	ND(0.01)	NA	Durham, NC	Urban	NR	6	
(continued)	1	0	ND(0.001)	NA	Stockholm, Sweden	Urban	89	13	
	3	1	ND-0.031	0.020	Akron, OH	Industrial	87	8	near incinerators
	2	0	ND(0.015-0.028)	NA	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.013)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.019	0.019	Waldo, OH	Rural	87	8	background site
	1	1	0.004	0.004	Stockholm	Urban	89	14	
	1	1	0.0033	0.0033	Stockholm	Urban	89	14	
	1	1	0.0014	0.0014	Stockholm	Urban	89	14	
	1	1	0.0003	0.0003	Stockholm	Urban	89	14	
	1	1	0.0001	0.0001	Bloomington, IN	Urban	86	15	
	7	0	ND(0.0062-0.11)	NA	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	0.0920	0.0920	Commerce, CA	Urban	87	10	near freeway
	6	1	ND-0.11	0.0397	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	0	ND(0.030-0.12)	NA	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	0	ND(0.017-0.10)	NA	El Toro, CA	Urban	87-88	10	mostly residential
	4	2	ND-0.14	0.0606	Cal. Transit, CA	Urban	88-89	10	near highway
	2	0	ND(0.024-0.040)	NA	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	0	ND(0.015-0.043)	NA	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	19	ND-0.029	0.0104	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.001-0.006	0.0035	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	13	ND-0.09	0.032	Franklin County, OH	Urban	95	12	
	3	2	ND-0.0188	0.0143	Franklin County, OH	Rural	95	12	
	2	2	0.082-0.18	0.13	Franklin County, OH	Industrial	95	12	near waste to energy facility
	16	NR	NR	0.10	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	ND(0.000091)-0.011	0.0025	Various U.S. Sites	Rural	98-99	17	background
HpCDFs	16	12	ND-0.43	0.13	Niagra Falls, NY	Urban	86-87	1	
	16	12	ND-8.76	1.67	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
HpCDFs (continued)	7	NR	ND-1.0	0.37	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	26	ND-1.58	0.47	Wallingford, CT	Urban	88	5	
	1	1	0.11	0.11	Stockholm, Sweden	Urban	89	13	
	2	2	0.1-1.2	0.65	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	2-5	3.5	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.37-0.39	0.38	Akron, OH	Industrial	87	8	near incinerators
	2	2	0.26-0.64	0.45	Columbus, OH	Industrial	87	8	near incinerators
	1	1	0.15	0.15	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.29	0.29	Waldo, OH	Rural	87	8	background site
	3	1	ND-0.65	0.312	Albany, NY	Urban	87-88	9	
	1	0	ND(0.14)	NA	Binghamton, NY	Urban	88	9	
	2	1	ND(0.41)-0.07	0.138	Utica, NY	Urban	88	9	
	2	2	0.13-0.26	0.195	Niagra Falls, NY	Industrial	87	9	
	1	1	0.11	0.11	Stockholm	Urban	89	14	
	1	1	0.081	0.081	Stockholm	Urban	89	14	
	1	1	0.036	0.036	Stockholm	Urban	89	14	
	1	1	0.015	0.015	Stockholm	Urban	89	14	
	7	5	ND-1.40	0.288	Reseda, CA	Urban	87-89	10	mostly residential
	1	1	1.80	1.80	Commerce, CA	Urban	87	10	near freeway
	6	4	ND-1.20	0.327	North Long Beach, CA	Urban	87-89	10	mostly residential
	5	3	ND-0.66	0.822	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	1	ND-0.13	0.0860	El Toro, CA	Urban	87-88	10	mostly residential
	4	3	ND-2.25	0.724	Cal. Transit, CA	Urban	88-89	10	near highway
	2	1	ND-0.33	0.174	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	1	ND-0.30	0.161	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.022-0.314	0.128	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.020-0.070	0.042	Connecticut	Rural	93-94	11	near resource recovery facilities
	16	NR	NR	1.33	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road

Table B-2. Environmental Levels of Dibenzofurans in Air (pg/m^3) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
Octachlorodibenzofurans (MW=444.76)									
1,2,3,4,6,7,8,9-OCDF	16	11	ND-0.22	0.09	Niagra Falls, NY	Urban	86-87	1	
	15	8	ND-3.38	0.62	Niagra Falls, NY	Industrial	86-87	1	downwind industrial complex
	NR	NR	NR	0.07	Greenbay, WI	Urban	NR	2	
	1	1	0.06	0.06	Los Angeles, CA	Urban	87	3	
	7	NR	ND-0.56	0.21	Bridgeport, CT	Urban	87-88	4	composite of 2-7 samples
	28	18	ND-0.70	0.21	Wallingford, CT	Urban	88	5	
	NR	NR	NR	0.14	Rutland, VT	Urban	NR	6	
	NR	NR	NR	0.03	Durham, NC	Urban	NR	6	
	1	1	0.02	0.02	Stockholm, Sweden	Urban	89	13	
	2	0	ND(0.11-1.0)	NA	Hamburg, Germany	Urban	NR	7	urban air & inside traffic tunnel
	2	2	0.78-7.0	3.89	Hamburg, Germany	Industrial	NR	7	downwind incinerator & industrial complex
	3	3	0.17-0.19	0.18	Akron, OH	Industrial	87	8	near incinerators
	2	1	ND-0.21	0.18	Columbus, OH	Industrial	87	8	near incinerators
	1	0	ND(0.16)	NA	Columbus, OH	Urban	87	8	next to interstate highway
	1	1	0.077	0.077	Waldo, OH	Rural	87	8	background site
	3	1	ND(0.93)-0.3	0.312	Albany, NY	Urban	87-88	9	
	1	0	ND(0.3)	NA	Binghamton, NY	Urban	88	9	
	2	0	ND(0.12-1.10)	NA	Utica, NY	Urban	88	9	
	2	2	0.12-0.18	0.15	Niagra Falls, NY	Industrial	87	9	
	1	1	0.016	0.016	Stockholm	Urban	89	14	
	1	1	0.0072	0.0072	Stockholm	Urban	89	14	
	1	1	0.003	0.003	Stockholm	Urban	89	14	
	1	1	0.0009	0.0009	Stockholm	Urban	89	14	
	6	3	ND-0.13	0.116	Reseda, CA	Urban	87-89	10	mostly residential

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location range	Location description	Sample year	Ref. no.	Comments
1,2,3,4,6,7,8,9-OCDF	5	2	ND-0.43	0.152	North Long Beach, CA	Urban	87-89	10	mostly residential
(continued)	5	3	ND-0.29	0.162	San Bernadino, CA	Urban	87-89	10	mostly residential
	7	4	ND-0.13	0.0756	El Toro, CA	Urban	87-88	10	mostly residential
	4	2	ND-2.17	0.662	Cal. Transit, CA	Urban	88-89	10	near highway
	2	1	ND-0.12	0.164	Carson, CA	Industrial	88-89	10	on site at gas cooking equipment manufacturer
	2	2	0.32-0.43	0.374	West Long Beach, CA	Urban	88-89	10	mostly residential
	20	20	0.009-0.179	0.0551	Connecticut	Urban	93-94	11	near resource recovery facilities
	4	4	0.011-0.028	0.0193	Connecticut	Rural	93-94	11	near resource recovery facilities
	14	14	0.038-0.366	0.14	Franklin County, OH	Urban	95	12	
	3	3	0.0403-0.0899	0.0668	Franklin County, OH	Rural	95	12	
	2	2	0.261-0.56	0.411	Franklin County, OH	Industrial	95	12	near waste-to-energy facility
	16	NR	NR	0.344	Phoenix, AZ	Urban	94	16	close proximity to a heavily traveled road
	53	53	0.0022-0.052	0.017	Various U.S. Sites	Rural	98-99	17	background

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects;
NA = Not available;
NR = Not reported;
ND = Non-detect.

Sources:

1. Smith et al. (1989)
2. Harless et al. (1990)
3. Maisel and Hunt (1990)
4. Hunt and Maisel (1990)
5. CDEP (1988)
6. Harless et al. (1991)
7. Rappe and Kjeller (1987)
8. Edgerton et al. (1989)
9. Smith et al. (1990)
10. Hunt et al. (1990)
11. CDEP (1995)
12. OEPA (1995)
13. Naf et al. (1990)
14. Broman et al. (1991)
15. Eitzer and Hites (1989)
16. Hunt et al. (1997)
17. Cleverly et al. (2000)

Table B-3. Environmental Levels of PCBs in Air (pg/m^3)

IUPAC Number	Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
					Tetrachloro-PCB					
77	3,3'4,4'-TeCB	53	52	0.0051-0.14	0.054	Various U.S. Sites	Rural	98-99	2	
					Pentachloro-PCB					
118	2,3',4,4',5-PeCB	143	143	NR	2.3	Egbert, ON	Rural	88-89	1	
114	2,3,4,4',5-PeCB	143	143	NR	1.2	Egbert, ON	Rural	88-89	1	
105	2,3,3',4,4'-PeCB	143	143	NR	0.16	Egbert, ON	Rural	88-89	1	
118	2,3',4,4',5-PeCB	53	50	0.1-4	0.82	Various U.S. Sites	Rural	98-99	2	
105	2,3,3',4,4'-PeCB	53	50	0.039-1.3	0.3	Various U.S. Sites	Rural	98-99	2	
126	3,3',4,4',5-PeCB	53	52	0.00088-0.04	0.0062	Various U.S. Sites	Rural	98-99	2	
					Hexachloro-PCB					
156	2,3,3',4,4',5-HxCB	143	143	NR	0.07	Egbert, ON	Rural	88-89	1	
156	2,3,3',4,4',5-HxCB	53	50	0.0075-0.24	0.05	Various U.S. Sites	Rural	98-99	2	
157	2,3,3',4,4',5'-HxCB	53	50	0.0016-0.051	0.011	Various U.S. Sites	Rural	98-99	2	
169	3,3',4,4',5,5'-HxCB	53	52	ND(0.00006)-0.0036	0.00068	Various U.S. Sites	Rural	98-99	2	
					Heptachloro-PCB					
189	2,3,3',4,4',5,5'-HpCB	143	143	NR	0.01	Egbert, ON	Rural	88-89	1	

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects;
NA = not available;
NR = not reported;
ND = Non-detect.

Sources:

1. Hoff et al. (1992)
2. Cleverly et al. (2000)

Table B-4. Environmental Levels of Dioxins in Soil (ppt)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
Tetrachlorodibenzo-p-dioxins (MW=321.98)									
2,3,7,8-TCDD	23	23	10-36000	2133	Midland, MI	Industrial	1983	1	
	62	59	ND-270	55	Midland, MI	Residential	1983	1	
	13	1	ND-2	<1	Henry, IL	Residential	1984	1	
	22	6	ND-5	1	Middletown, OH	Residential	1983	1	
	4	0	ND(1.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	2	Finland	Industrial	NR	2	
	33	33	22-52000	4300	Midland, MI	Industrial	NR	3	
	11	9	ND-590	145	Midland, MI	Industrial	NR	3	
	20	13	ND-9.4	2	US	Industrial	NR	3	Urban area
	8	4	ND-3.1	2	Sweden	Urban	1989	4	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	5	Agriculture
	12	12	1-7	3	England	Residential	1990	6	Rural
	19	6	ND-4.2	1	England	Urban	NR	7	
	3	0	ND(0.2-2.0)	NA	Various parts of Europe	Rural	NR	8	
	2	2	2.4-0.84	1.62	Various parts of Europe	Industrial	NR	8	
	65	NR	ND-2.1	<0.5	British Isles	Background	NR	9	
	NR	NR	200000	NR	Muggenburger st. Hamburg,Germany	Industrial	1985	10	Maximum contents reported
	NR	NR	2800	NR	Kirchsteinbek, Hamburg,Germany	Industrial	1985	10	Maximum contents reported
	NR	NR	900	NR	Ochsenwerder Landscheideweg, Hamburg,Germany	Contaminated site	1985	10	Maximum contents reported
	NR	NR	874000	NR	Moorefleeter Brack Hamburg,Germany	Contaminated site	1985	10	Maximum contents reported
	13	0	ND	NA	Salzburg, Austria	Urban	1990/91	11	
	5	0	ND	NA	Salzburg, Austria	Industrial	1990/91	11	
	6	0	ND	NA	Salzburg, Austria	Rural	1990/91	11	
	53	0	ND	NA	British Columbia, Canada	Background	NR	12	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
2,3,7,8-TCDD	31	8	ND-85	5.18	British Columbia, Canada	Near Impacted site	NR	12	
(continued)	47	9	ND-550	15.44	British Columbia, Canada	Impacted site	NR	12	
	14	NR	ND(0.2)	NA	Western Germany	Background	NR	13	Plowland
	7	NR	ND(0.2)	NA	Western Germany	Background	NR	13	Grassland
	9	NR	0.5-3.0	1.4	Western Germany	Background	NR	13	Deciduous forest
	11	NR	ND-4.0	92	Western Germany	Background	NR	13	Coniferous forest
	3	2	ND-0.57	0.393	Ohio	Background	1995	14	
	4	4	4.2-56.99	28.520	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	15	ND-10.91	2.273	Ohio	Urban	1995	14	
	34	15	0.02-7.96	0.61	Connecticut	Urban	1987/90	17	Pre-operational
	8	3	ND-1.1	0.28	Yarmouth, ME	Background	1996	18	
	162	161	0.0011-20	0.61	Denver Front Range	Various Land Uses	99-00	19	background
TCDDs	1	1	320	320	Midland, MI	Industrial	1983	1	
	7	5	ND-290	109	Midland, MI	Residential	1983	1	
	5	0	ND(1.0)	NA	Middletown, OH	Residential	1983	1	
	3	0	ND(1.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	89	Finland	Industrial	NR	2	
	11	NR	ND-7	< 1	Canada	Urban	1983	15	Near Incinerator
	12	NR	ND-430	69	Canada	Urban	1987	15	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	15	
	29	NR	ND-1200	69	Canada	Urban	83-88	15	
	8	8	37-217	98	Sweden	Urban	1989	4	Near Stockholm
	4	0	ND	NA	Elk River, MN	Agriculture	1988	5	
	12	12	17-120	42	England	Residential	1990	6	Rural
	19	19	9-160	65	England	Urban	NR	7	
	2	2	11.2-55.5	33.4	Various parts of Europe	Industrial	NR	8	
	1	1	3.2	3.2	Various parts of Europe	Rural	NR	8	
	65	NR	ND-69	9.4	British Isles	Background	NR	10	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
TCDDs (continued)	30	0	ND	NA	Ontario and U.S. Midwestern States	Rural	NR	16	
	20	0	ND	NA	Ontario and U.S. Midwestern States	Industrial	NR	16	
	47	11	ND-430	40.3	Ontario and U.S. Midwestern States.	Urban	NR	16	
	13	2	0-1.6	0.75	Salzburg, Austria	Urban	1990/91	11	
	5	4	ND-9.8	4.8	Salzburg, Austria	Industrial	1990/91	11	
	6	1	ND-1.8	0.3	Salzburg, Austria	Rural	1990/91	11	
	53	19	ND-240	12.48	British Columbia, Canada	Background	NR	12	
	31	11	ND-1100	71.93	British Columbia, Canada	Near Impacted site	NR	12	
	47	19	ND-11000	1009.58	British Columbia, Canada	Impacted site	NR	12	
	14	NR	0.4-3.4	2	Western Germany	Background	NR	13	Plowland
	7	NR	0.9-6.9	2.8	Western Germany	Background	NR	13	Grassland
	9	NR	16.1-235.8	70.5	Western Germany	Background	NR	13	Deciduous forest
	11	NR	19-392.1	92	Western Germany	Background	NR	13	Coniferous forest
	34	28	0.09-33.3	3.63	Connecticut	Urban	1987/90	17	Pre-operational
	8	5	ND-5.17	1.95	Yarmouth, ME	Background	1996	18	
Pentachlorodibenzo-p-dioxins (MW=356.42)									
1,2,3,7,8-PeCDD	NR	NR	NR	15	Finland	Industrial	NR	2	
	8	7	2.6-18.3	10	Sweden	Urban	1989	4	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	5	Agriculture
	19	7	ND-11	2	England	Urban	NR	7	
	3	0	ND(0.1-2)	NA	various parts of Europe	Rural	NR	8	
	2	2	18-34	26	various parts of Europe	Industrial	NR	8	
	65	NR	ND-2.4	<0.5	British Isles	Background	NR	9	
	13	2	1.1-4.6	0.4	Salzburg, Austria	Urban	1990/91	11	
	5	1	ND-1.9	0.4	Salzburg, Austria	Industrial	1990/91	11	
	6	0	ND	NA	Salzburg, Austria	Rural	1990/91	11	
	53	3	ND-4.4	0.16	British Columbia, Canada	Background	NR	12	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,7,8-PeCDD	31	5	ND-670	45.94	British Columbia, Canada	Near Impacted site	NR	12	
(continued)	47	17	ND-410	40.28	British Columbia, Canada	Impacted site	NR	12	
	14	NR	ND(0.4)	NA	Western Germany	Background	NR	13	Plowland
	7	NR	0.4-0.4	0.4	Western Germany	Background	NR	13	Grassland
	9	NR	1.1-29.1	8.3	Western Germany	Background	NR	13	Deciduous forest
	11	NR	ND-8.9	5.1	Western Germany	Background	NR	13	Coniferous forest
	3	0	ND	NA	Ohio	Background	1995	14	
	4	4	21.52-393.18	180.008	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	18	3.2-24.62	6.584	Ohio	Urban	1995	14	
	34	34	0.04-15.0	1.74	Connecticut	Urban	1987/90	17	Pre-operational
	8	4	ND-0.98	0.43	Yarmouth, ME	Background	1996	18	
	162	160	0.0017-54	1.4	Denver Front Range	Various Land Uses	99-00	19	background
PeCDDs	1	1	240	240	Midland, MI	Industrial	1983	1	
	7	2	ND-120	31	Midland, MI	Residential	1983	1	
	5	0	ND(10)	NA	Middletown, OH	Residential	1983	1	
	3	0	ND(4.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	900	Finland	Industrial	NR	2	
	11	NR	ND-580	53	Canada	Urban	1983	15	Near Incinerator
	12	NR	ND-540	81	Canada	Urban	1987	15	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	15	
	29	NR	ND-130	12.8	Canada	Urban	83-88	15	
	8	8	46-476	159	Sweden	Urban	1989	4	Near Stockholm
	4	1	ND-38	10	Elk River, MN	Rural	1988	5	Agriculture
	12	12	4-50	20	England	Residential	1990	6	Rural
	19	19	6-190	69	England	Urban	NR	7	
	1	1	4.6	4.6	various parts of Europe	Rural	NR	8	
	2	2	220-270	245	various parts of Europe	Industrial	NR	8	
	65	NR	ND-46	6.6	British Isles	Background	NR	9	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
PeCDDs (continued)	47	7	ND-580	38.4	Ontario and U.S. Midwestern States	Urban	NR	16	
	30	0	ND	NA	Ontario and U.S. Midwestern States	Rural	NR	16	
	20	0	ND	NA	Ontario and U.S. Midwestern States	Industrial	NR	16	
	13	7	0.8-36.3	4.2	Salzburg, Austria	Urban	1990/91	11	
	5	4	ND-15.6	7.3	Salzburg, Austria	Industrial	1990/91	11	
	6	5	ND-4.9	0.8	Salzburg, Austria	Rural	1990/91	11	
	53	16	ND-190	8.96	British Columbia, Canada	Background	NR	12	
	31	8	ND-4700	358.61	British Columbia, Canada	Near Impacted site	NR	12	
	47	25	ND-9100	1049.05	British Columbia, Canada	Impacted site	NR	12	
	14	NR	1.2-5.3	2.3	Western Germany	Background	NR	13	Plowland
	7	NR	0.9-23.8	6.1	Western Germany	Background	NR	13	Grassland
	9	NR	19.5-285.2	98.1	Western Germany	Background	NR	13	Deciduous forest
	11	NR	32.6-192.4	91.1	Western Germany	Background	NR	13	Coniferous forest
	35	31	0.16-108	11.73	Connecticut	Urban	1987/90	17	Pre-operational
	8	6	ND-5.7	3.0	Yarmouth, ME	Background	1996	18	
Hexachlorodibenzo-p-dioxins (MW=390.87)									
1,2,3,4,7,8-HxCDD	NR	NR	NR	<2	Finland	Industrial	NR	2	
	8	8	4.3-8.0	6	Sweden	Urban	1989	4	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	5	Agriculture
	3	0	ND(0.1-2)	NA	various parts of Europe	Rural	NR	8	
	2	2	13-28	21	various parts of Europe	Industrial	NR	8	
	13	8	ND-3.2	0.8	Salzburg, Austria	Urban	1990/91	11	
	5	1	ND-0.8	0.2	Salzurg, Austria	Industrial	1990/91	11	
	6	2	0.7-1.1	0.3	Salzburg, Austria	Rural	1990/91	11	
	53	3	ND-6.7	0.2	British Columbia, Canada	Background	NR	12	
	31	8	ND-420	37.14	British Columbia, Canada	Near Impacted site	NR	12	
	47	17	ND-490	56.99	British Columbia, Canada	Impacted site	NR	12	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8-HxCDD	14	NR	0.8-1.4	1.2	Western Germany	Background	NR	13	Plowland
(continued)	7	NR	ND(0.8)	NA	Western Germany	Background	NR	13	Grassland
	9	NR	1.5-20.9	6.5	Western Germany	Background	NR	13	Deciduous forest
	11	NR	2.1-14.0	5.8	Western Germany	Background	NR	13	Coniferous forest
	3	1	ND-0.74	0.350	Ohio	Background	1995	14	
	4	4	20.61-297.59	142.287	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	18	2.2-21.94	6.144	Ohio	Urban	1995	14	
	35	35	0.08-8.49	1.29	Connecticut	Urban	1987/90	17	Pre-operational
	8	7	ND-2.6	1.22	Yarmouth, ME	Background	1996	18	
	162	161	0.0049-65	2.5	Denver Front Range	Various Land Uses	99-00	19	background
1,2,3,6,7,8-HxCDD	NR	NR	NR	2100	Finland	Industrial	NR	2	
	8	8	3.3-32.2	12	Sweden	Urban	1989	4	Near Stockholm
	4	1	ND-14	4	Elk River, MN	Rural	1988	5	Agriculture
	3	0	ND(0.1-2)	NA	various parts of Europe	Rural	NR	8	
	2	2	19-64	42	various parts of Europe	Industrial	NR	8	
	13	9	ND-5.6	1.7	Salzburg, Austria	Urban	1990/91	11	
	5	2	ND-2.3	1.2	Salzburg, Austria	Industrial	1990/91	11	
	6	2	1.1-1.9	0.5	Salzburg, Austria	Rural	1990/91	11	
	53	28	ND-185	13.13	British Columbia, Canada	Background	NR	12	
	31	16	ND-10000	777.70	British Columbia, Canada	Near Impacted site	NR	12	
	47	34	ND-8600	680.58	British Columbia, Canada	Impacted site	NR	12	
	14	NR	1.1-1.8	1.5	Western Germany	Background	NR	13	Plowland
	7	NR	1.4-2.9	1.9	Western Germany	Background	NR	13	Grassland
	9	NR	3.1-49.4	12.4	Western Germany	Background	NR	13	Deciduous forest
	11	NR	3.7-28.8	11.1	Western Germany	Background	NR	13	Coniferous forest
	3	3	0.52-1.39	0.817	Ohio	Background	1995	14	
	4	4	18.15-295.49	137.798	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	18	1.2-40.17	10.940	Ohio	Urban	1995	14	
	35	34	0.25-17.3	2.66	Connecticut	Urban	1987/90	17	Pre-operational

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	8	8	1.3-5.8	2.89	Yarmouth, ME	Background	1996	18	
1,2,3,6,7,8-HxCDD	162	161	0.0044-200	6.5	Denver Front Range	Various Land Uses	99-00	19	background
(continued)	NR	NR	NR	700	Finland	Industrial	NR	2	
1,2,3,7,8,9-HxCDD	8	7	ND-16.6	8	Sweden	Urban	1989	4	Near Stockholm
	4	2	ND-9.9	5	Elk River, MN	Rural	1988	5	Agriculture
	3	0	ND(0.1-2)	NA	various parts of Europe	Rural	NR	8	
	2	2	6.2-19	13	various parts of Europe	Industrial	NR	8	
	13	7	ND-4.6	1.1	Salzburg, Austria	Urban	1990/91	11	
	5	2	1.6-2.5	1.1	Salzburg, Austria	Industrial	1990/91	11	
	6	1	ND-2.1	0.4	Salzburg, Austria	Rural	1990/91	11	
	53	16	ND-55.5	3.42	British Columbia, Canada	Background	NR	12	
	31	13	ND-1200	99.24	British Columbia, Canada	Near Impacted site	NR	12	
	47	28	ND-2700	228.74	British Columbia, Canada	Impacted site	NR	12	
	14	NR	1.6-2.4	2.0	Western Germany	Background	NR	13	Plowland
	7	NR	1.7-1.7	1.7	Western Germany	Background	NR	13	Grassland
	9	NR	3.6-82.0	19.1	Western Germany	Background	NR	13	Deciduous forest
	11	NR	5.3-54.3	16.2	Western Germany	Background	NR	13	Coniferous forest
	3	3	0.75-2.11	1.23	Ohio	Background	1995	14	
	4	4	96.1-422.85	201.608	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	18	1.47-36.59	10.839	Ohio	Urban	1995	14	
	35	34	0.28-15.70	2.75	Connecticut	Urban	1987/90	17	Pre-operational
	8	8	0.97-3.10	2.41	Yarmouth, ME	Background	1996	18	
	162	161	0.0047-120	4	Denver Front Range	Various Land Uses	99-00	19	background
HxCDDs	1	1	4000	4000	Midland, MI	Industrial	1983	1	
	8	6	ND-410	151	Midland, MI	Residential	1983	1	
	5	1	ND-72	14	Middletown, OH	Residential	1983	1	
	3	0	ND(5.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	7200	Finland	Industrial	NR	2	
	11	NA	ND-170	15	Canada	Urban	1983	15	Near Incinerator

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	12	NA	ND-70	9	Canada	Urban	1987	15	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	15	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
HxCDDs (continued)	29	0	ND	NA	Canada	Urban	83-88	15	
	8	8	43-349	156	Sweden	Urban	1989	4	Near Stockholm
	4	4	12-99	48	Elk River, MN	Rural	1988	5	Agriculture
	12	12	8-43	23	England	Residential	1990	6	Rural
	19	19	23-340	154	England	Urban	NR	7	
	1	1	4.7	4.7	Various parts of Europe	Rural	NR	8	
	2	2	200-330	265	Various parts of Europe	Industrial	NR	8	
	65	NR	2.8-165	38	British Isles	Background	NR	9	
	47	13	ND-410	38.12	Ontario and U.S. Midwestern States	Urban	NR	16	
	30	0	ND	NA	Ontario and U.S. Midwestern States	Rural	NR	16	
	20	8	ND-240	44.1	Canada and U.S.A.	Industrial	NR	16	
	13	13	4.8-53	18.8	Salzburg, Austria	Urban	1990/91	11	
	5	5	20.3-48.0	30.3	Salzburg, Austria	Industrial	1990/91	11	
	6	5	ND-44.3	12.0	Salzburg, Austria	Rural	1990/91	11	
	53	37	ND-1250	82.46	British Columbia, Canada	Background	NR	12	
	31	18	ND-29000	2794.7	British Columbia, Canada	Near Impacted site	NR	12	
	47	39	ND-36000	3393.51	British Columbia, Canada	Impacted site	NR	12	
	14	NR	2-13.1	7.0	Western Germany	Background	NR	13	Plowland
	7	NR	3.9-26.0	14.9	Western Germany	Background	NR	13	Grassland
	9	NR	39.9-901.0	202.0	Western Germany	Background	NR	13	Deciduous forest
	11	NR	55.7-397.0	156.2	Western Germany	Background	NR	13	Coniferous forest
	35	34	0.29-170.0	28.7	Connecticut	Urban	1987/90	17	Pre-operational
	7	7	9.4-30	19.6	Yarmouth, ME	Background	1996	18	
Heptachlorodibenzo-p-dioxins (MW=425.31)									
1,2,3,4,6,7,8-HpCDD	NR	NR	NR	4700	Finland	Industrial	NR	2	
	8	8	43-492	144	Sweden	Urban	1989	4	Near Stockholm
	4	4	37-360	194	Elk River, MN	Rural	1988	5	Agriculture
	13	13	5.9-121.8	30.3	Salzburg, Austria	Urban	1990/91	11	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,6,7,8-HpCDD (continued)	5	5	13.6-92.0	30.6	Salzburg, Austria	Industrial	1990/91	11	
	6	6	1.8-24.6	8.1	Salzburg, Austria	Rural	1990/91	11	
	53	43	ND-2100	141.3	British Columbia, Canada	Background	NR	12	
	31	22	ND-37000	3589.22	British Columbia, Canada	Near Impacted site	NR	12	
	47	42	ND-530000	16877.14	British Columbia, Canada	Impacted site	NR	12	
	14	NR	4.1-21.9	9.1	Western Germany	Background	NR	13	Plowland
	7	NR	7.1-34.8	14.6	Western Germany	Background	NR	13	Grassland
	9	NR	22.8-398.7	120.7	Western Germany	Background	NR	13	Deciduous forest
	11	NR	35.9-271.7	109.0	Western Germany	Background	NR	13	Coniferous forest
	3	3	9.4-31.6	17.773	Ohio	Background	1995	14	
	4	4	139.24-1508.86	765.160	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	18	11.69-902.55	190.081	Ohio	Urban	1995	14	
	35	35	2.34-270	55.3	Connecticut	Urban	1987/90	17	Pre-operational
	8	8	12.9-160	68.1	Yarmouth, ME	Background	1996	18	
	160	161	0.36-3,700	170	Denver Front Range	Various Land Uses	99-00	19	background
1,2,3,4,6,7,9-HpCDD	NR	NR	NR	7100	Finland	Industrial	NR	2	
HpCDDs	1	1	75000	75000	Midland, MI	Industrial	1983	1	
	8	88	150-2400	813	Midland, MI	Residential	1983	1	
	5	5	23-200	113	Middletown, OH	Residential	1983	1	
	3	3	25-91	54	MN	Pristine	1983	1	
	11	NR	ND-390	90	Canada	Urban	1983	15	Near Incinerator
	12	NR	ND-300	43	Canada	Urban	1987	15	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	15	
	29	NR	ND-1100	93	Canada	Urban	83-88	15	
	8	8	83-904	277	Sweden	Urban	1989	4	Near Stockholm
	4	4	62-640	346	Elk River, MN	Rural	1988	5	Agriculture
	12	12	20-130	64	England	Residential	1990	6	Rural
	19	19	77-5500	817	England	Urban	NR	7	
	3	1	ND-17	9.0	Various parts of Europe	Rural	NR	8	

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
HpCDDs (continued)	2	2	370-1600	985	Various parts of Europe	Industrial	NR	8	
	65	NR	7.5-234	66	British Isles	Background	NR	9	
	30	3	ND-91	5.4	Ontario and U.S. Midwestern States.	Rural	NR	16	
	47	25	ND-2400	212	Ontario and U.S. Midwestern States.	Urban	NR	16	
	20	19	ND-5000	1197	Canada and U.S.A.	Industrial	NR	16	
	13	13	10.3-197.1	51.1	Salzburg, Austria	Urban	1990/91	11	
	5	5	24.0-166.0	57.3	Salzburg, Austria	Industrial	1990/91	11	
	6	6	3.5-45.3	15.0	Salzburg, Austria	Rural	1990/91	11	
	53	43	ND-3350	233.29	British Columbia, Canada	Background	NR	12	
	31	22	ND-5200	5460.29	British Columbia, Canada	Near Impacted site	NR	12	
	47	42	ND-760000	25253.48	British Columbia, Canada	Impacted site	NR	12	
	14	NR	3.2-26.3	14.2	Western Germany	Background	NR	13	Plowland
	7	NR	11.1-62.9	25.7	Western Germany	Background	NR	13	Grassland
	9	NR	45.0-1151.6	275.3	Western Germany	Background	NR	13	Deciduous forest
	11	NR	74.2-522.7	219.9	Western Germany	Background	NR	13	Coniferous forest
	35	35	4.59-568	121	Connecticut	Urban	1987/90	17	Pre-operational
	8	8	19.5-240	118	Yarmouth, ME	Background	1996	18	
Octachlorodibenzo-p-dioxin (MW=460.76)									
1,2,3,4,6,7,8,9-OCDD	1	1	375000	375000	Midland, MI	Industrial	1983	1	
	8	8	330-12000	3914	Midland, MI	Residential	1983	1	
	5	5	170-10600	2418	Middletown, OH	Residential	1983	1	
	3	3	92-200	140	MN	Pristine	1983	1	
	NR	NR	NR	6200	Finland	Industrial	NR	2	
	11	NR	ND-3500	663	Canada	Urban	1983	15	Near Incinerator
	12	NR	ND-1500	570	Canada	Urban	1987	15	Near Incinerator
	43	NR	ND-100	38	Canada	Rural	83-88	15	
	29	NR	ND-16000	2464	Canada	Urban	83-88	15	
	8	8	113-2659	687	Sweden	Urban	1989	4	Near Stockholm

Table B-4. Environmental Levels of Dioxins in Soils (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,6,7,8,9-OCDD	4	4	340-3300	1655	Elk River, MN	Rural	1988	5	Agriculture
(continued)	12	12	20-150	58	England	Residential	1990	6	
	19	19	176-99000	9980	England	Urban	NR	7	
	1	1	14	14	Various parts of Europe	Rural	NR	8	
	2	2	140-160	160	Various parts of Europe	Industrial	NR	8	
	65	NR	29-832	191	British Isles	Background	NR	9	
	30	17	44-810	67.33	Ontario and U.S. Midwestern States.	Rural	NR	16	
	47	38	ND-12000	1599	Ontario and U.S. Midwestern States.	Urban	NR	16	
	20	20	15-26000	3442	Canada and U.S.A.	Industrial	NR	16	
	3	3	75.76-298.32	160.893	Ohio	Background	1995	14	
	4	4	653.25-1973.490	1495.390	Ohio	Impacted site	1995	14	Near waste-to-energy facility
	18	18	76.61-6995.43	1560.161	Ohio	Urban	1995	14	
	35	35	20.4-4,970	814.3	Connecticut	Urban	1987/90	17	Pre-operational
	8	8	145-4,000	967	Yarmouth, ME	Background	1996	18	
	162	161	0.14-18,000	900	Denver Front Range	Various Land Uses	99-00	19	background

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects if congener-specific detection limits were given; when detection limits were not given, zero was used for nondetects.
NA = Not applicable.
ND = Non-detect.
NR = Not reported.
Detection limits varied by study and as was different for different compounds, but generally were 1 to 5 ng/kg (ppt). Descriptions provided were those given by reference or surmised from study description when not given.

Sources:

1. U.S. EPA (1985)
2. Kitunen and Salkinoja-Salonen (1990)
3. Nestrick et al. (1986)
4. Broman et al. (1990)
5. Reed et al. (1990)
6. Stenhouse and Badsha (1990)
7. Creaser et al. (1990)
8. Rappe and Kjeller (1987)
9. Creaser et al. (1989)
10. Sievers and Friesel (1989)
11. Boos et al. (1992)
12. BC Environment (1995)
13. Rotard et al. (1994)
14. U.S. EPA (1996)
15. Pearson et al. (1990)
16. Birmingham (1990)
17. MRI (1992)
18. Tewhey Associates (1997)
19. U.S. EPA Region 8 (2000)

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
Tetrachlorodibenzofurans (MW=305.98)									
2,3,7,8-TCDF	2	2	27-450	238	Midland, MI	Industrial	1983	1	
	8	3	ND-15	5	Midland, MI	Residential	1983	1	
	5	2	ND-6	2	Middletown, OH	Residential	1983	1	
	3	0	ND(1.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	<2	Finland	Industrial	NR	2	
	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
	12	12	3-50	17	England	Residential	1990	4	Rural
	13	7	ND-6.1	1.4	Salzurg, Austria	Urban	1990/91	5	
	5	3	ND-12.0	4.1	Salzburg, Austria	Industrial	1990/91	5	
	6	1	ND-1.9	0.3	Salzburg, Austria	Rural	1990/91	5	
	53	28	ND-32	3.21	British Columbia, Canada	Background	1995	6	
	31	16	ND-520	47.86	British Columbia, Canada	Near Impacted site	1995	6	
	47	23	ND-550	60.68	British Columbia, Canada	Impacted site	1995	6	
	14	NR	0.7-3.4	1.8	West Germany	Background	NR	7	Plowland
	7	NR	0.7-3.6	2.2	West Germany	Background	NR	7	Grassland
	9	NR	7.2-67.8	25.4	West Germany	Background	NR	7	Deciduous forest
	11	NR	10.0-60.6	27.9	West Germany	Background	NR	7	Coniferous forest
	3	0	ND	NA	Ohio	Background	1995	8	
	4	4	11.4-184.66	85.892	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	18	0.67-16.19	4.118	Ohio	Urban	1995	8	
	34	33	0.08-15.1	2.29	Connecticut	Urban	1987/90	15	Pre-operational
	8	4	ND-1.2	0.38	Yarmouth, ME	Background	1996	16	
	162	161	0.00067-8.4	0.38	Denver Front Range	Various Land Uses	99-00	17	background
2,3,4,8/2,3,7,8-TCDF	8	8	8.4-57.5	22	Sweden	Urban	1989	9	Near Stockholm
TCDFs	1	0	ND(2.0)	NA	Midland, MI	Residential	1983	1	
	1	0	ND(1.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	300	Finland	Industrial	NR	2	
	11	NR	ND-71	10	Canada	Urban	1983	10	Near Incinerator
	12	0	ND	NA	Canada	Urban	1987	10	Near Incinerator

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
TCDFs (continued)	43	1	ND-280	6.5	Canada	Rural	83-88	10	
	29	NR	ND-120	15	Canada	Urban	83-88	10	
	8	8	109-454	237	Sweden	Urban	1989	9	Near Stockholm
	4	1	ND-1.2	<1	Elk River, MN	Rural	1988	3	Agriculture
	12	12	20-300	102	England	Residential	1990	4	Rural
	19	19	29-950	232	England	Urban	NR	11	
	3	3	7.7-11	9.3	Various parts of Europe	Rural	NR	12	
	2	2	320-370	345	Various parts of Europe	Industrial	NR	12	
	65	NR	ND-237	25	British Isles	Background	NR	13	
	30	0	ND	NA	Ontario and U.S. Midwestern states	Rural	NR	14	
	47	13	ND-120	11.87	Ontario and U.S. Midwestern states	Urban	NR	14	
	20	3	ND-1850	152.5	Ontario and U.S. Midwestern states	Industrial	NR	14	
	13	8	ND-44.3	13.9	Salzburg, Austria	Urban	1990/91	5	
	5	4	ND-59.4	36.9	Salzburg, Austria	Industrial	1990/91	5	
	6	3	ND-36.7	9.0	Salzburg, Austria	Rural	1990/91	5	
	53	32	ND-260	17.13	British Columbia, Canada	Background	1995	6	
	31	17	ND-9300	538.93	British Columbia, Canada	Near Impacted site	1995	6	
	47	34	ND-3200	374.58	British Columbia, Canada	Impacted site	1995	6	
	14	NR	4.6-28.8	15.7	West Germany	Background	NR	7	Plowland
	7	NR	1.9-34.8	15.7	West Germany	Background	NR	7	Grassland
	9	NR	90.7-959.5	338.2	West Germany	Background	NR	7	Deciduous forest
	11	NR	134.4-1602.2	431.4	West Germany	Background	NR	7	Coniferous forest
	34	32	0.12-202	23.36	Connecticut	Urban	1987/90	15	Pre-operational
	8	6	ND-15	5.4	Yarmouth, ME	Background	1996	16	
Pentachlorodibenzofurans (MW=340.42)									
1,2,3,7,8-PeCDF	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
	12	12	1-10	3	England	Residential	1990	4	Rural

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,7,8-PeCDF (continued)	53	3	ND-7.10	0.31	British Columbia, Canada	Background	1995	6	
	31	9	ND-140	15.67	British Columbia, Canada	Near Impacted site	1995	6	
	47	9	ND-160	17.66	British Columbia, Canada	Impacted site	1995	6	
	3	0	ND	NA	Ohio	Background	1995	8	
	4	4	20.11-298.89	139.577	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	17	ND-18.51	5.504	Ohio	Urban	1995	8	
	34	34	0.04-15.0	1.74	Connecticut	Urban	1987/90	15	Pre-operational
	8	4	ND-0.75	0.26	Yarmouth, ME	Background	1996	16	
	162	161	0.0032-30	0.82	Denver Front Range	Various Land Uses	99-00	17	background
2,3,4,7,8-PeCDF	NR	NR	NR	580	Finland	Industrial	NR	2	
	8	8	3.1-26.5	11	Sweden	Urban	1989	9	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
	12	12	1-5	2	England	Residential	1990	4	Rural
	3	3	0.6-1	0.8	various parts of Europe	Rural	NR	12	
	2	2	23-65	44	various parts of Europe	Industrial	NR	12	
	13	11	ND-3.5	1.6	Salzburg, Austria	Urban	1990/91	5	
	5	5	2.8-11.1	5.0	Salzburg, Austria	Industrial	1990/91	5	
	6	5	ND-2.0	0.7	Salzburg, Austria	Rural	1990/91	5	
	53	1	ND-9.3	0.18	British Columbia, Canada	Background	1995	6	
	31	9	ND-270	27.44	British Columbia, Canada	Near Impacted site	1995	6	
	47	16	ND-210	23.33	British Columbia, Canada	Impacted site	1995	6	
	14	NR	0.7-3.1	1.7	West Germany	Background	NR	7	Plowland
	7	NR	1.2-5.3	2.6	West Germany	Background	NR	7	Grassland
	9	NR	5.6-85.9	30.2	West Germany	Background	NR	7	Deciduous forest
	11	NR	8.1-96.6	32.1	West Germany	Background	NR	7	Coniferous forest
	3	1	ND-0.17	0.210	Ohio	Background	1995	8	
	4	4	26.55-434.37	199.942	Ohio	Impacted Site	1995	8	Near waste-to-energy facility
	18	17	ND-26.61	7.562	Ohio	Urban	1995	8	
	34	33	0.11-17.0	2.36	Connecticut	Urban	87-90	15	Pre-operational

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	8	4	ND-1.2	0.51	Yarmouth, ME	Impacted site	1996	16	Near pole yard facility
2,3,4,7,8-PeCDF (continued)	162	161	ND(0.0026)-64	1.7	Denver Front Range	Various Land Uses	99-00	17	background
1,2,3,7,8/1,2,3,4,8-PeCDF	NR	NR	NR	82	Finland	Industrial	NR	2	
	8	8	7.4-32.1	16	Sweden	Urban	1989	9	Near Stockholm
	13	13	1.5-6.7	3.2	Salzburg, Austria	Urban	1990/91	5	
	5	5	2.3-13.4	31.0	Salzburg, Austria	Industrial	1990/91	5	
	6	5	ND-4.9	2.3	Salzburg, Austria	Rural	1990/91	5	
	14	NR	0.5-3.4	1.8	West Germany	Background	NR	7	Plowland
	7	NR	0.9-5.0	2.7	West Germany	Background	NR	7	Grassland
	9	NR	5.9-93.0	36.2	West Germany	Background	NR	7	Deciduous forest
	11	NR	10.5-107.8	36.2	West Germany	Background	NR	7	Coniferous forest
PeCDFs	1	1	900	900	Midland, MI	Industrial	1983	1	
	8	2	ND-110	19	Midland, MI	Residential	1983	1	
	5	0	ND(8)	NA	Middletown, OH	Residential	1983	1	
	3	0	ND(9)	NA	MN	Pristine	1983	1	
	NR	NR	NR	27000	Finland	Industrial	NR	2	
	11	0	ND	NA	Canada	Urban	1983	10	Near Incinerator
	12	0	ND	NA	Canada	Urban	1987	10	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	10	
	29	NR	ND-160	35	Canada	Urban	83-88	10	
	8	8	36-457	182	Sweden	Urban	1989	9	Near Stockholm
	4	3	18-45	26	Elk River, MN	Rural	1988	3	Agriculture
	12	12	6-70	31	England	Residential	1990	4	Rural
	19	19	19-830	189	England	Urban	NR	11	
	2	2	200-450	325	Various parts of Europe	Industrial	NR	12	
	3	3	6.7-14	11.2	Various parts of Europe	Rural	NR	12	
	65	NR	ND-185	23	British Isles	Background	NR	13	
	47	4	ND-110	3.5	Ontario and U.S. Midwestern states	Urban	NR	14	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	20	5	ND-285	21.5	Ontario and U.S. Midwestern states	Industrial	NR	14	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
PeCDFs (continued)	30	0	ND	NA	Ontario and U.S. Midwestern states	Rural	NR	14	
	13	13	3.0-67.0	23.8	Salzburg, Austria	Urban	1990/91	5	
	5	5	22.0-64.1	46.6	Salzburg, Austria	Industrial	1990/91	5	
	6	5	ND-20.5	9.9	Salzburg, Austria	Rural	1990/91	5	
	53	27	ND-635	22.93	British Columbia, Canada	Background	1995	6	
	31	17	ND-23000	1991.63	British Columbia, Canada	Near Impacted site	1995	6	
	47	30	ND-8000	767.86	British Columbia, Canada	Impacted site	1995	6	
	14	NR	1.4-29.5	11.6	West Germany	Background	NR	7	Plowland
	7	NR	4.6-38.1	18.4	West Germany	Background	NR	7	Grassland
	9	NR	74.0-973.7	362.8	West Germany	Background	NR	7	Deciduous Forest
	11	NR	91.8-1167.8	400.1	West Germany	Background	NR	7	Coniferous Forest
	34	34	0.59-343.0	42.97	Connecticut	Urban	1987/90	15	Pre-operational
	8	7	ND-16	8.81	Yarmouth, ME	Background	1996	16	
Hexachlorodibenzofurans (MW=374.87)									
1,2,3,4,7,8/1,2,3,4,7,9-HxCDF	NR	NR	NR	920	Finland	Industrial	NR	2	
	8	8	6.5-29.1	16	Sweden	Urban	1989	9	Near Stockholm
	13	13	1.0-11.3	4.4	Salzburg, Austria	Urban	1990/91	5	
	5	5	3.2-14.0	7.2	Salzburg, Austria	Industrial	1990/91	5	
	6	4	ND-5.1	2.1	Salzburg, Austria	Rural	1990/91	5	
	14	NR	0.9-3.3	1.7	West Germany	Background	NR	7	Plowland
1,2,3,4,7,8/1,2,3,4,7,9-HxCDF	7	NR	1.0-4.8	2.6	West Germany	Background	NR	7	Grassland
	9	NR	3.7-129.0	35.1	West Germany	Background	NR	7	Deciduous Forest
	11	NR	5.4-88.6	24.5	West Germany	Background	NR	7	Coniferous Forest
1,2,3,4,7,8-HxCDF	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
	53	6	ND-16	1.09	British Columbia, Canada	Background	1995	6	
	31	9	ND-900	99.55	British Columbia, Canada	Near Impacted site	1995	6	
	47	23	ND-2800	141.22	British Columbia, Canada	Impacted site	1995	6	
	3	1	ND-0.23	0.187	Ohio	Background	1995	8	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8-HxCDF	4	4	37-420	196.750	Ohio	Impacted site	1995	8	Near waste-to-energy facility
(continued)	18	15	ND-34	8.059	Ohio	Urban	1995	8	
	34	35	0.21-49.0	4.84	Connecticut	Urban	1987/90	15	Pre-operational
	8	5	ND-1.6	0.75	Yarmouth, ME	Background	1996	16	
	162	161	0.0079-77	2.3	Denver Front Range	Various Land Uses	99-00	17	background
1,2,3,6,7,8-HxCDF	NR	NR	NR	<2	Finland	Industrial	NR	2	
	8	8	7.7-28.9	14	Sweden	Urban	1989	9	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
	13	13	0.6-6.2	2.7	Salzburg, Austria	Urban	1990/91	5	
	5	5	2.5-6.9	4.3	Salzburg, Austria	Industrial	1990/91	5	
	6	4	ND-3.2	1.2	Salzburg, Austria	Rural	1990/91	5	
	53	4	ND-15	0.62	British Columbia, Canada	Background	1995	6	
	31	9	ND-1400	144.73	British Columbia, Canada	Near Impacted site	1995	6	
	47	20	ND-1100	89.42	British Columbia, Canada	Impacted site	1995	6	
	14	NR	0.7-2.4	1.4	West Germany	Background	NR	7	Plowland
	7	NR	0.7-3.7	1.9	West Germany	Background	NR	7	Grassland
	9	NR	3.3-83.4	26.0	West Germany	Background	NR	7	Deciduous Forest
	11	NR	5.4-77.4	21.2	West Germany	Background	NR	7	Coniferous Forest
	3	3	0.47-0.55	0.523	Ohio	Background	1995	8	
	4	4	31.68-437.19	209.110	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	17	ND-28.13	8.120	Ohio	Urban	1995	8	
	35	35	0.20-17.8	2.32	Connecticut	Urban	1987/90	15	Pre-operational
	8	5	ND-1.1	0.60	Yarmouth, ME	Background	1996	16	
	162	161	0.037-48	1.5	Denver Front Range	Various Land Uses	99-00	17	background
1,2,3,7,8,9-HxCDF	NR	NR	NR	<2	Finland	Industrial	NR	2	
	8	4	ND-3.8	1	Sweden	Urban	1989	9	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
	13	0	ND	NA	Salzburg, Austria	Urban	1990/91	5	
	5	1	ND-4.2	0.2	Salzburg, Austria	Industrial	1990/91	5	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	6	1	ND-2.8	0.5	Salzurg, Austria	Rural	1990/91	5	
1,2,3,7,8,9-HxCDF	53	3	ND-13	0.36	British Columbia, Canada	Background	1995	6	
(continued)	31	5	ND-40	3.35	British Columbia, Canada	Near Impacted site	1995	6	
	47	7	ND-300	12.11	British Columbia, Canada	Impacted site	1995	6	
	14	NR	0.5-0.9	0.7	West Germany	Background	NR	7	Plowland
	7	NR	0.7-1.8	1.1	West Germany	Background	NR	7	Grassland
	9	NR	1.0-27.1	7.6	West Germany	Background	NR	7	Deciduous Forest
	11	NR	ND-16.3	4.4	West Germany	Background	NR	7	Coniferous Forest
	3	0	ND	NA	Ohio	Background	1995	8	
	4	4	1.79-24.16	11.550	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	6	ND-1.98	0.506	Ohio	Urban	1995	8	
	35	18	0.04-4.02	0.56	Connecticut	Urban	1987/90	15	Pre-operational
	8	1	ND-0.55	0.07	Yarmouth, ME	Background	1996	16	
	162	161	0.075-30	0.92	Denver Front Range	Various Land Uses	99-00	17	background
2,3,4,6,7,8-HxCDF	NR	NR	NR	<2	Finland	Industrial	NR	2	
	8	7	ND-21.5	8	Sweden	Urban	1989	9	
	4	1	ND-7.1	2	Elk River, MN	Rural	1988	3	Agriculture
	30	0	ND	NA	Ontario and U.S. Midwestern states	Rural	NR	14	
	13	11	ND-9.6	3.0	Salzburg, Austria	Urban	1990/91	5	
	5	3	ND-5.5	2.7	Salzburg, Austria	Industrial	1990/91	5	
	6	4	ND-4.1	1.2	Salzburg, Austria	Rural	1990/91	5	
	53	1	ND-9	0.17	British Columbia, Canada	Background	1995	6	
	31	7	ND-1400	111.82	British Columbia, Canada	Near Impacted site	1995	6	
	47	14	ND-520	35.7	British Columbia, Canada	Impacted site	1995	6	
	14	NR	0.7-2.8	1.3	West Germany	Background	NR	7	Plowland
	7	NR	1.0-3.7	2.2	West Germany	Background	NR	7	Grassland
	9	NR	2.1-53.8	18.5	West Germany	Background	NR	7	Deciduous Forest
	11	NR	4.1-62.5	17.2	West Germany	Background	NR	7	Coniferous Forest
	3	3	0.47-0.89	0.637	Ohio	Background	1995	8	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	4	4	26.13-327.62	156.660	Ohio	Impacted site	1995	8	Near waste-to-energy facility
2,3,4,6,7,8-HxCDF (continued)	18	18	1.21-20.79	6.990	Ohio	Urban	1995	8	
	35	35	0.21-18.70	2.54	Connecticut	Urban	1987/90	15	Pre-operational
	8	7	ND-2.0	1.43	Yarmouth, ME	Background	1996	16	
	162	161	0.0086-87	2.6	Denver Front Range	Various Land Uses	99-00	17	background
HxCDFs	1	1	3100	3100	Midland, MI	Industrial	1983	1	
	8	3	ND-260	62	Midland, MI	Residential	1983	1	
	5	0	ND(8.0)	NA	Middletown, OH	Residential	1983	1	
	3	0	ND(9.0)	NA	MN	Pristine	1983	1	
	NR	NR	NR	110000	Finland	Industrial	NR	2	
	11	0	ND	NA	Canada	Urban	1983	10	Near Incinerator
	12	0	ND	NA	Canada	Urban	1987	10	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	10	
	29	NR	ND-120	9	Canada	Urban	83-88	10	
	8	8	53-308	145	Sweden	Urban	1989	9	Near Stockholm
	4	4	7-150	66	Elk River, MN	Rural	1988	3	Agriculture
	12	12	6-50	24	England	Residential	1990	4	Rural
	19	19	17-660	156	England	Urban	NR	11	
	3	3	11-16	13	Various parts of Europe	Rural	NR	12	
	2	2	270-1900	1085	Various parts of Europe	Industrial		12	
	65	NR	4.3-212	41	British Isles	Background	NR	13	
	30	0	ND	NA	Ontario and U.S. Midwestern states	Rural	NR	14	
	47	6	ND-260	12.1	Ontario and U.S. Midwestern states	Urban	NR	14	
	20	7	ND-420	62.3	Ontario and U.S. Midwestern states	Industrial	NR	14	
	13	13	8.5-61.9	25.5	Salzburg, Austria	Urban	1990/91	5	
	5	5	13.0-73.4	38.3	Salzburg, Austria	Industrial	1990/91	5	
	6	4	ND-32.7	10.4	Salzburg, Austria	Rural	1990/91	5	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	53	32	ND-610	50.65	British Columbia, Canada	Background	1995	6	
	31	18	ND-79000	7387.93	British Columbia, Canada	Near Impacted site	1995	6	
HxCDFs (continued)	47	38	ND-97000	6361.66	British Columbia, Canada	Impacted site	1995	6	
	14	NR	5.6-21.1	10.7	West Germany	Background	NR	7	Plowland
	7	NR	4.2-31.7	15.2	West Germany	Background	NR	7	Grassland
	9	NR	28.2-699.4	229.0	West Germany	Background	NR	7	Deciduous Forest
	11	NR	45.6-655.3	169.5	West Germany	Background	NR	7	Coniferous Forest
	35	35	0.72-373.0	40.99	Connecticut	Urban	1987/90	15	Pre-operational
	7	7	5.5-2.5	16.0	Yarmouth, ME	Background	1996	16	
Heptachlorodibenzofurans (MW=409.31)									
1,2,3,4,6,7,8-HpCDF	NR	NR	NR	190000	Finland	Industrial	NR	2	
	8	8	31-134	73	Sweden	Urban	1989	9	Near Stockholm
	4	4	11-80	47	Elk River, MN	Rural	1988	3	Agriculture
	13	13	5.7-38.8	17.1	Salzburg, Austria	Urban	1990/91	5	
	5	5	8.2-85	28.7	Salzburg, Austria	Industrial	1990/91	5	
	6	6	3.1-13.5	7.2	Salzburg, Austria	Rural	1990/91	5	
	53	30	ND-300	42.26	British Columbia, Canada	Background	1995	6	
	31	19	ND-43000	3334.85	British Columbia, Canada	Near Impacted site	1995	6	
	47	34	ND-71000	4107.19	British Columbia, Canada	Impacted site	1995	6	
	14	NR	3.2-24.7	9.5	West Germany	Background	NR	7	Plowland
	7	NR	4.6-33.9	13.1	West Germany	Background	NR	7	Grassland
	9	NR	24.7-697.0	183.6	West Germany	Background	NR	7	Deciduous Forest
	11	NR	23.3-645.9	139.9	West Germany	Background	NR	7	Coniferous Forest
	3	3	3.3-6.46	4.060	Ohio	Background	1995	8	
	4	4	106.75-1340.6	640.950	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	18	6.11-138.76	41.747	Ohio	Urban	1995	8	
	35	35	1.01-105.0	17.0	Connecticut	Urban	1987/90	15	Pre-operational
	8	8	5.8-26	14.2	Yarmouth, ME	Background	1996	16	
	162	161	0.083-450	26	Denver Front Range	Various Land Uses	99-00	17	background

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8,9-HpCDF	NR	NR	NR	<5	Finland	Industrial	NR	2	
	8	2	ND-6.3	1	Sweden	Urban	1989	9	Near Stockholm
	4	0	ND	NA	Elk River, MN	Rural	1988	3	Agriculture
1,2,3,4,7,8,9-HpCDF	13	11	ND-4.2	1.3	Salzburg, Austria	Urban	1990/91	5	
(continued)	5	2	ND-4.1	2.6	Salzburg, Austria	Industrial	1990/91	5	
	6	4	ND-1.7	0.7	Salzburg, Austria	Rural	1990/91	5	
	53	6	ND-45	1.59	British Columbia, Canada	Background	1995	6	
	31	8	ND-900	81.76	British Columbia, Canada	Near Impacted site	1995	6	
	47	22	ND-7100	236.27	British Columbia, Canada	Impacted site	1995	6	
	14	NR	0.4-1.6	1.0	West Germany	Background	NR	7	Plowland
	7	NR	0.8-2.8	1.7	West Germany	Background	NR	7	Grassland
	9	NR	2.3-63.4	15.8	West Germany	Background	NR	7	Deciduous forest
	11	NR	1.6-50.3	10.3	West Germany	Background	NR	7	Coniferous forest
	3	1	ND-0.35	0.267	Ohio	Background	1995	8	
	4	4	9.3-123.81	57.888	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	16	ND-15.05	3.815	Ohio	Urban	1995	8	
	35	33	0.03-9.70	1.21	Connecticut	Urban	1987/90	15	Pre-operational
	8	6	0.98-2.1	1.01	Yarmouth, ME	Background	1996	16	
	162	161	0.0052-27	2.1	Denver Front Range	Various Land Uses	99-00	17	background
HpCDFs	1	1	15400	15400	Midland, MI	Industrial	1983	1	
	NR	NR	NR	140000	Finland	Industrial	NR	2	
	8	6	ND-820	300	Midland, MI	Residential	1983	1	
	5	1	ND-43	9	Middletown, OH	Residential	1983	1	
	3	0	ND(9.0)	NA	MN	Pristine	1983	1	
	11	NR	ND-180	30	Canada	Urban	1983	10	Near Incinerator
	12	0	ND	NA	Canada	Urban	1987	10	Near Incinerator
	43	0	ND	NA	Canada	Rural	83-88	10	
	29	NR	ND-410	29	Canada	Urban	83-88	10	
	8	8	31-187	81	Sweden	Urban	1989	9	Near Stockholm

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	4	4	30-260	100	Elk River, MN	Rural	1988	3	Agriculture
	12	12	4-59	20	England	Residential	1990	4	Rural
	19	19	16-458	152	England	Urban	NR	11	
	3	3	14-22	18	Various parts of Europe	Rural	NR	12	
HpCDFs (continued)	2	2	260-4500	2380	Various parts of Europe	Industrial	NR	12	
	65	NR	1.5-138	26	British Isles	Background	NR	13	
	47	10	ND-820	60.2	Ontario and U.S. Midwestern states	Urban	NR	14	
	20	15	ND-3750	550	Ontario and U.S. Midwestern states	Industrial	NR	14	
	30	0	ND	NA	Ontario and U.S. Midwestern states	Rural	NR	14	
	13	13	7.8-61.6	27.1	Salzburg, Austria	Urban	1990/91	5	
	5	5	10.8-85.0	34.2	Salzburg, Austria	Industrial	1990/91	5	
	6	6	5.5-19.2	9.8	Salzburg, Austria	Rural	1990/91	5	
	53	33	ND-890	112.99	British Columbia, Canada	Background	1995	6	
	31	19	ND-130000	9330.42	British Columbia, Canada	Near Impacted Site	1995	6	
	47	36	ND-580000	20235.95	British Columbia, Canada	Impacted site	1995	6	
	14	NR	3.2-31.2	12.9	West Germany	Background	NR	7	Plowland
	7	NR	4.6-44.4	17.5	West Germany	Background	NR	7	Grassland
	9	NR	33.7-922.9	245.5	West Germany	Background	NR	7	Deciduous forest
	11	NR	32.4-876.6	187.4	West Germany	Background	NR	7	Coniferous
	35	35	1.66-188.0	33.21	Connecticut	Urban	1987/90	15	Pre-operational
	8	8	12.9-82	39.4	Yarmouth, ME	Background	1996	16	
Octachlorodibenzofurans (MW=444.76)									
1,2,3,4,6,7,8,9-OCDF	1	1	8600	8600	Midland, MI	Industrial	1983	1	
	8	6	ND-660	240	Midland, MI	Residential	1983	1	
	5	1	ND-50	10	Middletown, OH	Residential	1983	1	
	3	0	ND(10)	NA	MN	Pristine	1983	1	
	NR	NR	NR	3000	Finland	Industrial	NR	2	

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	11	NR	ND-33	4	Canada	Urban	1983	10	Near Incinerator
	12	NR	ND-230	43	Canada	Urban	1987	10	Near Incinerator

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,6,7,8,9-OCDF (continued)	43	0	ND	NA	Canada	Rural	83-88	10	
	29	NR	ND-600	50	Canada	Urban	83-88	10	
	8	1	ND-19.0	2	Sweden	Urban	1989	9	Near Stockholm
	4	3	60-270	113	Elk River, MN	Rural	1988	3	Agriculture
	12	12	10-90	30	England	Residential	1990	4	Rural
	19	19	7-1100	196	England	Urban	NR	11	
	1	1	5.7	5.7	Various parts of Europe	Rural	NR	12	
	65	NR	ND-144	27	British Isles	Background	NR	13	
	47	15	ND-660	60	Canada and USA	Urban	NR	14	
	20	15	ND-5200	632	Canada and USA	Industrial	NR	14	
	30	0	ND	NA	Canada and USA	Rural	NR	14	
	2	2	68-71	69.5	Various parts of Europe	Industrial	NR	12	
	3	3	4.7-18.02	10.717	Ohio	Background	1995	8	
	4	4	44.74-307.96	184.495	Ohio	Impacted site	1995	8	Near waste-to-energy facility
	18	18	3.53-199.37	44.282	Ohio	Urban	1995	8	
	35	35	20.4-4,970	814.3	Connecticut	Urban	1987/90	15	Pre-operational
	8	8	13-95	42.3	Yarmouth, ME	Background	1996	16	
	162	161	0.32-1,500	72	Denver Front Range	Various Land Uses	99-00	17	background

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects if congener-specific detection limits were given; when detection limits were not given, zero was used for nondetects.
NA = Not available.
NR = Not reported.
ND = Non-detect.
Detection limits varied by study and were different for different compounds, but generally were 1 to 5 ng/kg (ppt). Descriptions provided were those given by reference or surmised from study description when not given.

Sources:
1. U.S. EPA (1985)
2. Kitunen and Salkinoja-Salonen (1990)
3. Reed et al. (1990)
4. Stenhouse and Badsha (1990)
5. Boos et al. (1992)
6. BC Environment (1995)
7. Rotard et al. (1994)
9. Broman et al. (1990)
10. Pearson et al. (1990)
11. Creaser et al. (1990)
12. Rappe and Kjeller (1987)
13. Creaser et al. (1989)
14. Birmingham (1990)
15. MRI (1992)
17. U.S. EPA Region 8 (2000)

Table B-5. Environmental Levels of Dibenzofurans in Soil (ppt) (continued)

8. U.S. EPA (1996)

16. Tewhey Associates (1997)

Table B-6. Environmental Levels of Dioxins in Water (ppq)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Samp. year	Ref. no.	Comments
Tetrachlorodibenzo-p-dioxins (MW=321.98)									
2,3,7,8-TCDD	1	0	ND(0.7)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	2	0	ND(.02-.024)	NA	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
TCDDs	185	1	ND-40	2.70	Ontario, Canada	NR	83-89	3	raw surface drinking water
	22	0	ND(.4-2.6)	NA	New York State	NR	86-88	1	treated surface drinking water
	1	1	1.7	1.7	Lockport, New York	NR	88	1	raw surface drinking water
	2	2	.05-.084	.067	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
Pentachlorodibenzo-p-dioxins (MW=356.42)									
1,2,3,7,8-PeCDD	1	0	ND(1.0)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	2	0	ND(.025-.039)	NA	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
PeCDDs	1	0	ND(1.0)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	22	0	ND(1.2-7.4)	NA	New York State	NR	86-88	1	treated surface drinking water
	2	2	.067-.12	.094	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
Hexachlorodibenzo-p-dioxins (MW=390.87)									
1,2,3,4,7,8-HxCDD	1	0	ND(1.8)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	2	1	ND-.054	.027	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
1,2,3,6,7,8-HxCDD	1	0	ND(1.5)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	2	1	ND-.12	.06	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
1,2,3,7,8,9-HxCDD	1	0	ND(1.5)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	2	1	ND-.075	.038	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water

Table B-6. Environmental Levels of Dioxins in Water (ppq) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Samp. year	Ref. no.	Comments
HxCDDs	1	0	ND(1.5)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	22	0	ND(.4-4.7)	NA	New York State	NR	86-88	1	treated surface drinking water
	2	2	.13-.67	.4	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
Heptachlorodibenzo-p-dioxins (MW=425.31)									
1,2,3,4,6,7,8-HpCDD	1	0	ND(2.8)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	2	2	.15-.30	.22	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
HpCDDs	1	0	ND(2.8)	NA	Lockport, New York	NR	88	1	raw surface drinking water
	22	0	ND(.4-6.8)	NA	New York State	NR	86-88	1	treated surface drinking water
	2	2	.17-.64	.40	Eman River, Sweden	PCB contaminated	NR	2	raw surface drinking water
Octachlorodibenzo-p-dioxin (MW=460.76)									
1,2,3,4,6,7,8,9-OCDD	185	32	ND-175	10.6	Ontario, Canada	NR	83-89	3	raw surface drinking water
	214	4	ND-46	3.16	Ontario, Canada	NR	83-89	3	treated surface drinking water

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, one-half the limit of detection was used in non-detects. Therefore, it is possible to have mean concentrations greater than the range (e.g., reported detection limit for nondetects greater than the positive sample).
NA = not applicable;
ND = non-detected (limit of detection);
NR = not reported;
Descriptions provided were those given by reference or surmised from study description when not given.

Sources: 1. Meyer et al. (1989)
2. Rappe et al. (1989a)
3. Jobb et al. (1990)

Table B-7. Environmental Levels of Dibenzofurans in Water (ppq)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Samp. year	Ref. no.	Comments
Tetrachlorodibenzofurans (MW=305.98)									
2,3,7,8-TCDF	2	2	.022-.026	.024	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
	1	0	ND(0.7)	NA	Lockport, New York	NR	88	2	raw surface drinking water
TCDFs	22	1	ND-2.6	0.12	New York State	NR	86-88	2	treated surface drinking water
	1	1	18	18	Lockport, New York	NR	88	2	raw surface drinking water
	2	2	.21-.23	0.22	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
Pentachlorodibenzofurans (MW=340.42)									
1,2,3,7,8-PeCDF	1	1	2.0	2.0	Lockport, New York	NR	88	2	raw surface drinking water
2,3,4,7,8-PeCDF	2	2	.014-.019	.016	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
	1	0	ND(1.0)	NA	Lockport, New York	NR	88	2	raw surface drinking water
1,2,3,4,8/1,2,3,7,8-PeCDF	2	2	.013-.025	.019	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
PeCDFs	1	1	27	27	Lockport, New York	NR	88	2	raw surface drinking water
	22	0	ND(0.3-4.0)	NA	New York State	NR	86-88	2	treated surface drinking water
	2	2	.13-.21	.17	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
Hexachlorodibenzofurans (MW=374.87)									
1,2,3,4,7,8-HxCDF	1	1	39	39	Lockport, New York	NR	88	2	raw surface drinking water
1,2,3,6,7,8-HxCDF	1	1	9.2	9.2	Lockport, New York	NR	88	2	raw surface drinking water
	2	2	.019-.025	.022	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
2,3,4,6,7,8-HxCDF	1	0	ND(1.3)	NA	Lockport, New York	NR	88	2	raw surface drinking water
	2	1	ND-.027	.014	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
1,2,3,7,8,9-HxCDF	1	0	ND(1.2)	NA	Lockport, New York	NR	88	2	raw surface drinking water
	2	1	ND-.022	.011	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water

Table B-7. Environmental Levels of Dibenzofurans in Water (ppq) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Samp. year	Ref. no.	Comments
1,2,3,4,7,9/1,2,3,4,7,8-HxCDF	2	2	.021-.026	.024	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
HxCDFs	1	1	85	NA	Lockport, New York	NR	88	2	raw surface drinking water
	22	0	ND(.3-4.4)	NA	New York State	NR	86-88	2	treated surface drinking water
	2	2	.17-.19	.18	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
Heptachlorodibenzofurans (MW=409.31)									
1,2,3,4,6,7,8-HpCDF	1	1	210	210	Lockport, New York	NR	88	2	raw surface drinking water
	2	2	.083-.13	.11	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
1,2,3,4,7,8,9-HpCDF	2	2	.03-.058	.044	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
HpCDFs	1	1	210	210	Lockport, New York	NR	88	2	raw surface drinking water
	22	0	ND(.8-6.6)	NA	New York State	NR	86-88	2	treated surface drinking water
	2	2	.18-.35	.26	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water
Octachlorodibenzofurans (MW=444.76)									
1,2,3,4,6,7,8,9-OCDF	22	2	ND-0.8	2.45	New York State	NR	86-88	2	treated surface drinking water
	1	1	230	230	Lockport, New York	NR	88	2	raw surface drinking water
	2	2	.15-.36	.26	Eman River, Sweden	PCB contaminated	NR	1	raw surface drinking water

Footnote References

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, one-half the detection limit was used for non-detects. Therefore, it is possible to have mean concentrations greater than the range (e.g., reported detection limit for nondetects greater than the positive sample).
NA = not applicable;
ND = non-detected (limit of detection);
NR = not reported.
Descriptions provided were those given by reference or surmised from study description when not given.

Sources: 1. Rappe et al. (1989a)
2. Meyer et al. (1989)

Table B-8. Environmental Levels of Dioxins in Sediments (ppt)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
Tetrachlorodibenzo-p-dioxins (MW=321.98)										
2,3,7,8-TCDD	18	0	ND	NA	Dry	South Central Finland	Various	88/89	1	A,B
	9	8	ND-730	236	Dry	Newark, NJ	Industrial	85/86	2	0-2", A,C
	4	4	75-2500	1769	Dry	Newark, NJ	Industrial	85/86	2	2-4", A,C
	2	2	190-1200	695	Dry	Newark, NJ	Industrial	85/86	2	4-8", A,C
	1	1	680	680	Dry	Newark, NJ	Industrial	85/86	2	12-16", A,C
	1	1	150	150	Dry	Newark, NJ	Industrial	85/86	2	20-24", A,C
	2	2	660-1100	880	Dry	Newark, NJ	Industrial	85/86	2	24-28", A,C
	3	1	ND-7600	367	Dry	Newark, NJ	Industrial	85/86	2	28-32", A,C
	3	3	390-2900	1227	Dry	Newark, NJ	Industrial	85/86	2	32-36", A,C
	1	1	93	93	Dry	Newark, NJ	Industrial	85/86	2	40-44", A,C
	2	1	ND-7600	3800	Dry	Newark, NJ	Industrial	85/86	2	48-52", A,C
	1	1	21,000	21000	Dry	Newark, NJ	Industrial	85/86	2	108-111", A,C
	1	0	ND	NA	Dry	Long Island Sound	Reference Site	NR	3	A
	12	6	ND-57	13	Dry	New England	Industrial	NR	3	A/3 sites
	4	0	ND	NA	Dry	Seattle, WA	Industrial	NR	3	A
	4	0	ND	NA	NR	Central Minnesota	Rural	NR	4	A
	3	2	ND-2.4	1.5	NR	Stockholm Sweden	Various	NR	5	A
	2	2	1.0-1.4	1.2	Dry	Baltic Sea	Reference Site	NR	6	A
	4	4	1.9-26	9.6	Dry	Iggesund Sweden	Industrial	NR	6	A/papermill

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
2,3,7,8-TCDD (continued)	4	4	0.03-0.11	0.06	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	0-1 cm, E
	1	1	0.04	0.04	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	4-6 cm, E
	1	1	0.01	0.01	Dry	Fjord between Demark, Sweden, and Norway	Industrial	87	7	9-13 cm, E
	5	5	3.4-1,500	375	NR	Hamburg Germany	Urban	NR	8	
	4	1	ND-3	1.19	NR	Dala River, Sweden	Industrial	88	9	0-1 cm
	6	6	1.2-32	12.0	NR	Lake Vattern, Sweden	Industrial	88	9	0-1 cm
	5	3	ND-110	28.1	NR	Lake Vanern, Sweden	Industrial	88	9	0-1 cm
	61	54	NR	0.30	Dry	Southern Mississippi	NR	94	10	--
	12	0	ND	NA	Dry	British Columbia	Background	NR	11	--
	14	2	ND-2.7	0.23	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	1	ND-1.1	0.16	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	6	ND-0.78	0.27	Dry	Various U.S. Lakes	Background	--	12	--
	162	125	0.04-23.10	2.30	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	10	ND-510	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	5	0	ND	ND	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
TCDDs	18	14	ND-1,400	372	Dry	South Central Finland	Various	88/89	1	AB
	1	1	26	26	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	0-0.5 cm, A,D
	1	1	12	12	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	5-6 cm, A,D
	1	0	ND	NA	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	8-9 cm, A,D
	4	0	ND	NA	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	0	ND	NA	NR	Ontario Canada	Industrial	88	14	A/25 sites
	12	7	ND-44	17	NR	NY/Mass	NR	NR	15	A
	3	3	21-69	38	NR	Stockholm Sweden	Various	NR	5	A
	4	4	21-66	45	Dry	Iggesund Sweden	Industrial	NR	6	A/paper mill
	2	2	19-35	27	Dry	Baltic Sea	Reference Site	NR	6	A
	4	4	1.4-6.7	4.2	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	0-2 cm, E
	1	1	13	13	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	4-6 cm, E
	1	1	5.0	5.0	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	9-13 cm, E
	5	5	80-1,700	564	NR	Hamburg Germany	Urban	NR	8	
	12	0	ND	NA	Dry	British Columbia	Background	NR	11	--
	14	4	ND-210.0	26.0	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
TCDDs (continued)	7	2	ND-32.0	5.3	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	10	ND-21.2	6.45	Dry	Various U.S. Lakes	Background	--	12	--
	162	150	0.07-48.7	9.34	Dry	Connecticut	Urban	87-90	17	Pre-operational
	5	0	ND	ND	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
Pentachlorodibenzo-p-dioxins (MW=356.42)										
1,2,3,7,8-PeCDD	4	3	ND-25	7.68	NR	Dala River, Sweden	Industrial	88	9	0-1 cm
	6	6	7.4-95	44.1	NR	Lake Vattern, Sweden	Industrial	88	9	0-1 cm
	5	4	ND-100	49.6	NR	Lake Vanern, Sweden	Industrial	88	9	0-1 cm
	12	0	ND	NA	Dry	British Columbia	Background	NR	11	--
	14	3	ND-30.0	4.2	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	1	ND-6.6	0.94	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	6	ND-3.91	0.99	Dry	Various U.S. Lakes	Background	--	12	--
	161	154	0.03-48.7	3.49	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	2	ND-22	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	5	2	ND-0.18	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
PeCDDs	1	1	12	12	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	0-0.5 cm, A,D
	1	1	11	11	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	5-6 cm, A,D
	1	0	ND	NA	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	8-9 cm, A,D
	4	0	ND	NA	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	0	ND	NA	NR	Ontario Canada	Industrial	88	14	A/25 sites
	12	7	ND-235	50	NR	NY/Mass	NR	NR	15	A
	3	3	86-230	138	NR	Stockholm Sweden	Various	NR	5	A
	4	4	52-500	209	Dry	Iggesund Sweden	Industrial	NR	6	A/paper mill
	2	2	52-100	76	Dry	Baltic Sea	Reference Site	NR	6	A
	4	4	1.7-41	19	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	0-2 cm, E
	1	1	6.6	6.6	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	4-6 cm, E
	1	1	15	15	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	9-13 cm, E
	5	5	260-2,700	1,112	NR	Hamburg Germany	Urban	NR	8	
	12	0	ND	NA	Dry	British Columbia	Background	NR	11	--
	14	5	ND-400.0	79.8	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	1	ND-86.0	12.3	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
PeCDDs (continued)	11	10	ND-28.7	9.1	Dry	Various U.S. Lakes	Background	--	12	--
	162	158	0.03-327.0	28.85	Dry	Connecticut	Urban	87-90	17	Pre-operational
	5	5	0.11-4.9	1.5	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
Hexachlorodibenzo-p-dioxins (MW=390.87)										
1,2,3,4,7,8-HxCDD	4	3	ND-19	6.68	NR	Dala River, Sweden	Industrial	88	9	0-1 cm
	6	6	6.1-33	20.5	NR	Lake Vattern, Sweden	Industrial	88	9	0-1 cm
	5	5	14-94	36.0	NR	Lake Vanern, Sweden	Industrial	88	9	0-1 cm
	12	1	ND-7.9	0.66	Dry	British Columbia	Background	NR	11	--
	14	4	ND-82.0	7.9	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	1	ND-11.0	1.6	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	10	ND-6.87	1.8	Dry	Various U.S. Lakes	Background	--	12	--
	166	149	0.05-31.60	4.24	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	4	ND-9.6	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	5	2	ND-0.49	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
1,2,3,6,7,8-HxCDD	4	4	4.9-120	36.4	NR	Dala River, Sweden	Industrial	88	9	0-1 cm
	6	6	21-450	188	NR	Lake Vattern, Sweden	Industrial	88	9	0-1 cm
	5	5	36-600	236	NR	Lake Vanern, Sweden	Industrial	88	9	0-1 cm

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
1,2,3,6,7,8-HxCDD (continued)	12	2	ND-67.0	11.2	Dry	British Columbia	Background	NR	11	--
	14	9	ND-540.0	127.2	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	3	ND-220.0	51.07	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	10	ND-21.6	4.7	Dry	Various U.S. Lakes	Background	--	12	--
	166	163	0.10-107.0	15.26	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	10	ND-46	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	5	4	ND-1.7	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
1,2,3,7,8,9-HxCDD	4	4	3.9-51	18.1	NR	Dala River, Sweden	Industrial	88	9	0-1 cm
	6	6	18-200	95.5	NR	Lake Vattern, Sweden	Industrial	88	9	0-1 cm
	5	5	18-330	149	NR	Lake Vanern, Sweden	Industrial	88	9	0-1 cm
	12	1	ND-17.5	1.5	Dry	British Columbia	Background	NR	11	--
	14	6	ND-290.0	47.9	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	3	ND-39.0	12.1	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	10	ND-14.55	4.04	Dry	Various U.S. Lakes	Background	--	12	--
	166	164	0.09-98.3	11.24	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	4	ND-25	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	5	5	0.28-5.9	2.5	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
HxCDDs	1	1	10	10	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	0-0.5 cm, A,D
	1	1	8	8	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	5-6 cm, A,D
	1	0	ND	NA	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	13	8-9 cm, A,D
	4	2	ND-14	5.2	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	6	ND-5,700	1,157	NR	Ontario Canada	Industrial	88	14	A/25 sites
	12	10	ND-1,335	399	NR	NY/Mass	NR	NR	15	A
	3	3	16-49	28	NR	Stockholm Sweden	Various	NR	5	A
	2	2	120-170	145	Dry	Baltic Sea	Reference Site	NR	6	A
	4	4	130-1,900	608	Dry	Iggesund Sweden	Industrial	NR	6	A/paper mill
	4	4	2.3-27.0	14	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	0-2 cm, E
	1	1	16	16	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	4-6 cm, E
	1	1	14	14	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	9-13 cm, E
	5	5	580-7,500	2,744	NR	Hamburg Germany	Urban	NR	8	
	12	4	ND-355.0	55.9	Dry	British Columbia	Background	NR	11	--
	14	9	ND-3500	678.4	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	3	ND-1000	236.4	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
HxCDDs (continued)	11	10	ND-157	43.3	Dry	Various U.S. Lakes	Background	--	12	--
	166	165	0.09-950.0	130.2	Dry	Connecticut	Urban	87-90	17	Pre-operational
	5	5	2.4-46	20	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
Heptachlorodibenzo-p-dioxins (MW=425.31)										
1,2,3,4,6,7,8-HpCDD	12	5	ND-810.0	116.5	Dry	British Columbia	Background	NR	11	--
	14	11	ND-5100.0	811.9	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	3	ND-850.0	185.1	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	10	ND-431	100.6	Dry	Various U.S. Lakes	Background	--	12	--
	166	166	0.94-2,680	306.9	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	19	28-2,100	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	5	5	11-130	59	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
HpCDDs	4	4	7.3-110	71	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	20	ND-320,000	51,680	NR	Ontario Canada	Industrial	88	14	A/25 sites
	12	11	ND-18,950	4,168	NR	NY/Mass	NR	NR	15	A
	3	3	880-5,700	2,233	NR	Stockholm Sweden	Various	NR	5	A
	2	2	79-210	145	Dry	Baltic Sea	Reference Site	NR	6	A
	4	4	90-340	190	Dry	Iggesund Sweden	Industrial	NR	6	A/paper mill

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
HpCDDs (continued)	4	4	2.2-19	12.4	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	0-2 cm, E
	1	1	7.2	7.2	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	4-6 cm, E
	1	1	7.1	7.1	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	9-13 cm, E
	5	5	1,300-8,600	4,040	NR	Hamburg Germany	Urban	NR	8	
	12	5	ND-1500	210.8	Dry	British Columbia	Background	NR	11	--
	14	1	ND-8000	1329	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	3	ND-1500	325.7	Dry	Brisith Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	10	ND-828	199.0	Dry	Various U.S. Lakes	Background	--	12	--
	166	166	1.77-5,820	647.0	Dry	Connecticut	Urban	87-90	17	Pre-operational
	5	5	17-300	134	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core
Octachlorodibenzo-p-dioxin (MW=460.76)										
1,2,3,4,6,7,8,9-OCDD	18	3	ND-42	6.1	Dry	South Central Finland	Various	88/89	1	A,B
	9	9	3,100-14,000	8,100	Dry	Newark, NJ	Industrial	85/86	2	0-2", A,C
	4	4	5,300-23,000	14,100	Dry	Newark, NJ	Industrial	85/86	2	2-4", A,C
	2	2	10,000-31,000	20,500	Dry	Newark, NJ	Industrial	85/86	2	4-8", A,C
	1	1	7,500	7,500	Dry	Newark, NJ	Industrial	85/86	2	12-16", A,C
	1	1	5,900	5,900	Dry	Newark, NJ	Industrial	85/86	2	20-24", A,C

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
1,2,3,4,6,7,8,9-OCDD	2	2	11,000-19,000	15,000	Dry	Newark, NJ	Industrial	85/86	2	24-28", A,C
(continued)	2	2	5,500-22,000	13,800	Dry	Newark, NJ	Industrial	85/86	2	28-32", A,C
	3	3	5,600-42,000	17,800	Dry	Newark, NJ	Industrial	85/86	2	32-36", A,C
	1	1	5,500	5,500	Dry	Newark, NJ	Industrial	85/86	2	40-44", A,C
	2	2	4,400-24,000	14,200	Dry	Newark, NJ	Industrial	85/86	2	48-52", A,C
	1	1	38,000	38,000	Dry	Newark, NJ	Industrial	85/86	2	108-111", A,C
	1	1	560	560	Dry	Siskiwit Lake, Isle Royale, Lake Superior	Pristine	NR	13	0-0.5 cm, A,D
	1	1	390	390	Dry	Siskiwit Lake, Isle Royale, Lake Superior	Pristine	NR	13	5-6 cm, A,D
	1	1	54	54	Dry	Siskiwit Lake, Isle Royale, Lake Superior	Pristine	NR	13	8-9 cm, A,D
	4	4	450-600	518	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	20	ND-980,000	141,420	NR	Ontario Canada	Industrial	88	14	A/25 sites
	12	12	1,990-15,500	8,201	NR	NY/Mass	NR	NR	15	A
	7	7	12-250	145	Dry	Jackfish Bay, Lake Superior	Various	NR	16	Papermill, atmospheric contamination
	3	3	260-3,100	1,290	NR	Stockholm Sweden	Various	NR	5	A
	2	2	89-250	170	Dry	Baltic Sea	Reference Site	NR	6	A
	4	4	96-330	194	Dry	Iggesund Sweden	Industrial	NR	6	A/paper mill
	4	4	3.6-45	24	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	0-2 cm, E

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
1,2,3,4,6,7,8,9-OCDD (continued)	1	1	10	10	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	4-6 cm, E
	1	1	6.9	6.9	Dry	Fjord between Denmark, Sweden, and Norway	Industrial	87	7	9-13 cm, E
	5	5	2,800-15,000	7,560	NR	Hamburg Germany	Urban	NR	8	
	4	4	180-16,830	5195	NR	Dala River, Sweden	Industrial	88	9	0-1 cm
	6	6	800-2200	1775	NR	Lake Vattern, Sweden	Industrial	88	9	0-1 cm
	5	5	1320-6090	3040	NR	Lake Vanern, Sweden	Industrial	88	9	0-1 cm
	12	8	ND-4600	622.1	Dry	Brisith Columbia	Background	NR	11	--
	14	12	ND-23000	3079	Dry	British Columbia	Near Impacted Sites	NR	11	Chemical Sources
	7	4	ND-2700	540.5	Dry	British Columbia	Near Impacted Sites	NR	11	Combustion Sources
	11	11	3.0-990	400.4	Dry	Various U.S. Lakes	Background	--	12	--
	166	166	7.70-9,170	2,131	Dry	Connecticut	Urban	87-90	17	Pre-operational
	19	19	310-17,000	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	18	
	10	10	1,600-39,000	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	19	Sedimentation area
	5	5	150-7,200	2,560	Dry	Southern Mississippi Lakes	Pristine	95-96	20	Upper stratum of sediment core

[a] Key: A LOD (Ref 1) = 20 to 50 ppt, LOD (Ref 2) = 22 to 60 ppt, LOD (Ref 3) = 0.4 ppt, LOD (Ref 4) = 0.7 to 12.0 ppt, LOD (Ref 5) = 0.61 to 4.1 ppt, LOD (Ref 8) = 10 to 500 ppt, LOD (Ref 10) = 3 ppt, LOD (Ref 12) = 1 to 20 ppt, LOD (Ref 13) = 1 to 6.6 ppt.
B Dry surface sediments from 18 lakes.
C Industry produced 2,4,5-Trichlorophenate (2,4,5-T precursor).
D No anthropogenic inputs into drainage basin--only atmospheric sources into lake.
E Mg-Production Facility.

Table B-8. Environmental Levels of Dioxins in Sediments (ppt) (continued)

Notes

NR = Not Reported
NA = Not Applicable
ND = Not Detected
ppt = Parts per trillion

Sources:

1. Koistinen et al. (1990)
2. Bopp et al. (1991)
3. Norwood et al. (1989)
4. Reed et al. (1990)
5. Rappe and Kjeller (1987)
6. Rappe et al. (1989b)
7. Oehme et al. (1989)
8. Gotz and Schumacher (1990)
9. Kjeller et al. (1990)
10. Fiedler et al. (1995)
11. B.C. Environment (1995)
12. Cleverly et al. (1996)
13. Czuczwa et al. (1984)
14. McKee et al. (1990)
15. Petty et al. (1982)
16. Sherman et al. (1990)
17. MRI (1992)
18. Wenning et al. (1992)
19. Rappe et al. (1997a)
20. Rappe et al. (1997b)

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
Tetrachlorodibenzofurans (MW=305.98)										
2,3,7,8-TCDF	18	0	ND(20-50)	NA	Dry	South Central Finland	Various	88/89	1	A,B
	9	9	24-490	232	Dry	Newark, NJ	Industrial	85/86	2	0-2", A,C
	4	4	150-1,400	855	Dry	Newark, NJ	Industrial	85/86	2	2-4", A,C
	2	2	580-1,200	890	Dry	Newark, NJ	Industrial	85/86	2	4-8", A,C
	1	1	370	370	Dry	Newark, NJ	Industrial	85/86	2	12-16", A,C
	1	1	300	300	Dry	Newark, NJ	Industrial	85/86	2	20-24", A,C
	2	2	300-390	345	Dry	Newark, NJ	Industrial	85/86	2	24-28", A,C
	3	2	ND-530	243	Dry	Newark, NJ	Industrial	85/86	2	28-32", A,C
	3	3	190-730	370	Dry	Newark, NJ	Industrial	85/86	2	32-36", A,C
	1	1	140	140	Dry	Newark, NJ	Industrial	85/86	2	40-44", A,C
	2	2	80-3,100	1,590	Dry	Newark, NJ	Industrial	85/86	2	48-52", A,C
	1	1	4,500	4,500	Dry	Newark, NJ	Industrial	85/86	2	108-111", A,C
	1	1	15	15	Dry	Long Island Sound	Reference Site	NR	3	A
	12	12	8.8-1,400	566	Dry	New England	Industrial	NR	3	A/3 sites
	4	0	ND(0.7-12)	NA	Dry	Seattle, WA	Industrial	NR	3	A
	4	1	ND-0.31	0.08	NR	Central Minnesota	Rural	NR	4	A/4 sites
	2	2	8.3-14	11	Dry	Baltic Sea	Reference Site	NR	5	A
	4	4	11-210	72	Dry	Iggesund Sweden	Industrial	NR	5	A/papermill
	4	4	0.7-9.6	5.2	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	0-2cm, E

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
2,3,7,8-TCDF (continued)	1	1	13	13	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	4-6cm, E
	1	1	5.2	5.2	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	9-13cm, E
	4	4	4.9-170	46.5	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	41-320	176	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	54-810	241	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	1	ND-17	1.42	Dry	British Columbia	Background	NR	8	--
	14	3	ND-3.0	3.8	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	2	ND-12.0	3.0	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	8	ND-8.44	1.95	Dry	Various U.S. Lakes	Background	--	9	--
	142	141	0.03-101	13.56	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	19	2.8-480	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	3	ND-0.18	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
TCDFs	1	1	15	15	Dry	Siskiwit Lake, Isle Royale, Lake Superior	Pristine	NR	10	0-0.5cm, A,D
	1	1	18	18	Dry	Siskiwit Lake, Isle Royale, Lake Superior	Pristine	NR	10	5-6cm, A,D
	1	0	ND(0.4)	NA	Dry	Siskiwit Lake, Isle Royale, Lake Superior	Pristine	NR	10	8-9cm, A,D
	4	2	ND-0.54	0.21	NR	Central Minnesota	Rural	NR	4	A/4 sites

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
TCDFs (continued)	25	0	ND(10-700)	NA	NR	Ontario Canada	Industrial	88	11	A/25 sites
	12	11	ND-200	58	NR	NY/MASS	NR	NR	12	A
	7	7	2.4-6,223	1,260	Dry	Jackfish Bay, Lake Superior	Various	NR	13	Papermill/ atmospheric contamination
	3	3	120-290	187	NR	Stockholm Sweden	Various	NR	14	A
	2	2	87-130	109	Dry	Baltic Sea	Reference Site	NR	5	A
	4	4	79-360	180	Dry	Iggesund Sweden	Industrial	NR	5	A/papermill
	4	4	6.7-54	30	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	0-2cm, E
	1	1	63	63	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	4-6cm, E
	1	1	23	23	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	9-13cm, E
	5	5	170-1070	526	NR	Hamburg Germany	Urban	NR	15	
	12	1	ND-17.0	1.42	Dry	British Columbia	Background	NR	8	--
	14	5	ND-88	15.9	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	2	ND-47.0	9.9	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	11	1.68-91.7	25.7	Dry	Various U.S. Lakes	Background	--	9	--
	142	141	0.03-290	62.78	Dry	Connecticut	Urban	87-90	16	Pre-operational
	5	3	ND-0.18	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
Pentachlorodibenzofurans (MW=340.42)										
1,2,3,7,8-PeCDF	4	4	5.6-110	34.4	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	27-120	74.3	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	50-300	120	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	0	ND	NA	Dry	British Columbia	Background	NR	8	--
	14	2	ND-8.8	0.68	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	1	ND-4.4	0.63	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	8	ND-3.1	0.94	Dry	Various U.S. Lakes	Background	--	9	--
	163	160	0.01-37.80	4.98	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	6	ND-36	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	2	ND-0.3	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
2,3,4,7,8-PeCDF	4	4	7.8-99	34.7	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	25-110	74.2	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	36-250	108	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	0	ND	NA	Dry	British Columbia	Background	NR	8	--
	14	2	ND-14.0	1.06	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	1	ND-7.5	1.07	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
2,3,4,7,8-PeCDF	11	9	ND-5.3	1.52	Dry	Various U.S. Lakes	Background	--	9	--
(continued)	163	158	0.01-49.50	5.36	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	11	ND-420	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	2	ND-0.078	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
PeCDFs	1	1	5.0	5.0	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	0-0.5cm A,D
	1	1	2.0	2.0	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	5-6cm A,D
	1	0	ND(0.4)	NA	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	8-9cm A,D
	4	2	ND-25	7.4	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	0	ND(10-700)	NA	NR	Ontario Canada	Industrial	88	11	A/25 sites
	12	9	ND-193	64	NR	NY/MASS	NR	NR	12	A
	3	3	130-260	177	NR	Stockholm Sweden	Various	NR	14	A
	2	2	66-125	96	Dry	Baltic Sea	Reference Site	NR	5	A
	4	4	48-58	55	Dry	Iggesund Sweden	Industrial	NR	5	A/papermill
	4	4	7.7-81	47	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	0-2cm, E
	1	1	24	24	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	4-6cm, E
	1	1	44	44	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	9-13cm, E

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
PeCDFs (continued)	5	5	1,300-5,200	2,980	NR	Hamburg Germany	Urban	NR	15	
	12	3	ND-86.0	14.3	Dry	British Columbia	Background	NR	8	--
	14	8	ND-710.0	134.4	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	2	ND-310.0	53.5	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	11	0.384-66.8	17.8	Dry	Various U.S. Lakes	Background	--	9	--
	163	163	0.20-775.0	103.0	Dry	Connecticut	Urban	87-90	16	Pre-operational
	5	2	ND-0.52	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
Hexachlorodibenzofurans (MW=374.87)										
1,2,3,4,7,8-HxCDF	4	4	9.3-120	44.3	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	28-170	89.5	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	32-460	163	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	1	ND-13.0	1.08	Dry	British Columbia	Background	NR	8	--
	14	5	ND-82.0	12.3	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	2	ND-30.0	5.26	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	10	ND-4.67	1.87	Dry	Various U.S. Lakes	Background	--	9	--
	166	163	0.03-193.0	16.12	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	10	ND-410	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	1	ND-0.11	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
1,2,3,6,7,8-HxCDF	4	4	3.7-73	26.7	NR	Dala River, Sweden	Industrial	88	7	0-1 cm

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
	6	6	15-110	64.7	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	25-140	73.4	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	1	ND-12.0	1.00	Dry	British Columbia	Background	NR	8	--
	14	3	ND-98.0	10.2	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	1	ND-24.0	3.4	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	0	ND	NA	Dry	Various U.S. Lakes	Background	--	9	--
	166	165	0.01-66.70	6.95	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	8	ND-73	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	0	ND	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
1,2,3,7,8,9-HxCDF	4	3	ND(2)-25	9.38	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	2	ND-4.4	1.58	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	2	ND-14	5.68	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	0	ND	NA	Dry	British Columbia	Background	NR	8	--
	14	2	ND-40.0	2.9	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	2	ND-30.0	5.4	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	1	ND-0.20	0.25	Dry	Various U.S. Lakes	Background	--	9	--

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
1,2,3,7,8,9-HxCDF (continued)	166	84	0.01-10.30	1.26	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	10	ND-29	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	0	ND	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
2,3,4,6,7,8-HxCDF	4	4	1.8-78	26.2	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	32-130	77.7	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	36-110	70.8	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	0	ND	NA	Dry	British Columbia	Background	NR	8	--
	14	0	ND	NA	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	0	ND	NA	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	10	ND-4.43	1.68	Dry	Various U.S. Lakes	Background	--	9	--
	166	164	0.11-71.10	8.41	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	0	ND	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	0	ND	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
HxCDF	1	1	2.0	2.0	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	0-0.5cm, A,D
	1	1	2.0	2.0	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	5-6cm, A,D
	1	0	ND(0.4)	NA	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	8-9cm, A,D

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
HxCDF (continued)	4	1	ND-12	3.0	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	17	ND-6,500	1,339	NR	Ontario Canada	Industrial	88	11	A/25 sites
	12	10	ND-377	133	NR	NY/MASS	NR	NR	12	A
	3	3	92-250	187	NR	Stockholm Sweden	Various	NR	14	A
	2	2	78-150	114	Dry	Baltic Sea	Reference Site	NR	5	A
	4	4	59-150	104	Dry	Iggesund Sweden	Industrial	NR	5	A/papermill
	4	4	23-283	148	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	0-2cm, E
	1	1	166	166	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	4-6cm, E
	1	1	131	131	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	9-13cm, E
	5	5	930-8,600	4,106	NR	Hamburg Germany	Urban	NR	15	
	12	3	ND-405.0	59.3	Dry	British Columbia	Background	NR	8	--
	14	10	ND-3300	840.7	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	2	ND-1700	347.1	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	10	ND-145	38.0	Dry	Various U.S. Lakes	Background	--	9	--
	166	166	0.44-908.0	132.0	Dry	Connecticut	Urban	87-90	16	Pre-operational
	5	2	ND-1.8	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
Heptachlorodibenzofurans (MW=409.31)										
1,2,3,4,6,7,8-HpCDF	8	8	59-2180	558	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	12	12	130-1030	584	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	10	10	21-8400	1764	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	3	ND-310.0	43.97	Dry	British Columbia	Background	NR	8	--
	14	11	ND-2800	604.0	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	3	ND-700	134.1	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	1	ND-0.14	33.2	Dry	Various U.S. Lakes	Background	--	9	--
	166	166	0.23-1,148	93.58	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	18	ND-1,800	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	5	0.33-3.0	1.2	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
1,2,3,4,7,8,9-HpCDF	4	3	ND-42	14.2	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	4.3-91	33.2	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	4	ND-260	78.3	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	1	ND-7.7	0.64	Dry	British Columbia	Background	NR	8	--
	14	3	ND-59.0	8.2	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
1,2,3,4,7,8,9-HpCDF (continued)	7	1	ND-17.0	2.43	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	8	ND-8.9	2.13	Dry	Various U.S. Lakes	Background	--	9	--
	166	158	0.07-205.0	6.52	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	7	ND-48	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	0	ND	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
HpCDFs	4	3	ND-30	16	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	20	ND-53,000	11,715	NR	Ontario Canada	Industrial	88	11	A/25 sites
	12	10	ND-2,436	1,039	NR	NY/MASS	NR	NR	12	A
	3	3	190-1,500	997	NR	Stockholm Sweden	Various	NR	14	A
	2	2	79-180	130	Dry	Baltic Sea	Reference Site	NR	5	A
	4	4	11-410	178	Dry	Iggesund Sweden	Industrial	NR	5	A/papermill
	4	4	20-158	100	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	0-2cm, E
	1	1	43	43	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	4-6cm, E
	1	1	192	192	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	9-13cm, E
	5	5	560-4,300	2,358	NR	Hamburg Germany	Urban	NR	15	
	12	3	ND-790.0	115.6	Dry	British Columbia	Background	NR	8	--

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
HpCDFs (continued)	14	11	ND-9900	1772	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	3	ND-2000	3743	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	10	ND-349	82.8	Dry	Various U.S. Lakes	Background	--	9	--
	166	166	0.56-1,270	190.2	Dry	Connecticut	Urban	87-90	16	Pre-operational
	5	5	0.39-5.9	2.1	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core
Octachlorodibenzofurans (MW=444.76)										
1,2,3,4,6,7,8,9-OCDF	18	3	ND-160	14	Dry	South Central Finland	Various	88/89	1	A,B
	1	1	4	4	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	0-0.5cm, A,D
	1	1	3.2	3.2	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	5-6cm, A,D
	1	1	1.1	1.1	Dry	Siskiwit Lake, Isle Royale, Lake Michigan	Pristine	NR	10	8-9cm, A,D
	4	1	ND-23	5.8	NR	Central Minnesota	Rural	NR	4	A/4 sites
	25	21	ND-400,000	34,912	NR	Ontario Canada	Industrial	88	11	A/25 sites
	12	11	ND-1,010	460	NR	NY/MASS	NR	NR	12	A
	3	1	ND-39	14	NR	Stockholm Sweden	Various	NR	14	A
	2	1	ND-3.8	1.9	Dry	Baltic Sea	Reference Site	NR	5	A
	4	2	ND-15	5	Dry	Iggesund Sweden	Industrial	NR	5	A/Papermill
	4	4	58-151	96	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	0-2cm, E
1,2,3,4,6,7,8,9-OCDF (continued)	1	1	43	43	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	4-6cm, E

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Weight basis	Location	Location description	Sample year	Ref. no.	Comments[a]
	1	1	192	192	Dry	Fjord between Sweden, Norway and Denmark	Industrial	87	6	9-13cm, E
	5	5	660-5,200	2,712	NR	Hamburg Germany	Urban	NR	15	
	4	4	150-4250	1212	NR	Dala River, Sweden	Industrial	88	7	0-1 cm
	6	6	170-1310	602	NR	Lake Vattern, Sweden	Industrial	88	7	0-1 cm
	5	5	230-79,250	19,356	NR	Lake Vanern, Sweden	Industrial	88	7	0-1 cm
	12	3	ND-330.0	31.7	Dry	British Columbia	Background	NR	8	--
	14	10	ND-3200	639.0	Dry	British Columbia	Near Impacted Sites	NR	8	Chemical Sources
	7	3	ND-520.0	100.7	Dry	British Columbia	Near Impacted Sites	NR	8	Combustion Sources
	11	9	ND-385	103.6	Dry	Various U.S. Lakes	Background	--	9	--
	166	166	7.70-9,170	2,131	Dry	Connecticut	Urban	87-90	16	Pre-operational
	19	18	ND-2,400	NR	Dry	L. Passaic River & Newark Bay	Industrial	90	17	
	5	4	ND-4.8	NR	Dry	Southern Mississippi Lakes	Pristine	95-96	18	Upper stratum of sediment core

[a] Key:
A LOD (Ref. 1) = 20 to 50 ppt, LOD (Ref. 2) = 32 ppt, LOD (Ref. 3) = 0.4 ppt, LOD (Ref. 4) = 0.7 to 12.0 ppt, LOD (Ref. 5) = 0.61 to 4.1 ppt, LOD (Ref. 8) = 10 to 700 ppt, LOD (Ref. 10) = 3 ppt, LOD (ref. 12) = 1 to 20 ppt, LOD (Ref. 13) = 1 to 6.6 ppt.
B Dry surface sediments from 18 lakes.
C Industry produced 2,4,5 trichlorophenate (2,4,5T precursor).
D No anthropogenic inputs into drainage basin -- only atmospheric sources into lake.
E Mg-production facility.

Table B-9. Environmental Levels of Dibenzofurans in Sediment (ppt) (continued)

Notes

NR = Not Reported
NA = Not Applicable
ND = Not Detected
ppt = Parts per trillion

Sources:

1. Koistinen et al. (1990)
2. Bopp et al. (1991)
3. Norwood et al. (1989)
4. Reed et al. (1990)
5. Rappe et al. (1989b)
6. Oehme et al. (1989)
7. Kjeller et al. (1990)
8. BC Environment (1995)
9. Cleverly et al. (1996)
10. Czuczwa et al. (1984)
11. McKee et al. (1990)
12. Petty et al. (1982)
13. Sherman et al. (1990)
14. Rappe and Kjeller (1987)
15. Gotz and Schumacher (1990)
16. MRI (1992)
17. Wenning et al. (1992)
18. Rappe et al. (1997b)

Table B-10. Environmental Levels of PCBs in Sediment (ppt)

IUPAC number	Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
Tetrachloro-PCB (MW=291.99)											
77	3,3',4,4'-TCB	18	13	ND-550	138	Dry	South Central Finland	Various	88/89	1	A,B
		8	8	500-360,000	64,250	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		5	5	5,000-27.5M	9.47M	NR	Waukegan, Illinois	Urban	78	3	5 sites
		NR	NR	NR	ND(500)	Dry	Green Bay, Lake Michigan	Various	NR	4	A
		11	11	3.16-93.3	26.6	Dry	Various U.S. Lakes	Background	--	5	--
81	3,4,4',5-TCB	8	3	ND-90,000	26,880	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		NR	NR	NR	ND(500)	Dry	Green Bay, Lake Michigan	Various	NR	4	A
Pentachloro-PCB (MW=326.44)											
126	3,3',4,4',5-PeCB	18	1	ND-110	6.1	Dry	South Central Finland	Various	88/89	1	A,B
		8	2	ND-10,000	2,380	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		NR	NR	NR	ND(500)	Dry	Green Bay, Lake Michigan	Various	NR	4	A
		11	9	ND-18.6	4.48	Dry	Various U.S. Lakes	Background	--	5	--
105	2,3,3',4,4'-PeCB	10	10	52-120	96.4	Dry	South Central Finland	Various	88/89	1	A,B,C
		8	8	6,000-490,000	85,120	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		38	NR	NR	10,000	Dry	Lake Ontario	Various	81	6	Bottom Sediment
		5	5	102,000-131M	35.14M	NR	Waukegan, Illinois	Urban	78	3	5 Locations

Table B-10. Environmental Levels of PCBs in Sediment (ppt) (continued)

IUPAC number	Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
105	2,3,3',4,4'-PeCB (continued)	NR	NR	NR	5,800	Dry	Green Bay, Lake Michigan	Various	NR	4	A
		11	11	18.3-446.0	123.2	Dry	Various U.S. Lakes	Background	--	5	--
114	2,3,4,4',5-PeCB	8	1	ND-110,000	13,750	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		NR	NR	NR	1,000	Dry	Green Bay, Lake Michigan	Various	NR	4	A
118	2,3',4,4',5-PeCB	8	8	86,000-1.48M	351,620	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		38	NR	NR	15,000	Dry	Lake Ontario	Various	81	6	Bottom Sediment
		NR	NR	NR	11,000	Dry	Green Bay, Lake Michigan	Various	NR	4	A
		2	0	0.01	0.01	Dry	Alicante, Spain	Coastal	89/90	7	
		11	11	53.4-1350	323.2	Dry	Various U.S. Lakes	Background	--	5	--
Hexachloro-PCB (MW=360.88)											
156	2,3,3',4,4',5-HxCB	38	NR	NR	2,100	Dry	Lake Ontario	Various	81	6	Bottom Sediment
		NR	NR	NR	1,700	Dry	Green Bay, Lake Michigan	Various	NR	4	A
		11	11	4.6-203	45.9	Dry	Various U.S. Lakes	Background	--	5	--
157	1,2,3',4,4',5'HxCB	11	11	1.3-53.2	12.2	Dry	Various U.S. Lakes	Background	--	5	--
167	2,3',4,4',5,5'-HxCB	8	2	ND-80,000	15,500	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		NR	NR	NR	ND(500)	Dry	Green Bay, Lake Michigan	Various	NR	4	A

Table B-10. Environmental Levels of PCBs in Sediment (ppt) (continued)

IUPAC number	Chemical	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments[a]
169	3,3',4,4',5,5'-HxCB	18	0	ND(20-50)	NA	Dry	South Central Finland	Various	88/89	1	A,B
		8	3	ND-19,000	4,800	Dry	Eastern Wisconsin	Industrial	88/89	2	A,D
		NR	NR	NR	ND(500)	Dry	Green Bay, Lake Michigan	Various	NR	4	A
		11	10	ND-2.47	0.94	Dry	Various U.S. Lakes	Background	--	5	--
Heptachloro-PCB (MW=396.33)											
189	2,3,3',4,4',5,5'HpCB	NR	NR	NR	ND(500)	Dry	Green Bay, Lake Michigan	Various	NR	4	A

[a] Key: A LOD (Ref. 1)=20 to 50 ppt, LOD (Ref. 6)=1,000 ppt, LOD (Ref. 16)=500 ppt.
B Dry Surface Sediments from 18 lakes.
C All collected samples not analyzed.
D Superfund/Michigan "Area of Concern" Site.

NOTES:

NR = Not Reported
NA = Not Applicable
ND = Not Detected
ppt = Parts per trillion

Sources:

1. Koistinen et al. (1990)
2. Sonzogni et al. (1991)
3. Huckins et al. (1988)
4. Smith et al. (1990)
5. Cleverly et al. (1996)
6. Oliver and Niimi (1988)
7. Prats et al. (1992)

Table B-11. Environmental Levels of Dioxins in Fish (ppt)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
Tetrachlorodibenzo-p-dioxins (MW=321.98)												
2,3,7,8-TCDD	Eel	Liver	6	6	1.2-9.1	3.32	NR	Various, Netherlands	NR	NR	1	one sample near dump site
	Eel	Fillet	5	5	2.4-3.3	3.04	Fat	Rhine River, Germany	NR	88	2	up & downstream Basal
	Trout	Fillet	1	1	1.4	1.4	Fat	Neckar River, Germany	Urban	88	2	composite sample
	Grayling	Fillet	1	1	3.8	3.8	Fat	Neckar River, Germany	Urban	88	2	
	Barbel	Fillet	1	1	5.1	5.1	Fat	Neckar River, Germany	Urban	88	2	
	Carp	Fillet	1	1	2.5	2.5	Fat	Neckar River, Germany	Urban	88	2	
	Chub	Fillet	1	0	ND(2.3)	NA	Fat	Neckar River, Germany	Urban	88	2	composite sample
	Eel	Fillet	5	5	0.9-1.5	1.3	Fat	Neckar River, Germany	Urban	87-88	2	
	Bream		14	14	1.4-94.4	18.0	Fresh	Hamburg, Germany	Urban	84	3	
	Perch		3	3	1.8-8.1	5.9	Fresh	Hamburg, Germany	Urban	84	3	
	Herring	Whole	1	0	ND(0.1)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	0	ND(0.1)	NA	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	0	ND(0.1)	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Salmon	Muscle	2	2	4.6-19.0	11.8	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	wild salmon
	Salmon	Muscle	2	2	0.2-0.3	0.25	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	hatched salmon
	Perch	NR	3	3	2.6-19	11.5	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	caught near pulp mill
	Artic Char	NR	5	5	6.5-25	14.3	Fresh	Lake Vattern, Sweden	NR	NR	4	
	Carp	Whole	3	0	ND(6.6)	NA	NR	Mississippi River, MN	Industrial	NR	5	Elk River power station
	Carp	Whole	3	0	ND(6.6)	NA	NR	Lake Orono, MN	Industrial	NR	5	Elk River power station
	Blue Crab	Meat	2	2	106-116	111	Wet	Passaic River, NJ	Urban	NR	6	
	Lobster	Meat	2	2	4.7-6.3	5.5	Wet	New York Bight	Dump Site	NR	6	former sewage sludge

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDD (continued)	Str. Bass	Fillets	2	2	83.9-734	409	Wet	Newark Bay, NJ	Urban	NR	6	
	Lake Trout	Whole	1	1	1.0	1.0	Wet	Lake Superior	NR	84	7	mean 5 samples
	Lake Trout	Whole	1	1	8.6	8.6	Wet	Lake Huron	NR	84	7	mean 5 samples
	Lake Trout	Whole	3	3	3.5-5.8	4.4	Wet	Lake Michigan	NR	84	7	range 3 sample sites
	Walleye	Whole	1	1	1.8	1.8	Wet	Lake Erie	NR	84	7	mean 5 samples
	Walleye	Whole	1	1	6.6	6.6	Wet	Lake St. Clair	NR	84	7	mean 5 samples
	Lake Trout	Whole	1	1	48.9	48.9	Wet	Lake Ontario	NR	84	7	mean 5 samples
	Lake Trout	Whole	10	10	3.0-8.7	4.2	Wet	Lake Michigan	NR	84	7	
	Br. Trout	Whole	1	1	6	6	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Br. Trout	Fillets	1	1	5	5	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Whole	1	1	14	14	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Fillets	1	1	5	5	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Whole	1	1	18	18	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Fillets	1	1	8	8	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Whole	1	1	20	20	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Cod	Fillets	4	0	ND(1.0)	NA	Fresh	Various, Sweden	Industrial	88	9	
	Haddock	Fillets	1	0	ND(0.2)	NA	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
	P. Flounder	Fillets	1	0	ND(0.2)	NA	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
	Plaice	Fillets	1	0	ND(0.5)	NA	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
	Flounder	Fillets	1	0	ND(0.5)	NA	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDD (continued)	Eel	Fillets	4	1	ND-1.4	0.35	Fresh	Various, Sweden	Industrial	87-88	9	
	Mussel	Muscle	3	0	ND(0.5)	NA	Fresh	Grenlandsfjord,Sweden	Industrial	87	9	
	Shrimp	Muscle	2	0	ND(2.0)	NA	Fresh	Grenlandsfjord,Sweden	Industrial	88	9	
	Cod	Fillets	6	NR	ND-3.8	NR	Fresh	Frierfjord, Sweden	Industrial	87	9	only conc. range given
	Carp	Whole	2	2	3-28	16	NR	Lake Huron	NR	NR	10	samples composite 3-5 fish
	Pike	Muscle	8	8	40-833	186	Fat	Lake Vanern, Sweden	Industrial	88	11	samples composite 2-5 fish
	Pike	Muscle	1	1	78	78	Fat	Hedesunda Bay, Sweden	Industrial	88	11	composite 5 fish
	Various[c]	Mixed[d]	314	220	NR	6.84	Wet	Various, US	Various	86-89	12	samples composite 3-5 fish
	Sucker	Whole	15	6	ND-0.85	0.45	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.74-1.39)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(0.96-1.49)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.17)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(0.99-1.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(1.00)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Carp	Whole	5	2	ND-0.46	0.48	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	not available	Whole	2	0	ND(1.15-2.35)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.27)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.34-0.75)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
2,3,7,8-TCDD (continued)	Rainbow Trout	Fillet	2	2	1.87-2.26	2.06	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Brook Trout	Fillet	1	0	ND(0.58)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(0.99)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	0.31	0.31	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.30)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.10-1.00)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.10-0.11)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.16)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(1.00)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(1.00)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(1.02)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(1.04-1.11)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(1.01)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
2,3,7,8-TCDD (continued)	Winter Flounder	Whole	2	1	ND-1.20	1.02	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Bluefish	Whole	1	1	0.75	0.75	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	White Catfish	Whole	1	1	0.75	0.75	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(0.99)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	7.2-12	8.8	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	4.3-6.4	5.5	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	3.2-4.9	4.1	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	1.3-1.4	1.35	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	1	ND-2	1.53	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	2.5-8.8	5.86	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
	Mullet	Fillet	2	1	ND-10	5.1	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	7.1	NA	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Herring	Fillet	1	1	1.4	1.4	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	4.7	4.7	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	23	23	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Redfish	NR	1	1	2.8	2.8	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Plaice	Whole	3	3	0.13-0.18	0.16	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Mackerel	Whole	1	1	0.07	0.07	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Herring	Whole	1	1	0.19	0.19	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Cod	Whole	1	1	0.05	0.05	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
2,3,7,8-TCDD (continued)	Skate	Whole	1	0	ND(0.16)	NA	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Coley	Whole	1	1	0.06	0.06	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Fish	Whole	1	1	0.09	0.09	Wet	Port Talbot, UK	Urban/ Industrial	88	17	

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Ocean Fish	Mixed	13	NR	NR	2.3	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	3.09	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fish	NR	138	NR	0-246	5.45	Fat	Germany	NR	93-96	19	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	1.2	Fat	Catalonia, Spain	NR	99	20	purchased in supermarkets
	Freshwater Fish	NR	NR	nR	nR	1.89	Fat	Russia	NR	96	21	purchased in supermarkets
TCDDs	Bream	NR	13	13	2.5-102	17.6	Fresh	Hamburg, Germany	Urban	84	3	
	Perch	NR	2	2	9.0-10.5	9.8	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	1	ND-3.9	1.3	NR	Mississippi River, MN	Industrial	NR	5	Elk River power station
	Carp	Whole	3	0	ND(6.6)	NA	NR	Lake Orono, MN	Industrial	NR	5	Elk River power station
	Blue Crab	Meat	2	2	118-150	134	Wet	Passaic River, NJ	Urban	NR	6	
	Lobster	Meat	2	2	6.6-8.3	7.4	Wet	New York Bight	Dump Site	NR	6	former sewage sludge
	Str. Bass	Fillets	2	2	85.4-734	410	Wet	Newark Bay, NJ	Urban	NR	6	
	Br. Trout	Whole	1	1	11	11	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Br. Trout	Fillets	1	1	9	9	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Whole	1	1	29	29	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Fillets	1	1	11	11	NR	Lake Ontario	NR	NR	8	composite 3 samples
TCDDs (continued)	Lake Trout	Whole	1	1	32	32	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Fillets	1	1	12	12	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Whole	1	1	22	22	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Fillets	1	1	9	9	NR	Lake Ontario	NR	NR	8	composite 3 samples

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Oyster	Whole	3	3	120-240	163.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	39-87	59	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	24-62	37.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	16-45	30.5	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	4.2-38	21.1	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	9.5	9.5	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Ocean Fish	Mixed	13	NR	NR	4.06	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	4.44	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
Pentachlorodibenzo-p-dioxins (MW=356.42)												
1,2,3,7,8-PeCDD	Herring	Whole	1	1	0.6	0.6	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	2	1.1-2.8	1.95	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	2	2.0-4.7	3.35	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Carp	Whole	2	2	2-11	6	NR	Lake Huron	NR	NR	10	samples composite 3-5 fish
	Pike	Muscle	8	8	70-250	129	Fat	Lake Vanern, Sweden	Industrial	88	11	samples composite 2-5 fish
	Pike	Muscle	1	1	39	39	Fat	Hedesunda Bay, Sweden	Industrial	88	11	composite 5 fish
	Sucker	Whole	15	2	ND-0.54	0.72	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,7,8-PeCDD (continued)	Lm Bass	Fillet	4	0	ND(0.75-2.18)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(2.74-2.99)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(0.92-0.95)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Redeye Bass	Fillet	1	0	ND(0.92)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Carp	Whole	5	1	ND-0.38	0.80	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	not available	Whole	2	0	ND(1.94-5.33)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.97)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.48-0.70)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(1.11-1.50)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.75)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.62)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(1.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	0.57	0.57	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(1.40)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.37-0.92)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,7,8-PeCDD (continued)	Chain Pickerel	Fillet	3	0	ND(0.19-0.49)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(0.92)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(0.97)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Summer Flounder	Whole	1	0	ND(1.21)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(0.92-0.95)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(0.95)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(1.20-1.24)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(1.61)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(1.01)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(0.92)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	6.3-14	9.77	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	16-26	21.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	10-10	10	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	4.3-4.9	4.6	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	2.6-6.3	4.45	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	8.2-19	14.73	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
1,2,3,7,8-PeCDD	Mullet	Fillet	2	2	0.63-5.6	3.12	Fat	S. Mississippi	NR	94	13	purchased at supermarket
(continued)	Spanish Mackerel	Fillet	1	1	17	17	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Herring	Fillet	1	1	3.5	3.5	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	12	12	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	1.3	1.3	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Redfish	NR	1	1	6.5	6.5	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Plaice	Whole	3	3	0.10-0.38	0.24	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Mackerel	Whole	1	1	0.10	0.10	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Herring	Whole	1	1	0.60	0.60	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Cod	Whole	1	0	ND(0.06)	NA	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Skate	Whole	1	1	0.07	0.07	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Coley	Whole	1	0	ND(0.04)	NA	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Fish	Whole	1	1	0.18	0.18	Wet	Port Talbot, UK	Urban/ Industrial	88	17	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	5.2	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fish	NR	138	NR	0-247	6.2	Fat	Germany	NR	93-96	19	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	0.8	Fat	Catalonia, Spain	NR	96	20	purchased at supermarkets
	Freshwater Fish	NR	NR	NR	NR	3.4	Fat	Russia	NR	96	21	purchased at supermarkets

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
PeCDDs	Bream		13	13	3.2-27.8	12.1	Fresh	Hamburg, Germany	Urban	84	3	
	Perch		2	2	9.8-29.8	19.8	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	3	3.5-4.5	3.9	NR	Mississippi River, MN	Industrial	NR	5	Elk River power station
	Carp	Whole	3	0	ND(6.6)	NA	NR	Lake Orono, MN	Industrial	NR	5	Elk River power station
	Blue Crab	Meat	2	2	17.2-18.0	17.6	Wet	Passaic River, NJ	Urban	NR	6	
	Lobster	Meat	2	2	10.0-11.0	10.5	Wet	New York Bight	Dump Site	NR	6	former sewage sludge
	Str. Bass	Fillets	2	2	5.2-10.6	7.9	Wet	Newark Bay, NJ	Urban	NR	6	
	Br. Trout	Whole	1	1	8	8	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Br. Trout	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Whole	1	1	31	31	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Fillets	1	1	15	15	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Whole	1	1	39	39	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Fillets	1	1	9	9	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Whole	1	1	6	6	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Fillets	1	1	5	5	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Ocean Fish		13	0	ND	NA	Fat	Various U.S. Sites		NR	9	
	Fresh Fish		10	NR	NR	5.2	Fat	Various U.S. Sites		NR	9	
	Various[c]	Mixed[d]	34	34	0.15-2.67	0.77	Wet	Various, US	Background[e]	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	140-350	216.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	440-680	556.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	250-560	390	Fat	S. Mississippi	NR	94	13	purchased at supermarket

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
PeCDDs (continued)	Crawfish	Head	2	2	43-47	45	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	14-31	22.5	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	24	24	Fat	S. Mississippi	NR	94	13	purchased at supermarket
Hexachlorodibenzo-p-dioxins (MW=390.8)												
1,2,3,4,7,8-HxCDD	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	2	0.2-0.3	0.25	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	0	ND(0.2)	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Carp	Whole	2	2	3-5	4	NR	Lake Huron	NR	NR	10	samples composite 3-5 fish
	Pike	Muscle	8	8	6.7-22	12.8	Fat	Lake Vanern, Sweden	Industrial	88	11	samples composite 2-5 fish
	Pike	Muscle	1	1	11	11	Fat	Hedesunda Bay, Sweden	Industrial	88	11	composite 5 fish
	Sucker	Whole	15	2	ND-0.24	0.81	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.90-2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(2.47-2.87)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.25)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Carp	Whole	5	1	ND-0.70	1.08	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	not available	Whole	2	0	ND(1.50-3.31)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,4,7,8-HxCDD (continued)	Brown Trout	Fillet	2	0	ND(0.65-0.72)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Rainbow Trout	Fillet	2	0	ND(0.89-1.04)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(1.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(2.46)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(2.56)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(1.13)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.60-2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.22-1.04)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.22)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(2.46)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,4,7,8-HxCDD (continued)	Winter Flounder	Whole	2	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Bluefish	Whole	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(2.47)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	100	NR	1.67	Wet	Various, US	Various	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	4.2-14	7.87	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	16-26	22.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	7.2-7.5	7.37	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	3-4.1	3.55	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	1	ND-3.6	2.55	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	7.9-19	15.3	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
	Mullet	Fillet	2	0	ND-(0.26-1.25)	0.76	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	9.0	9.0	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Herring	Fillet	1	1	0.47	0.47	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	1.2	1.2	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	0.01	0.01	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Redfish	NR	1	1	0.5	0.5	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Fish	Whole	1	1	0.14	0.14	Wet	Port Talbot, UK	Urban/ Industrial	88	17	
	Fish	Whole	1	1	0.06	0.06	Wet	Stonehaven, UK	Rural	91	17	
1,2,3,4,7,8-HxCDD	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
(continued)	Fresh Fish	Mixed	10	NR	NR	3.01	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Fish	NR	138	NR	0-19.5	0.80	Fat	Germany	NR	93-96	19	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	0.40	Fat	Catalonia, Spain	NR	96	20	purchased at supermarkets
	Freshwater Fish	NR	NR	NR	NR	5.71	Fat	Russia	NR	96	21	purchased at supermarkets
1,2,3,6,7,8-HxCDD	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	1	ND-2.4	1.25	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	2	2.2-8.1	5.15	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Pike	Muscle	8	8	30-100	50.5	Fat	Lake Vanern, Sweden	Industrial	88	11	samples composite 2-5 fish
	Pike	Muscle	1	1	22	22	Fat	Hedesunda Bay, Sweden	Industrial	88	11	composite 5 fish
	Sucker	Whole	15	4	ND-0.46	0.97	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.90-2.40)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(2.87-3.71)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(3.49)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(1.84-1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Carp	Whole	5	3	ND-3.57	1.63	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	not available	Whole	2	0	ND(2.25-5.00)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,6,7,8-HxCDD (continued)	Brown Trout	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Brown Trout	Fillet	2	0	ND(0.65-0.72)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(1.74-1.78)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(1.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(1.84)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	1.36	1.36	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(1.13)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.60-1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.87-1.04)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.22)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Summer Flounder	Whole	1	1	0.67	0.67	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(1.84)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,6,7,8-HxCDD (continued)	Composite Bottom	Whole	1	0	ND(1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Winter Flounder	Whole	2	1	ND-0.40	0.67	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(1.84)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	White Catfish	Whole	1	1	0.68	0.68	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(1.85)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	217	NR	4.29	Wet	Various, US	Various	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	9.6-31	17.53	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	26-40	34.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	13-15	14	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	5.9-9.3	7.6	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	1	ND-5.4	3.43	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	11-26	20.33	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
	Mullett	Fillet	2	0	ND(0.026-1.25)	0.75	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	47	47	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Herring	Fillet	1	1	1.8	1.8	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	5.8	5.8	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	17	17	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Redfish	NR	1	1	8.4	8.4	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Ocean Fish	Mixed	13	ND	ND	NA	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
1,2,3,6,7,8-HxCDD	Fresh Fish	Mixed	10	NR	NR	5.31	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
(continued)	Fish	NR	138	NR	0-101	3.8	Fat	Germany	NR	93-96	19	official food inspection samples

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Fish & Seafood	NR	8	NR	NR	1.5	Fat	Catalonia, Spain	NR	96	20	purchased at supermarkets
	Freshwater Fish	NR	NR	NR	NR	4.3	Fat	Russia	NR	96	21	purchased at supermarkets
1,2,3,7,8,9-HxCDD	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	0	ND(0.2)	NA	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	0	ND(0.2)	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Pike	Muscle	8	0	ND(3-11)	NA	Fat	Lake Vanern, Sweden	Industrial	88	11	samples composite 2-5 fish
	Pike	Muscle	1	0	ND(6)	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	11	composite 5 fish
	Sucker	Whole	15	0	ND(0.60-3.37)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.90-2.40)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(2.47-2.87)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.25)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Carp	Whole	5	0	ND(1.15-2.69)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	not available	Whole	2	0	ND(1.50-2.48)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,7,8,9-HxCDD (continued)	Brown Trout	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.65-0.72)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Rainbow Trout	Fillet	2	0	ND(0.89-1.04)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(1.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(1.37)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(1.13)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.60-1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.22-1.04)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.22)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Summer Flounder	Whole	1	1	0.34	0.34	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(1.37-1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,7,8,9-HxCDD (continued)	Composite Bottom	Whole	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Bluefish	Whole	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(1.38)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	119	NR	1.15	Wet	Various, US	Various	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	8.2-20	12.6	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	30-40	34.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	16-19	17.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	6-8.1	7.05	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	1	ND-10	5.6	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	5-20	14	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
	Mullett	Fillet	2	0	ND(0.21-1.00)	0.6	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	13	13	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Herring	Fillet	1	1	0.25	0.25	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	1.0	1.0	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	5.2	5.2	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Redfish	NR	1	1	1.3	1.3	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
1,2,3,7,8,9-HxCDD	Plaice	Whole	3	3	0.02-0.05	0.04	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
(continued)	Mackerel	Whole	1	1	0.02	0.02	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Herring	Whole	1	1	0.07	0.07	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Cod	Whole	1	0	ND(0.02)	NA	Wet	Norwich, UK	NR	88	16	purchased at retail outlet

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Skate	Whole	1	1	0.04	0.04	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Coley	Whole	1	0	ND(0.04)	NA	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Fish	Whole	1	1	0.04	0.04	Wet	Port Talbot, UK	Urban/ Industrial	88	17	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	4.11	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fish	NR	138	NR	0-24	1.1	Fat	Germany	NR	93-96	19	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	1.2	Fat	Catalonia, Spain	NR	96	20	purchased at supermarkets
	Freshwater Fish	NR	NR	NR	NR	4.3	Fat	Russia	NR	96	21	purchased at supermarkets
HxCDDs	Bream		13	13	4.3-46.4	17.8	Fresh	Hamburg, Germany	Urban	84	3	
	Perch		2	2	18.6-21.5	20.0	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	3	2.3-11	6.9	NR	Mississippi River, MN	Industrial	NR	5	Elk River power station
	Carp	Whole	3	1	ND-3.0	1.0	NR	Lake Orono, MN	Industrial	NR	5	Elk River power station
	Blue Crab	Meat	2	2	0.3-1.5	0.9	Wet	Passaic River, NJ	Urban	NR	6	
	Lobster	Meat	2	2	3.0-3.4	3.2	Wet	New York Bight	Dump Site	NR	6	former sewage sludge
	Str. Bass	Fillets	2	2	0.6-0.7	0.65	Wet	Newark Bay, NJ	Urban	NR	6	
HxCDDs (continued)	Br. Trout	Whole	1	1	20	20	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Br. Trout	Fillets	1	1	25	25	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Whole	1	1	67	67	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Fillets	1	1	37	37	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Whole	1	1	114	114	NR	Lake Ontario	NR	NR	8	composite 3 samples

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Lake Trout	Fillets	1	1	27	27	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Whole	1	1	16	16	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Fillets	1	1	22	22	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Oyster	Whole	3	3	230-630	383.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	1500-2400	1966.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	790-950	880	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	120-140	130	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	44-100	72	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	77	77	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	12.5	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
Heptachlorodibenzo-p-dioxins (MW=425.31)												
1,2,3,4,6,7,8-HpCDD	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	1	ND-0.6	0.35	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	0	ND(0.2)	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Carp	Whole	2	2	3-4	3.5	NR	Lake Huron	NR	NR	10	samples composite 3-5 fish
1,2,3,4,6,7,8-HpCDD	Sucker	Whole	15	8	ND-8.16	2.59	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
(continued)	Lm Bass	Fillet	4	1	ND-0.75	1.54	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(12.94-19.27)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(10.70)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Sm Bass	Fillet	2	1	ND-0.23	0.11	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(1.26)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Carp	Whole	5	3	ND-7.14	7.18	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	not available	Whole	1	0	ND(6.96)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(4.91)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(1.31-4.45)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	2	1.67-2.21	1.94	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Brook Trout	Fillet	1	1	1.80	1.80	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(3.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(4.43)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	3.23	3.23	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(7.36)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Walleye	Fillet	2	0	ND(0.75-0.86)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
1,2,3,4,6,7,8-HpCDD (continued)	Chain Pickerel	Fillet	3	0	ND(3.08-5.09)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(2.29)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Sea Catfish	Fillet	1	1	0.51	0.51	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	North Hogsucker	Whole	1	1	0.74	0.74	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Summer Flounder	Whole	1	1	3.06	3.06	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Dolly Varden	Whole	2	2	0.77-0.79	0.78	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Composite Bottom	Whole	1	1	2.18	2.18	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Winter Flounder	Whole	2	2	0.61-0.80	0.71	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(4.10)	NA	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	White Catfish	Whole	1	1	0.89	0.89	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Crayfish	Whole	1	1	0.49	0.49	Wet	Various, US	Background	86-89	12	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	279	NR	10.5	Wet	Various, US	Various	86-89	12	samples composite 3-5 fish
	Oyster	Whole	3	3	27-90	48.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	110-140	126.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	64-70	67.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	22-29	25.5	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	19-33	26	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	53-170	121	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
1,2,3,4,6,7,8-HpCDD	Mullett	Fillet	2	2	1.2-7.2	4.2	Fat	S. Mississippi	NR	94	13	purchased at supermarket
(continued)	Spanish Mackerel	Fillet	1	1	52	52	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Herring	Fillet	1	1	0.45	0.45	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	3.6	3.6	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	10	10	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Redfish	NR	1	1	3.0	3.0	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Plaice	Whole	3	3	0.13-0.34	0.22	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Mackerel	Whole	1	1	0.48	0.48	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Herring	Whole	1	1	0.47	0.47	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Cod	Whole	1	0	ND(0.44)	NA	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Skate	Whole	1	1	0.26	0.26	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Coley	Whole	1	1	0.21	0.21	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Fish	Whole	1	1	0.52	0.52	Wet	Port Talbot, UK	Urban/ Industrial	88	17	
	Fish	Whole	1	1	0.28	0.28	Wet	Stonehaven, UK	Rural	91	17	
	Ocean Fish	Mixed	13	NR	NR	11.7	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	23.5	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fish	NR	138	NR	0.33-64	4.1	Fat	Germany	NR	93-96	19	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	96.2	Fat	Catalonia, Spain	NR	96	20	purchased at supermarkets
	Freshwater Fish	NR	NR	NR	NR	3.1	Fat	Russia	NR	96	21	purchased at supermarkets
HpCDDs	Bream		13	13	1.5-14.4	6.7	Fresh	Hamburg, Germany	Urban	84	3	
	Perch		2	2	3.5-7.1	5.3	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	3	15-22	19.3	NR	Mississippi River, MN	Industrial	NR	5	Elk River power station
	Carp	Whole	3	2	ND-11	7.0	NR	Lake Orono, MN	Industrial	NR	5	Elk River power station
	Blue Crab	Meat	2	0	ND(1.1)	NA	Wet	Passaic River, NJ	Urban	NR	6	
	Lobster	Meat	2	1	ND-8.5	4.25	Wet	New York Bight	Dump Site	NR	6	former sewage sludge

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Str. Bass	Fillets	2	2	4.0-11.4	7.7	Wet	Newark Bay, NJ	Urban	NR	6	
	Br. Trout	Whole	1	1	7	7	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Br. Trout	Fillets	1	1	9	9	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Whole	1	1	12	12	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Whole	1	1	16	16	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Whole	1	1	30	30	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Fillets	1	1	50	50	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Oyster	Whole	3	3	84-290	156.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	380-500	456.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	260-290	273.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	85-120	102.5	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	70-130	100	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	54	54	Fat	S. Mississippi	NR	94	13	purchased at supermarket
HpCDDs (continued)	Ocean Fish	Mixed	13	NR	NR	11.7	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	23.5	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
Octachlorodibenzo-p-dioxin (MW=460.76)												
1,2,3,4,6,7,8,9-OCDD	Eel	Fillet	5	5	28-60	44.4	Fat	Rhine River, Germany	NR	88	2	up & downstream Basal
	Trout	Fillet	1	0	ND(5.0)	NA	Fat	Neckar River, Germany	Urban	88	2	composite sample
	Grayling	Fillet	1	1	47	47	Fat	Neckar River, Germany	Urban	88	2	

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Barbel	Fillet	1	1	9.0	9	Fat	Neckar River, Germany	Urban	88	2	
	Carp	Fillet	1	1	23	23	Fat	Neckar River, Germany	Urban	88	2	
	Chub	Fillet	1	1	15	15	Fat	Neckar River, Germany	Urban	88	2	composite sample
	Eel	Fillet	5	5	25-40	30	Fat	Neckar River, Germany	Urban	87-88	2	
	Bream		14	14	1.4-5.1	2.5	Fresh	Hamburg, Germany	Urban	84	3	
	Perch		3	3	2.3-10.5	5.2	Fresh	Hamburg, Germany	Urban	84	3	
	Herring	Whole	1	1	1.1	1.1	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 5-10 fish
	Herring	Whole	2	1	ND-0.7	0.4	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 5-10 fish
	Herring	Whole	2	1	ND-0.3	0.2	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 5-10 fish
	Salmon	Muscle	2	1	ND-1.5	0.75	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	wild salmon
	Salmon	Muscle	2	2	0.8-1.9	1.35	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	hatched salmon
	Perch	NR	3	3	0.6-0.8	0.73	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	caught near pulp mill
	Carp	Whole	3	3	56-62	59	NR	Mississippi River, MN	Industrial	NR	5	Elk River power station
	Carp	Whole	3	3	35-43	39	NR	Lake Orono, MN	Industrial	NR	5	Elk River power station
	Blue Crab	Meat	2	2	34.3-78.8	56.6	Wet	Passaic River, NJ	Urban	NR	7	
1,2,3,4,6,7,8,9-OCDD	Lobster	Meat	2	2	6.3-10.9	8.6	Wet	New York Bight	Dump Site	NR	6	former sewage sludge
(continued)	Str. Bass	Fillets	2	2	5.1-49.5	27.3	Wet	Newark Bay, NJ	Urban	NR	6	
	Lake Trout	Whole	1	1	1.0	1.0	Wet	Lake Superior	NR	84	7	mean 5 samples
	Lake Trout	Whole	1	1	0.7	0.7	Wet	Lake Huron	NR	84	7	mean 5 samples
	Lake Trout	Whole	3	3	1.1-2.5	1.8	Wet	Lake Michigan	NR	84	7	range 3 sample sites
	Walleye	Whole	1	1	2.8	2.8	Wet	Lake Erie	NR	84	7	mean 5 samples
	Walleye	Whole	1	1	1.8	1.8	Wet	Lake St. Clair	NR	84	7	mean 5 samples

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Lake Trout	Whole	1	1	1.2	1.2	Wet	Lake Ontario	NR	84	7	mean 5 samples
	Lake Trout	Whole	10	10	0.8-3.7	1.6	Wet	Lake Michigan	NR	84	7	
	Br. Trout	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Br. Trout	Fillets	1	1	11	11	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Rb. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Whole	1	1	89	89	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Lake Trout	Fillets	1	1	28	28	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Whole	1	1	160	160	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Coho Salmon	Fillets	1	1	280	280	NR	Lake Ontario	NR	NR	8	composite 3 samples
	Cod	Fillets	4	3	ND-11	4.95	Fresh	Various, Sweden	Industrial	88	9	
	Haddock	Fillets	1	0	ND(3.6)	NA	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
	P. Flounder	Fillets	1	1	3.4	3.4	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
	Plaice	Fillets	1	1	424	424	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
1,2,3,4,6,7,8,9-OCDD	Flounder	Fillets	1	1	2.4	2.4	Fresh	Various, Sweden	Industrial	88	9	composite 10 samples
(continued)	Eel	Fillets	4	3	ND-770	204	Fresh	Various, Sweden	Industrial	87-88	9	
	Mussel	Muscle	3	3	12-140	62.0	Fresh	Grenlandsfjord,Sweden	Industrial	87	9	
	Shrimp	Muscle	2	1	ND-18	9.0	Fresh	Grenlandsfjord,Sweden	Industrial	88	9	
	Cod	Fillets	6	NR	0.63-2.2	NR	Fresh	Frierfjord, Sweden	Industrial	87	9	only conc. range given
	Carp	Whole	2	2	3-5	4	NR	Lake Huron	NR	NR	10	samples composite 3-5 fish
	Pike	Muscle	8	8	10-17	14.75	Fat	Lake Vanern, Sweden	Industrial	88	11	samples composite 2-5 fish

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Pike	Muscle	1	1	22	22	Fat	Hedesunda Bay, Sweden	Industrial	88	11	composite 5 fish
	Herring	Fillet	1	1	0.34	0.34	Fresh	Baltic Sea, Sweden	NR	88	14	sample composite 12 fillets
	Herring	NR	1	1	19	19	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Cod	NR	1	1	83	83	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Redfish	NR	1	1	11	11	Fat	Berlin, W. Germany	Urban	NR	15	purchased at different shops
	Plaice	Whole	3	3	1.40-3.20	2.12	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Mackerel	Whole	1	1	4.81	4.81	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Herring	Whole	1	1	3.4	3.4	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Cod	Whole	1	1	2.79	2.79	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Skate	Whole	1	1	1.36	1.36	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Coley	Whole	1	1	2.25	2.25	Wet	Norwich, UK	NR	88	16	purchased at retail outlet
	Fish	Whole	1	1	4.0	4.0	Wet	Port Talbot, UK	Urban/ Industrial	88	17	
	Fish	Whole	1	1	1.6	1.6	Wet	Stonehaven, UK	Rural	91	17	
	Ocean Fish	Mixed	13	NR	NR	31.6	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
1,2,3,4,6,7,8,9-OCDD	Fresh Fish	Mixed	10	NR	NR	122	Fat	Various U.S. Sites	Urban	NR	18	purchased at supermarket
(continued)	Oyster	Whole	3	3	250-1100	536.67	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Body	3	3	240-470	320	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Blue Crab	Claw	3	3	250-400	303.33	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Head	2	2	66-80	73	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Crawfish	Tail	2	2	210-240	225	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Catfish	Fillet	3	3	400-1100	800	Fat	S. Mississippi	Farm raised	94	13	purchased at supermarket
	Mullett	Fillet	2	2	8.7-32	20.35	Fat	S. Mississippi	NR	94	13	purchased at supermarket

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Spanish Mackerel	Fillet	1	1	76	76	Fat	S. Mississippi	NR	94	13	purchased at supermarket
	Fish	NR	138	NR	2-426	20.5	Fat	Germany	NR	93-96	19	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	126.9	Fat	Catalonia, Spain	NR	96	20	purchased at supermarkets
	Freshwater Fish	NR	NR	NR	NR	5.94	Fat	Russia	NR	96	21	purchased at supermarkets

Footnote References

[a] Ch. = Channel; Y. = Yellow; Sm. M. = Small Mouth; Str. = Striped; Br. = Brown; Rb. = Rainbow; P. = Pole.

[b] Various, Netherlands = samples taken from six locations around Ijsselmeer Lake; Various, Michigan = samples taken from Tittabawassee River, Grand River, Saginaw River, Saginaw Bay, and Lake Michigan; Various, Sweden = samples taken from Grenlandsfjord and Frierfjord; Various US = samples taken from 314 sites across the US, including industrial and background sites.

[c] Species were taken from both bottom feeders and open water feeders, and then composited.

[d] Whole fish samples and fillet samples were combined during analysis.

Table B-11. Environmental Levels of Dioxins in Fish (ppt) (continued)

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects;
NA = not applicable;
ND = non-detected (limit of detection);
NR = not reported;
Descriptions provided were those given by reference or surmised from study description when not given;
One half the detection limit was used in calculating means. Therefore, it is possible to have mean concentrations greater than the range (e.g., reported detection limit for nondetects greater than the positive sample).

Sources:
1. Van den Berg (1987)
2. Frommberger (1991)
3. Gotz and Schumacher (1990)
4. Rappe et al. (1989b)
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13. Fiedler et al. (1997)
14. DeWit et al. (1990)
15. Beck et al. (1989)
16. Startin et al. (1990)
17. MAFF (1992)
18. Schecter et al. (1996)
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20. Domingo et al. (1999)
21. Amirova et al. (1997)

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
Tetrachlorodibenzofurans (MW=305.98)												
2,3,7,8-TCDF	Eel	Liver	6	0	ND	NA	NR	Various, Netherlands	NR	NR	1	one sample near dump site
	Eel	Fillets	5	5	2.1-12	6.98	Fat	Rhine River, Germany	NR	88	2	up & downstream Basal
	Br. Trout	Fillets	1	1	45	45	Fat	Neckar River, Germany	Urban	88	2	composite sample
	Grayling	Fillets	1	1	108	108	Fat	Neckar River, Germany	Urban	88	2	
	Barbel	Fillets	1	1	57	57	Fat	Neckar River, Germany	Urban	88	2	
	Carp	Fillets	1	1	58	58	Fat	Neckar River, Germany	Urban	88	2	
	Chub	Fillets	1	1	128	128	Fat	Neckar River, Germany	Urban	88	2	composite sample
	Eel	Fillets	5	5	0.9-2.0	1.35	Fat	Neckar River, Germany	Urban	87-88	2	
	Herring	Whole	1	1	1.7	1.7	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	2	5.3-5.5	5.4	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
	Herring	Whole	2	2	3.0-6.2	4.6	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Salmon	Muscle	2	2	28-35	31.5	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	wild salmon
	Salmon	Muscle	2	2	7.8-9.0	8.4	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	hatched salmon
	Perch	NR	3	3	2.1-8.7	5.4	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	caught near pulp mill
	Artic Char	NR	5	5	21-75	55	Fresh	Lake Vattern, Sweden	NR	NR	4	
	Carp	Whole	3	3	1.8-3.0	2.6	NR	Mississippi River, MN	Industrial	NR	5	Elk river power station
	Carp	Whole	3	3	1.0-1.3	1.1	NR	Lake Orono, MN	Industrial	NR	5	Elk river power station
	Carp	Fillets	1	1	49	49	NR	NR	NR	78	6	contamimated site
	Catfish	Fillets	1	1	6	6	NR	Saginaw River	NR	84	6	contaminated site

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDF (continued)	Smk. Chub	Fillets	1	1	3	3	NR	NR	NR	85	6	contaminated site
	Str. Bass	Fillets	5	5	7-93	28.0	NR	Hudson River	NR	85	6	contaminated site
	Lg. M. Bass	Fillets	1	1	10	10	NR	Hudson River	NR	85	6	contaminated site
	Lake Trout	Fillets	3	3	11-56	31.7	NR	Lake Superior	NR	85	6	contaminted site
	Blue Crab	Meat	2	2	11.0-15.5	13.2	Wet	Passaic River, NJ	Urban	NR	7	
	Lobster	Meat	2	2	3.5-4.1	3.8	Wet	New York Bight	Dump Site	NR	7	former sewage sludge
	Str. Bass	Fillets	2	2	51.9-85.5	68.7	Wet	Newark Bay, NJ	Urban	NR	7	
	Lake Trout	Whole	1	1	14.8	14.8	Wet	Lake Superior	NR	84	8	mean 5 samples
	Lake Trout	Whole	1	1	22.8	22.8	Wet	Lake Huron	NR	84	8	mean 5 samples
	Lake Trout	Whole	3	3	34.8-42.3	39.5	Wet	Lake Michigan	NR	84	8	range 3 sample sites
	Walleye	Whole	1	1	11.3	11.3	Wet	Lake Erie	NR	84	8	mean 5 samples
	Walleye	Whole	1	1	24.8	24.8	Wet	Lake St. Clair	NR	84	8	mean 5 samples
	Lake Trout	Whole	1	1	18.5	18.5	Wet	Lake Ontario	NR	84	8	mean 5 samples
	Lake Trout	Whole	10	10	27.0-56.0	38.4	Wet	Lake Michigan	NR	84	8	
	Br. Trout	Whole	1	1	11	11	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Br. Trout	Fillets	1	1	8	8	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Whole	1	1	19	19	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Whole	1	1	15	15	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Whole	1	1	20	20	NR	Lake Ontario	NR	NR	9	composite 3 samples

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDF (continued)	Coho Salmon	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Cod	Fillets	4	4	0.2-1.4	0.62	Fresh	Various, Sweden	Industrial	88	10	
	Haddock	Fillets	1	1	0.75	0.75	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	P. Flounder	Fillets	1	1	0.28	0.28	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	Plaice	Fillets	1	1	1.4	1.4	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	Flounder	Fillets	1	1	1.2	1.2	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	Eel	Fillets	4	3	ND-68	17.1	Fresh	Various, Sweden	Industrial	88	10	
	Mussel	Muscle	3	3	16.1-61	32.4	Fresh	Grenlandsfjord,Sweden	Industrial	87	10	
	Shrimp	Muscle	2	2	6.1-37	21.6	Fresh	Grenlandsfjord,Sweden	Industrial	88	10	
	Cod	Fillets	6	NR	0.49-14.3	NR	Fresh	Frierfjord, Sweden	Industrial	87	10	only conc. range given
	Carp	Whole	2	2	11	NA	NR	Lake Huron	NR	NR	11	samples composite 3-5 fish
	Pike	Muscle	8	8	330-3000	774	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	1	430	430	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Various[c]	Mixed[d]	314	279	NR	13.6	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Sucker	Whole	15	12	ND-6.21	1.96	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.23-0.59)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	1	ND-0.86	1.24	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.95)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	2	0.19-0.30	0.25	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(0.49)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDF (continued)	Carp	Whole	5	4	ND-1.36	0.96	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	1	ND-0.29	0.37	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	2	0.75-0.90	0.83	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(0.48)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	1	2.30	2.30	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	1.77	1.77	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.41)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	1	ND-0.86	0.41	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.20-0.24)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(0.49)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(0.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(0.71)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDF (continued)	Dolly Varden	Whole	2	2	0.37	0.37	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	1	0.86	0.86	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	2	13.30-13.73	13.52	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	1	1.93	1.93	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	1	1.14	1.14	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(0.57)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	3	14-48	29.67	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	26-51	34.67	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	9.8-15	13.6	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	5.1-5.4	5.25	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	2.8-9.5	6.15	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	3	0.64-0.99	0.84	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	2	1.1-7.8	4.45	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	11	NA	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	1	7.6	7.6	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Herring	NR	1	1	57	57	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	98	98	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	78	78	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.90-1.86	1.32	Wet	Norwich, UK	NR	88	17	purchased at retail outlet

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,7,8-TCDF (continued)	Mackeral	Whole	1	1	2.61	2.61	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	2.47	2.47	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	1	0.22	0.22	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Skate	Whole	1	1	0.31	0.31	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	1	0.14	0.14	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.6	0.6	Wet	Port Talbot, UK	Urban/ Industrial	1988	18	
	Fish	Whole	1	1	0.29	0.29	Wet	Stonehaven, UK	Rural	1991	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	14.4	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0.18-42.81	66.5	Fat	Germany	NR	93-96	20	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	11.1	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	9.98	Fat	Russia	NR	96	22	purchased in supermarkets
TCDFs	Bream	NR	13	13	7.8-86.5	44.3	Fresh	Hamburg, Germany	Urban	84	3	
	Perch	NR	2	2	10.7-41.1	25.9	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	3	2.4-4.0	3.1	NR	Mississippi River, MN	Industrial	NR	5	Elk river power station
	Carp	Whole	3	3	1.0-1.3	1.2	NR	Lake Orono, MN	Industrial	NR	5	Elk river power station
	Blue Crab	Meat	2	2	133-164	149	Wet	Passaic River, NJ	Urban	NR	7	
	Lobster	Meat	2	2	23.0-31.2	27.1	Wet	New York Bight	Dump Site	NR	7	former sewage sludge
	Str. Bass	Fillets	2	2	77.2-108	92.4	Wet	Newark Bay, NJ	Urban	NR	7	
TCDFs (continued)	Br. Trout	Whole	1	1	11	11	NR	Lake Ontario	NR	NR	9	composite 3 samples

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Br. Trout	Fillets	1	1	8	8	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Whole	1	1	19	19	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Whole	1	1	18	18	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Whole	1	1	20	20	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Fillets	1	1	6	6	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Oyster	Whole	3	3	96-170	122	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	69-82	74.67	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	49-96	66	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	47-93	70	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	34-120	78.50	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	15	15	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Ocean Fish	Mixed	13	NR	NR	17.8	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	40.4	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
TCDFs other than 2,3,7,8-TCDF	Eel	Fillets	5	5	4.6-13	8.8	Fat	Rhine River, Germany	NR	88	2	up & downstream Basal
	Grayling	Fillets	1	1	142	142	Fat	Neckar River, Germany	Urban	88	2	
	Barbel	Fillets	1	1	77	77	Fat	Neckar River, Germany	Urban	88	2	
	Carp	Fillets	1	1	14	14	Fat	Neckar River, Germany	Urban	88	2	
	Chub	Fillets	1	1	17	17	Fat	Neckar River, Germany	Urban	88	2	sample composite 5 chubs
	Eel	Fillets	1	1	1.5	1.5	Fat	Neckar River, Germany	Urban	88	2	sample composite 2 eels

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
Pentachlorodibenzofurans (MW=340.42)												
1,2,3,7,8-PeCDF	Herring	Whole	1	1	0.4	0.4	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	2	1.4-2.5	1.95	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
	Herring	Whole	2	2	0.8-0.9	0.85	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Carp	Whole	2	2	1-5	3	NR	Lake Huron	NR	NR	11	samples composite 3-5 fish
	Pike	Muscle	8	8	43-140	73.2	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	1	39	39	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Various[c]	Mixed[d]	314	151	NR	1.71	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Sucker	Whole	15	1	ND-0.62	0.33	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.33-0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(0.76-0.82)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(0.59)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	1	ND-0.33	0.16	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	5	0	ND(0.56-0.80)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	1	ND-0.92	0.69	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.36)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.20-0.35)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,7,8-PeCDF (continued)	Rainbow Trout	Fillet	2	1	ND-0.47	0.51	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(0.90)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.25)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(0.77)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.20-0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.19-0.28)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(0.77)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(0.77)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	2	1.74-1.90	1.82	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,7,8-PeCDF	Bluefish	Whole	1	1	1.06	1.06	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
(continued)	White Catfish	Whole	1	1	0.73	0.73	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	34	34	0.1-1.90	0.43	Wet	Various, US	Background[e]	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	3	1.2-1.4	1.3	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	1.3-2.9	2.03	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	0.69-1.6	1.2	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	1.2-2	1.6	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	1.6-3.2	2.4	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	3	0.11-0.21	0.15	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	2	0.52-1.3	0.91	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	3.5	3.5	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	1	4.2	4.2	Fresh	Baltic Sea, Sweden		88	15	sample composite 12 fillets
	Herring	NR	1	1	16	16	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	48	48	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	31	31	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.14-0.23	0.18	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	1	0.08	0.08	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	0.47	0.47	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	1	0.05	0.05	Wet	Norwich, UK	NR	88	17	purchased at retail outlet

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,7,8-PeCDF	Skate	Whole	1	1	0.07	0.07	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
(continued)	Coley	Whole	1	1	0.07	0.07	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	8	NR	0.05-0.47	0.16	Wet	Norwich, UK	NR	88	18	
	Fish	Whole	1	1	0.08	0.08	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0-268	7.3	Fat	Germany	NR	93-96	20	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	3.7	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	2.46	Fat	Russia	NR	96	22	purchased in supermarkets
2,3,4,7,8-PeCDF	Herring	Whole	1	1	3.0	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	2	6.8-19.0	12.9	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
	Herring	Whole	2	2	8.8-8.9	8.85	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Carp	Whole	2	2	4-11	7.5	NR	Lake Huron	NR	NR	11	samples composite 3-5 fish
	Pike	Muscle	8	8	120-290	189	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	1	110	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	6	ND-1.36	0.46	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.33-0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(0.76-0.82)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
2,3,4,7,8-PeCDF	Rock Bass	Fillet	1	0	ND(0.59)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
(continued)	Sm Bass	Fillet	2	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	5	2	ND-0.34	0.35	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	1	ND-1.33	0.82	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.36)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.20-0.35)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	2	0.70	0.70	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(0.90)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.25)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(0.95)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(0.92)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.20-0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.19-0.28)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
2,3,4,7,8-PeCDF (continued)	Summer Flounder	Whole	1	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	2	0.64-0.70	0.67	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	1	0.93	0.93	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	1	1.39	1.39	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(0.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	201	NR	3.06	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	3	4.3-5.8	5.2	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	7-9	8.17	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	2.8-5.9	4.27	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	1.4-2.3	1.85	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	2.1-2.4	2.25	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	3	0.26-0.31	0.28	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	2	0.62-4.6	2.61	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	5.1	5.1	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	1	17.0	17.0	Fresh	Baltic Sea, Sweden		88	15	sample composite 12 fillets
	Herring	NR	1	1	29	29	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	3.1	3.1	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
2,3,4,7,8-PeCDF	Redfish	NR	1	1	25	25	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
(continued)	Plaice	Whole	3	3	0.39-1.58	0.95	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	1	0.37	0.37	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	1.96	1.96	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	1	0.03	0.03	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Skate	Whole	1	0	ND(0.04)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	1	0.04	0.04	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.68	0.68	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Fish	Whole	1	1	0.07	0.07	Wet	Stonehaven, UK	Rural	88-91	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	7.56	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0.12-669	14.4	Fat	Germany	NR	93-96	20	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	4.4	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	3.77	Fat	Russia	NR	96	22	purchased in supermarkets
PeCDFs	Bream	NR	13	13	13.9-114	65.4	Fresh	Hamburg, Germany	Urban	84	3	
	Perch	NR	2	2	62.3-153	108	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	3	15-45	26.3	NR	Mississippi River, MN	Industrial	NR	5	Elk river power station
	Carp	Whole	3	2	ND-13	9.0	NR	Lake Orono, MN	Industrial	NR	5	Elk river power station
	Blue Crab	Meat	2	2	89.7-94.1	91.9	Wet	Passaic River, NJ	Urban	NR	7	
PeCDFs (continued)	Lobster	Meat	2	2	29.8-37.3	33.6	Wet	New York Bight	Dump Site	NR	7	former sewage sludge
	Str. Bass	Fillets	2	2	34.3-82.6	58.4	Wet	Newark Bay, NJ	Urban	NR	7	

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Br. Trout	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Br. Trout	Fillets	1	1	3	3	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Whole	1	1	8	8	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Fillets	1	1	7	7	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Whole	1	1	39	39	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Fillets	1	1	8	8	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Whole	1	1	13	13	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Oyster	Whole	3	3	56-66	59.67	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	110-200	146.67	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	43-110	71.33	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	29-54	41.50	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	20-39	29.5	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	15	15	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Ocean Fish	Mixed	13	NR	NR	8.75	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	NR	NR	21.7	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
PeCDFs other than 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF	Grayling	Fillets	1	1	22	22	Fat	Neckar River, Germany	Urban	88	2	
	Barbel	Fillets	1	1	21	21	Fat	Neckar River, Germany	Urban	88	2	
	Carp	Fillets	1	1	17	17	Fat	Neckar River, Germany	Urban	88	2	
Hexachlorodibenzofurans (MW=374.87)												
1,2,3,4,7,8-HxCDF	Herring	Whole	1	1	0.2	0.2	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	2	0.4-0.7	0.55	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Herring	Whole	2	2	0.3	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Carp	Whole	2	2	2-5	3.5	NR	Lake Huron	NR	NR	11	samples composite 3-5 fish
	Pike	Muscle	8	8	10-33	14.4	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	1	11	11	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	0	ND(0.33-2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.41-2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(1.13-1.30)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(0.72)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(2.83-2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	5	1	ND-0.40	0.98	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	1	ND-1.24	0.81	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.23-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(0.45-0.58)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
1,2,3,4,7,8-HxCDF	Brook Trout	Fillet	1	0	ND(1.46)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
(continued)	Gray Redhorse	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(2.82)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Golden Redhorse	Whole	1	1	1.18	1.18	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.21-2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.20-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(2.83)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(2.83)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(2.83-2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(2.83)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
1,2,3,4,7,8-HxCDF	Various[c]	Mixed[d]	314	132	NR	2.35	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
(continued)	Oyster	Whole	3	1	ND-0.41	0.22	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	5.8-9.7	7.5	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	3-4.1	3.53	Fat	S. Mississippi	NR	94	14	purchased at supermarket

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Crawfish	Head	2	2	0.91-4.7	2.81	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	1	ND-1.9	1.53	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	1	ND-0.39	0.25	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	1	ND-7.6	3.94	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	2.5	2.5	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	NR	1	1	3.0	3.0	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	6.9	6.9	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	3.5	3.5	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.05-0.16	0.11	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	0	ND(0.02)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	0.12	0.12	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	0	ND(0.1)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Skate	Whole	1	1	0.04	0.04	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	1	0.03	0.03	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.06	0.06	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,4,7,8-HxCDF (continued)	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0.11-62	2.8	Fat	Germany	NR	93-96	20	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	2.2	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	4.66	Fat	Russia	NR	96	22	purchased in supermarkets
1,2,3,6,7,8-HxCDF	Herring	Whole	1	1	0.1	0.1	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	2	0.4-0.8	0.6	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
	Herring	Whole	2	2	0.2	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Pike	Muscle	8	8	5.6-22	11.9	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	1	5.6	5.6	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	0	ND(0.26-2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.41-2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(1.13-1.30)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(0.72)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(2.84-2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	5	0	ND(0.52-2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	1	ND-1.35	0.87	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,6,7,8-HxCDF	Brown Trout	Whole	1	0	ND(0.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
(continued)	Brown Trout	Fillet	2	0	ND(0.23-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(0.45-0.58)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.46)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(2.83)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.21-2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.20-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,6,7,8-HxCDF (continued)	Winter Flounder	Whole	2	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(2.84)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(2.85)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	66	NR	1.74	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	3	0.29-0.79	0.47	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	2.8-3.6	3.13	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	1.6-2.1	1.9	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	0.63-1.8	1.22	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	0	ND(0.7-1.05)	0.88	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	1	ND-0.18	0.02	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	0	ND(0.24-1.1)	0.67	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	2.1	2.1	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	1	1.7	1.7	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Herring	NR	1	1	4.2	4.2	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	13	13	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	6.0	6.0	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.02-0.06	0.04	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	1	0.06	0.06	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	0.16	0.16	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
1,2,3,6,7,8-HxCDF	Cod	Whole	1	0	ND(0.1)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
(continued)	Skate	Whole	1	1	0.05	0.05	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	1	0.06	0.06	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.04	0.04	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0-36.5	2.1	Fat	Germany	NR	93-96	20	official foor inspection samples
	Fish & Seafood	NR	8	NR	NR	0.7	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	1.69	Fat	Russia	NR	96	22	purchased in supermarkets
1,2,3,7,8,9-HxCDF	Pike	Muscle	8	0	ND(3-6)	NA	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	0	ND(6)	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	0	ND(0.26-2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.41-2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(1.13-1.30)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(0.72)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(2.77-2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
1,2,3,7,8,9-HxCDF (continued)	Carp	Whole	5	0	ND(0.52-2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	not available	Whole	2	0	ND(0.77-0.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.23-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(0.39-0.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.46)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	lack Redhorse	Whole	1	0	ND(2.76)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.21-2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.20-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(2.77)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
1,2,3,7,8,9-HxCDF	Dolly Varden	Whole	2	0	ND(2.77)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
(continued)	Composite Bottom	Whole	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(2.77-2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(2.77)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(2.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	3	NR	1.22	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	0	ND(0.15-0.22)	0.17	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	0	ND(0.09-0.13)	0.11	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	0	ND(0.6-0.9)	0.75	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	0.7-0.31	0.51	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	0	ND(0.85-1.4)	1.13	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	0	ND(0.05-0.08)	0.04	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	0	ND(0.34-1.6)	0.97	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	ND(0.22)	0.22	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	0	ND(0.04)	NA	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Plaice	Whole	3	1	ND-0.02	0.015	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	0	ND(0.04)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
1,2,3,7,8,9-HxCDF	Herring	Whole	1	0	ND(0.05)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
(continued)	Cod	Whole	1	0	ND(0.1)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Skate	Whole	1	0	ND(0.05)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	0	ND(0.04)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0-0.5	0.01	Fat	Germany	NR	93-96	20	official foor inspection samples
	Fish & Seafood	NR	8	NR	NR	0.5	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	2.74	Fat	Russia	NR	96	22	purchased in supermarkets
2,3,4,6,7,8-HxCDF	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	2	0.4-0.8	0.6	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
	Herring	Whole	2	2	0.3	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Pike	Muscle	8	7	ND(3-17)	7.96	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	0	ND(6)	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	0	ND(0.26-1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	4	0	ND(0.41-1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(1.13-1.30)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(0.72)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
2,3,4,6,7,8-HxCDF (continued)	Sm Bass	Fillet	2	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	5	1	ND-0.92	0.76	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	not available	Whole	2	0	ND(0.78-2.72)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Whole	1	0	ND(0.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.23-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(0.45-0.58)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(1.46)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(1.95)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	1.25	1.25	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(0.52)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.21-1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.20-0.42)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.20)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(1.97)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
2,3,4,6,7,8-HxCDF (continued)	Summer Flounder	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(1.95-1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Composite Bottom	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(1.96)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	100	NR	1.24	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	3	0.59-0.65	0.72	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	2.2-2.6	2.33	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	0	ND(0.6-0.85)	0.73	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	0.38-1.8	1.09	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	0	ND(0.85-1.35)	1.1	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	0	ND(0.04-0.07)	0.056	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	0	ND(0.3-1.4)	0.85	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	1.2	1.2	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	1	3.9	3.9	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Herring	NR	1	1	3.6	3.6	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
2,3,4,6,7,8-HxCDF (continued)	Cod	NR	1	1	8.2	8.2	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	7.2	7.2	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.04-0.13	0.08	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	1	0.03	0.03	Wet	Norwich, UK	NR	88	17	purchased at retail outlet

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Herring	Whole	1	1	0.15	0.15	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	0	ND(0.1)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Skate	Whole	1	1	0.04	0.04	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	1	0.03	0.03	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.07	0.07	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0-29	1.8	Fat	Germany	NR	93-96	20	official food inspection samples
	Fish & Seafood	NR	8	0	ND	NA	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	2.31	Fat	Russia	NR	96	22	purchased in supermarkets
HxCDFs	Bream	NR	13	13	5.7-47.4	25.2	Fresh	Hamburg, Germany	Urban	84	3	
	Perch	NR	2	2	21.9-53.8	37.8	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	2	ND-24	10.0	NR	Mississippi River, MN	Industrial	NR	5	Elk river power station
	Carp	Whole	3	3	2.7-5.1	3.5	NR	Lake Orono, MN	Industrial	NR	5	Elk river power station
	Blue Crab	Meat	2	2	9.3-9.4	9.35	Wet	Passaic River, NJ	Urban	NR	7	
HxCDFs (continued)	Lobster	Meat	2	2	7.7-7.9	7.8	Wet	New York Bight	Dump Site	NR	7	former sewage sludge
	Str. Bass	Fillets	2	2	2.0-4.4	3.2	Wet	Newark Bay, NJ	Urban	NR	7	
	Br. Trout	Whole	1	1	2	2	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Br. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Whole	1	1	8	8	NR	Lake Ontario	NR	NR	9	composite 3 samples

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Rb. Trout	Fillets	1	1	2	2	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Whole	1	1	16	16	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Oyster	Whole	3	3	6.6-22	13.53	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	86-150	115.33	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	3	35-73	49	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	8.9-63	35.95	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	7.5-53	30.25	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	11	NA	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
non-2,3,7,8-HxCDFs	Barbel	Fillets	1	1	2.1	2.1	Fat	Neckar River, Germany	Urban	88	2	
Heptachlorodibenzofurans (MW=409.31)												
1,2,3,4,6,7,8-HpCDF	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
1,2,3,4,6,7,8-HpCDF	Herring	Whole	2	2	0.8-1.2	1.0	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
(continued)	Herring	Whole	2	1	ND-0.9	0.5	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Carp	Whole	2	2	3-4	3.5	NR	Lake Huron	NR	NR	11	samples composite 3-5 fish
	Pike	Muscle	16	1	ND(3-7)-17	3.41	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	2	0	ND(6-11)	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	3	ND-1.88	0.96	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Lm Bass	Fillet	2	0	ND(1.44-1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(6.61-8.89)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.40)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	5	3	ND-1.31	0.71	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	1	ND-1.13	2.21	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.77-0.80)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	1	ND-0.48	0.56	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(4.13)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Gray Redhorse	Whole	1	0	ND(2.75)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Redhorse	Whole	1	0	ND(2.25)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	1	1.25	1.25	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,4,6,7,8-HpCDF (continued)	Longear Sunfish	Whole	1	0	ND(3.11)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.71-1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.27-1.28)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.35)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	1	0.27	0.27	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(1.44-1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	1	0.23	0.23	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(1.78)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(1.45)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	170	NR	1.91	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
	Oyster	Whole	3	3	1.3-1.8	1.5	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	6-7.7	6.83	Fat	S. Mississippi	NR	94	14	purchased at supermarket

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,4,6,7,8-HpCDF (continued)	Blue Crab	Claw	3	3	4.4-6.2	5.13	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	1-7.3	4.15	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	4.9-9.9	7.4	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	1	ND-42	0.18	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	2	1.5-3.1	2.3	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	2.1	2.1	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	1	0.38	0.38	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Herring	NR	1	1	1.6	1.6	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	10	10	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	1.5	1.5	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.04-0.10	0.07	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	1	0.07	0.07	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	0.14	0.14	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	0	ND(0.2)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Skate	Whole	1	1	0.06	0.06	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	1	0.05	0.05	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.10	0.10	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Fish	Whole	1	1	0.08	0.08	Wet	Stonehaven, UK	Rural	91	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
1,2,3,4,6,7,8-HpCDF (continued)	Fish	NR	138	NR	0-14.1	1.3	Fat	Germany	NR	93-96	20	official food inspection samples

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Fish & Seafood	NR	8	NR	NR	2.0	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	6.74	Fat	Russia	NR	96	22	purchased in supermarkets
1,2,3,4,7,8,9-HpCDF	Pike	Muscle	8	0	ND(3-11)	NA	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish
	Pike	Muscle	1	0	ND(6)	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Sucker	Whole	15	0	ND(0.71-4.23)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Lm Bass	Fillet	2	0	ND(2.61-2.26)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Whole	2	0	ND(2.64-5.92)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rock Bass	Fillet	1	0	ND(1.40)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sm Bass	Fillet	2	0	ND(2.61-2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Redeye Bass	Fillet	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Carp	Whole	3	0	ND(2.61-2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	not available	Whole	2	0	ND(1.12-1.64)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brown Trout	Fillet	2	0	ND(0.77-0.80)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Rainbow Trout	Fillet	2	0	ND(0.63-0.91)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Brook Trout	Fillet	1	0	ND(4.13)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
1,2,3,4,7,8,9-HpCDF	Gray Redhorse	Whole	1	0	ND(2.75)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
(continued)	Black Redhorse	Whole	1	0	ND(3.82)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Golden Redhorse	Whole	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Longear Sunfish	Whole	1	0	ND(3.11)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Walleye	Fillet	3	0	ND(0.71-2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Chain Pickerel	Fillet	3	0	ND(0.27-1.28)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Black Crappie	Fillet	1	0	ND(0.23)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Sea Catfish	Fillet	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	North Hogsucker	Whole	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Summer Flounder	Whole	1	0	ND(2.61)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Dolly Varden	Whole	2	0	ND(2.61)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Composite Bottom	Whole	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Winter Flounder	Whole	2	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Bluefish	Whole	1	0	ND(3.12)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	White Catfish	Whole	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Crayfish	Whole	1	0	ND(2.62)	NA	Wet	Various, US	Background	86-89	13	samples composite 3-5 fish
	Various[c]	Mixed[d]	314	13	NR	1.24	Wet	Various, US	Various	86-89	13	samples composite 3-5 fish
1,2,3,4,7,8,9-HpCDF (continued)	Oyster	Whole	3	0	ND(0.15-0.21)	0.17	Fat	S. Mississippi	NR	94	14	purchased at supermarket

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Blue Crab	Body	3	1	ND-0.79	0.33	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	0	ND(0.65-0.95)	0.8	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	2	0.19-0.47	0.28	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	0	ND(0.95-1.4)	1.18	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	0	ND(0.07-0.09)	0.08	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	0	ND(0.33-1.5)	0.92	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	0	ND(0.44)	0.44	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	0	ND(0.04)	NA	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Plaice	Whole	3	1	ND-0.02	0.03	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	0	ND(0.08)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	0	ND(0.06)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	0	ND(0.2)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Skate	Whole	1	0	ND(0.13)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Coley	Whole	1	0	ND(0.10)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	0	<0.01	<0.01	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,4,7,8,9-HpCDF (continued)	Fish	NR	138	NR	0-1.1	0.08	Fat	Germany	NR	93-96	20	official foor inspection samples
	Fish & Seafood	NR	8	NR	NR	0.3	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	2.26	Fat	Russia	NR	96	22	purchased in supermarkets
HpCDFs	Bream	NR	13	13	1.8-6.0	3.6	Fresh	Hamburg, Germany	Urban	84	3	
	Perch	NR	2	2	5.0-10.1	7.6	Fresh	Hamburg, Germany	Urban	84	3	
	Carp	Whole	3	1	ND-14	4.7	NR	Mississippi River, MN	Industrial	NR	5	Elk river power station
	Carp	Whole	3	0	ND(6.6)	NA	NR	Lake Orono, MN	Industrial	NR	5	Elk river power station
	Blue Crab	Meat	2	2	2.8-3.5	3.15	Wet	Passaic River, NJ	Urban	NR	7	
	Lobster	Meat	2	0	ND(0.9)	NA	Wet	New York Bight	Dump Site	NR	7	former sewage sludge
	Str. Bass	Fillets	2	2	1.3-2.4	1.8	Wet	Newark Bay, NJ	Urban	NR	7	
	Br. Trout	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Br. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Whole	1	1	1	1	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Whole	1	1	1	1	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Oyster	Whole	3	3	2.3-3.2	2.87	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	3	8.1-12	9.53	Fat	S. Mississippi	NR	94	14	purchased at supermarket
HpCDFs (continued)	Blue Crab	Claw	3	3	4.6-6.6	5.43	Fat	S. Mississippi	NR	94	14	purchased at supermarket

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Crawfish	Head	2	2	1.1-7.8	4.45	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	5.2-14	9.6	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	3.3	3.3	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fresh Fish	Mixed	10	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
Octachlorodibenzofurans (MW=444.76)												
1,2,3,4,6,7,8,9-OCDF	Bream	NR	14	10	ND-3.1	1.2	Fresh	Hamburg, Germany	Urban	84	3	
	Perch	NR	3	3	1.1-8.3	3.7	Fresh	Hamburg, Germany	Urban	84	3	
	Herring	Whole	1	0	ND(0.2)	NA	Fresh	Atlantic Coast, Sweden	Pristine	NR	4	composite 2-5 fish
	Herring	Whole	2	1	ND-0.3	0.2	Fresh	Baltic Sea, Sweden	Urban	NR	4	composite 2-5 fish
	Herring	Whole	2	0	ND(0.2)	NA	Fresh	Gulf of Bothnia, Sweden	Industrial	NR	4	composite 2-5 fish
	Salmon	Muscle	2	0	ND(2.0)	NA	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	wild salmon
	Salmon	Muscle	2	0	ND(0.5)	NA	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	hatched salmon
	Perch	NR	3	1	ND-1.7	0.57	Fresh	Gulf of Bothnia, Sweden	NR	NR	4	caught near pulp mill
	Carp	Whole	3	0	ND(6.6)	NA	NR	Mississippi River, MN	Industrial	NR	5	Elk river power station
	Carp	Whole	3	3	ND(6.6)	NA	NR	Lake Orono, MN	Industrial	NR	5	Elk river power station
	Blue Crab	Meat	2	0	ND(8.3)	NA	Wet	Passaic River, NJ	Urban	NR	7	
	Lobster	Meat	2	0	ND(8.4)	NA	Wet	New York Bight	Dump Site	NR	7	former sewage sludge
	Str. Bass	Fillets	2	0	ND(3.1)	NA	Wet	Newark Bay, NJ	Urban	NR	7	
	Lake Trout	Whole	1	1	0.4	0.4	Wet	Lake Superior	NR	84	8	mean 5 samples
1,2,3,4,6,7,8,9-OCDF	Lake Trout	Whole	1	1	0.1	0.1	Wet	Lake Huron	NR	84	8	mean 5 samples
(continued)	Lake Trout	Whole	3	3	0.3-1.0	0.85	Wet	Lake Michigan	NR	84	8	range 3 sample sites

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Walleye	Whole	1	1	0.9	0.9	Wet	Lake Erie	NR	84	8	mean 5 samples
	Walleye	Whole	1	1	0.4	0.4	Wet	Lake St. Clair	NR	84	8	mean 5 samples
	Lake Trout	Whole	1	1	0.4	0.4	Wet	Lake Ontario	NR	84	8	mean 5 samples
	Br. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Rb. Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Whole	1	1	2	2	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Lake Trout	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Whole	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Coho Salmon	Fillets	1	0	ND(7)	NA	NR	Lake Ontario	NR	NR	9	composite 3 samples
	Cod	Fillets	4	4	3.4-9.6	6.3	Fresh	Various, Sweden	Industrial	88	10	
	Haddock	Fillets	1	1	4.3	4.3	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	P. Flounder	Fillets	1	1	4.7	4.7	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	Plaice	Fillets	1	1	41	41	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	Flounder	Fillets	1	1	5.6	5.6	Fresh	Various, Sweden	Industrial	88	10	composite 10 samples
	Eel	Fillets	4	4	31-581	205	Fresh	Various, Sweden	Industrial	88	10	
	Mussel	Muscle	3	3	13.4-933	339	Fresh	Grenlandsfjord,Sweden	Industrial	87	10	
	Shrimp	Muscle	2	2	2.3-41	21.6	Fresh	Grenlandsfjord,Sweden	Industrial	88	10	
	Cod	Fillets	6	NR	ND-21	NR	Fresh	Frierfjord, Sweden	Industrial	87	10	only conc. range given
1,2,3,4,6,7,8,9-OCDF	Fresh Fish		10	0	ND	NA	Fat	Various U.S. Sites		NR	10	
(continued)	Carp	Whole	2	2	4-8	6	NR	Lake Huron	NR	NR	11	samples composite 3-5 fish
	Pike	Muscle	8	0	ND(3-11)	NA	Fat	Lake Vanern, Sweden	Industrial	88	12	samples composite 2-5 fish

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
	Pike	Muscle	1	0	ND(11)	NA	Fat	Hedesunda Bay, Sweden	Industrial	88	12	composite 5 fish
	Oyster	Whole	3	3	3.1-4.9	4.00	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Body	3	2	ND-0.77	0.5	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Blue Crab	Claw	3	0	ND(1.2-1.95)	1.52	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Head	2	0	ND(0.27-0.38)	0.16	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Crawfish	Tail	2	2	7.7-57	32.35	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Catfish	Fillet	3	0	ND(0.08-0.12)	0.96	Fat	S. Mississippi	Farm raised	94	14	purchased at supermarket
	Mullet	Fillet	2	2	1.5-6.6	4.05	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Spanish Mackerel	Fillet	1	1	1.8	1.8	Fat	S. Mississippi	NR	94	14	purchased at supermarket
	Herring	Fillet	1	0	ND(0.07)	NA	Fresh	Baltic Sea, Sweden	NR	88	15	sample composite 12 fillets
	Herring	NR	1	1	1.4	1.4	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Cod	NR	1	1	2.1	2.1	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Redfish	NR	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	16	purchased at different shops
	Plaice	Whole	3	3	0.08-0.23	0.16	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Mackeral	Whole	1	1	0.20	0.20	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Herring	Whole	1	1	0.19	0.19	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Cod	Whole	1	1	0.26	0.26	Wet	Norwich, UK	NR	88	17	purchased at retail outlet

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Chemical	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location[b]	Location description	Samp. year	Ref. no.	Comments
1,2,3,4,6,7,8,9-OCDF	Skate	Whole	1	1	0.14	0.14	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
(continued)	Coley	Whole	1	0	ND(0.30)	NA	Wet	Norwich, UK	NR	88	17	purchased at retail outlet
	Fish	Whole	1	1	0.14	0.14	Wet	Port Talbot, UK	Urban/ Industrial	88	18	
	Fish	Whole	1	1	0.20	0.02	Wet	Stonehaven, UK	Rural	91	18	
	Ocean Fish	Mixed	13	0	ND	NA	Fat	Various U.S. Sites	Urban	NR	19	purchased at supermarket
	Fish	NR	138	NR	0-46	1.2	Fat	Germany	NR	93-96	20	official food inspection samples
	Fish & Seafood	NR	8	NR	NR	8.8	Fat	Catalonia, Spain	NR	96	21	purchased in supermarkets
	Freshwater Fish	NR	NR	NR	NR	6.63	Fat	Russia	NR	96	22	purchased in supermarkets

Footnote References

[a] Br. = Brown; Smk. = Smoked; Str. = Striped; Lg. M. = Large Mouth; Rb. = Rainbow; P. = Pole; Y. = Yellow.

[b] Various, Netherlands = samples taken from six locations around IJsselmeer Lake; Various, Sweden = samples taken from Grenlandsfjord and Frierfjord; Various US = samples taken from 314 sites across the US, including industrial and background sites.

[c] Species were taken from both bottom feeders and open water feeders, and then composited.

[d] Whole fish samples and fillet samples were combined during analysis.

NOTES: Summary statistics provided in or derived from references; when reference did not compute mean, it was computed using one-half the detection limit for non-detects;
NA = not applicable;
ND = non-detected (limit of detection);
NR = not reported;
Descriptions provided were those given by reference or surmised from study description when not given;
One half the detection limit was used in calculating means. Therefore, it is possible to have mean concentrations greater than the range (e.g., reported detection limit for non detects greater than the positive sample).

Table B-12. Environmental Levels of Dibenzofurans in Fish (ppt) (continued)

Sources:

1. Van den Berg (1987)
2. Frommberger (1991)
3. Gotz and Schumacher (1990)
4. Rappe et al. (1989b)
5. Reed et al. (1990)
6. Gardner and White (1990)
7. Rappe et al. (1991)
8. DeVault et al. (1989)
9. Niimi and Oliver (1989a)
10. Oehme et al. (1989)
11. Stalling et al. (1983)
12. Kjeller et al. (1990)
13. U.S. EPA (1992)
14. Fiedler et al. (1997)
15. deWit et al. (1990)
16. Beck et al. (1989)
17. Startin et al. (1990)
18. MAFF (1992)
19. Schecter et al. (1996)
20. Malisch (1998)
21. Domingo et al. (1999)
22. Amirova et al. (1997)

Table B-13. Environmental Levels of PCBs in Fish (ppt)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
Tetrachloro-PCB (MW=291.99)												
3,3',4,4'-TCB	Baltic Herring	NR	6	NR	33-136	97	Wet	Finland	Urban	NR	1	
(77)	Rainbow Trout	NR	4	NR	80-150	100	Wet	Finland	Urban	NR	1	
	Other Fish	NR	4	NR	5.6-153	53	Wet	Finland	Urban	NR	1	3 samples of white fish and one pike perch
	Freshwater Fish	NR	NR	NR	NR	36	Wet	Canada	Urban	86-88	2	
	Ocean Fish	Mixed	NR	NR	NR	6.19	Wet	Various U.S. Locations	Urban	95	3	
	Fresh Fish	Mixed	NR	0	ND	NA	Wet	Various U.S. Locations	Urban	95	3	
	Blk. Bullhead	Whole	1	1	89,000	89,000	NR	Waukegan Harbor, IL	NR	78	4	composite 6 samples
	Lg. M. Bass	Whole	1	1	86,000	86,000	NR	Waukegan Harbor, IL	NR	78	4	
	Blk. Crappie	Whole	1	1	43,000	43,000	NR	Waukegan Harbor, IL	NR	78	4	composite 3 samples
	Wh. Sucker	Whole	1	1	50,000	50,000	NR	Waukegan Harbor, IL	NR	78	4	composite 6 samples
	Coho Salmon	Whole	1	1	2,000	2,000	NR	Waukegan Harbor, IL	NR	78	4	
	Wh. Crappie	Whole	1	1	24,000	24,000	NR	Waukegan Harbor, IL	NR	78	4	
	Y. Perch	Whole	1	1	23,000	23,000	NR	Waukegan Harbor, IL	NR	78	4	composite 5 samples
	Br. Trout	Whole	1	1	5,000	5,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
	Br. Trout	Fillets	1	1	2,000	2,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
	Lake Trout	Whole	1	1	18,000	18,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Lake Trout	Fillets	1	1	8,000	8,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Rb. Trout	Whole	2	2	6000-11,000	8,500	NR	Lake Ontario	NR	NR	5	
	Rb. Trout	Fillets	2	1	ND-4,000	2,000	NR	Lake Ontario	NR	NR	5	

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
3,3',4,4'-TCB	Coho Salmon	Whole	2	2	8000-10,000	9,000	NR	Lake Ontario	NR	NR	5	
(continued)	Coho Salmon	Fillets	2	2	3,000-5,000	4,000	NR	Lake Ontario	NR	NR	5	
	Carp	Whole	1	0	ND(5,000)	NA	NR	Saginaw Bay	NR	NR	6	
	White Catfish	Whole	3	3	38.6-120.6	89.3	Wet	San Joaquin River	Industrial	NR	9	
	Channel Catfish	Whole	2	2	14.2-1,095	554.7	Wet	Antioch	Industrial	NR	9	
	White Catfish	Whole	1	1	40.47	40.47	Wet	Sacramento River	Industrial	NR	9	
	Channel Catfish	Whole	1	1	25.99	25.99	Wet	Sacramento River	Industrial	NR	9	
	Yellowfin Goby	Whole	1	1	54.04	54.04	Wet	Sacramento River	Industrial	NR	9	
	Yellowfin Goby	Whole	1	1	54.92	54.92	Wet	San Pablo Bay	Industrial	NR	9	
	Staghorn Sculpin	Whole	1	1	38.62	38.62	Wet	San Pablo Bay	Industrial	NR	9	
	Diamond Turbot	Whole	1	1	78.91	78.91	Wet	San Pablo Bay	Industrial	NR	9	
	Starry Flounder	Whole	1	1	80.64	80.64	Wet	San Pablo Bay	Industrial	NR	9	
3,4,4',5-TCB	Br. Trout	Whole	1	1	24,000	24,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
(81)	Br. Trout	Fillets	1	1	10,000	10,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
	Lake Trout	Whole	1	1	90,000	90,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Lake Trout	Fillets	1	1	38,000	38,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Rb. Trout	Whole	2	2	13,000-30,000	21,500	NR	Lake Ontario	NR	NR	5	
	Rb. Trout	Fillets	2	1	ND-9,000	4,500	NR	Lake Ontario	NR	NR	5	

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
3,4,4',5-TCB	Coho Salmon	Whole	2	2	2,000-26,000	14,000	NR	Lake Ontario	NR	NR	5	
(81)	Coho Salmon	Fillets	2	2	8,000-14,000	11,000	NR	Lake Ontario	NR	NR	5	
(continued)	Carp	Whole	1	1	17,000	NA	NR	Saginaw Bay	NR	NR	6	
TCBs	Various[c]	Mixed[d]	362	263	NR	696,240	Wet	Various, US[b]	Various	86-89	7	samples composite 3-5 fish
Pentachloro-PCB (MW=326.44)												
3,3',4,4',5-PeCB	Baltic Herring	NR	6	NR	7.4-26	17	Wet	Finland	Urban	NR	1	
(126)	Rainbow Trout	NR	4	NR	5.2-35	17	Wet	Finland	Urban	NR	1	
	Other Fish	NR	4	NR	2.3-28	11	Wet	Finland	Urban	NR	1	3 samples of white fish and one pike perch
	Freshwater Fish	NR	NR	NR	NR	8	Wet	Canada	Urban	86-88	2	
	Ocean Fish	Mixed	NR	NR	NR	0.83	Wet	Various U.S. Locations	Urban	95	3	
	Fresh Fish	Mixed	NR	0	ND	NA	Wet	Various U.S. Locations	Urban	95	3	
	Carp	Whole	1	0	ND(5,000)	NA	NR	Saginaw Bay	NR	NR	6	
	White Catfish	Whole	3	3	14.1-66.1	36.9	Wet	San Joaquin River	Industrial	NR	9	
	Channel Catfish	Whole	2	2	17.7-211	114.2	Wet	Antioch	Industrial	NR	9	
	White Catfish	Whole	1	1	25.3	25.3	Wet	Sacramento River	Industrial	NR	9	
	Channel Catfish	Whole	1	1	21.4	21.4	Wet	Sacramento River	Industrial	NR	9	
	Yellowfin Goby	Whole	1	1	12.33	12.33	Wet	Sacramento River	Industrial	NR	9	

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
	Yellowfin Goby	Whole	1	1	15.52	15.52	Wet	San Pablo Bay	Industrial	NR	9	
3,3',4,4',5-PeCB (126) (continued)	Staghorn Sculpin	Whole	1	1	17.36	17.36	Wet	San Pablo Bay	Industrial	NR	9	
	Diamond Turbot	Whole	1	1	61.37	61.37	Wet	San Pablo Bay	Industrial	NR	9	
	Starry Flounder	Whole	1	1	27.67	27.67	Wet	San Pablo Bay	Industrial	NR	9	
2,3,3',4,4'-PeCB (105)	Baltic Herring	NR	6	NR	960-2,700	1,700	Wet	Finland	Urban	NR	1	
	Rainbow Trout	NR	4	NR	410-2,100	1,200	Wet	Finland	Urban	NR	1	
	Other Fish	NR	4	NR	113-1,100	400	Wet	Finland	Urban	NR	1	3 samples of white fish and one pike perch
	Ocean Fish	Mixed	NR	NR	NR	120	Wet	Various U.S. Locations	Urban	95	3	
	Fresh Fish	Mixed	NR	0	ND	NA	Wet	Various U.S. Locations	Urban	95	3	
	Blk. Bullhead	Whole	1	1	352,000	352,000	NR	Waukegan Harbor, IL	NR	78	4	composite 6 samples
	Lg. M. Bass	Whole	1	1	290,000	290,000	NR	Waukegan Harbor, IL	NR	78	4	
	Blk. Crappie	Whole	1	1	114,000	114,000	NR	Waukegan Harbor, IL	NR	78	4	composite 3 samples
	Wh. Sucker	Whole	1	1	483,000	483,000	NR	Waukegan Harbor, IL	NR	78	4	composite 6 samples
	Coho Salmon	Whole	1	1	45,000	45,000	NR	Waukegan Harbor, IL	NR	78	4	
	Wh. Crappie	Whole	1	1	242,000	242,000	NR	Waukegan Harbor, IL	NR	78	4	
	Y. Perch	Whole	1	1	80,000	80,000	NR	Waukegan Harbor, IL	NR	78	4	composite 5 samples
	Small Smelt	Whole	1	1	15,000	15,000	Wet	Port Credit, Lake Ontario	NR	86	8	composite 48 samples
	Large Smelt	Whole	1	1	38,000	38,000	Wet	Vineland, Lake Ontario	NR	82	8	composite 20 samples
	Salmonids	Whole	1	1	110,000	110,000	Wet	Lake Ontario	NR	81-82	8	composite 60 samples

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
	Br. Trout	Whole	1	1	55,000	55,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
2,3,3',4,4'-PeCB	Br. Trout	Fillets	1	1	24,000	24,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
(105)	Lake Trout	Whole	1	1	253,000	253,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
(continued)	Lake Trout	Fillets	1	1	101,000	101,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Rb. Trout	Whole	2	2	34,000-138,000	86,000	NR	Lake Ontario	NR	NR	5	
	Rb. Trout	Fillets	2	2	6,000-50,000	28,000	NR	Lake Ontario	NR	NR	5	
	Coho Salmon	Whole	2	2	48,000-121,000	84,500	NR	Lake Ontario	NR	NR	5	
	Coho Salmon	Fillets	2	2	19,000-56,000	37,500	NR	Lake Ontario	NR	NR	5	
	Carp	Whole	1	1	427,000	427,000	NR	Saginaw Bay	NR	NR	6	
2,3,4,4',5-PeCB	Ocean Fish	Mixed	NR	0	ND	NA	NR	Various U.S. Locations	Urban	95	3	
(114)	Fresh Fish	Mixed	NR	NR	NR	250	NR	Various U.S. Locations	Urban	95	3	
	Carp	Whole	1	1	57,000	57,000	NR	Saginaw Bay	NR	NR	6	
2,3',4,4',5-PeCB	Ocean Fish	Mixed	NR	NR	NR	320	NR	Various U.S. Locations	Urban	95	3	
(118)	Fresh Fish	Mixed	NR	NR	NR	1,800	NR	Various U.S. Locations	Urban	95	3	
	Small Smelt	Whole	1	1	37,000	37,000	Wet	Port Credit, Lake Ontario	NR	86	8	composite 48 samples
	Large Smelt	Whole	1	1	87,000	87,000	Wet	Vineland, Lake Ontario	NR	82	8	composite 20 samples
	Salmonids	Whole	1	1	250,000	250,000	Wet	Lake Ontario	NR	81-82	8	composite 60 samples
	Br. Trout	Whole	1	1	133,000	133,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
	Br. Trout	Fillets	1	1	60,000	60,000	NR	Vineland, Lake Ontario	NR	NR	5	composite 10 samples
	Lake Trout	Whole	1	1	634,000	634,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Lake Trout	Fillets	1	1	242,000	242,000	NR	Port Credit, Lake Ontario	NR	NR	5	composite 10 samples
	Rb. Trout	Whole	2	2	80,000-310,000	195,000	NR	Lake Ontario	NR	NR	5	

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
2,3',4,4',5-PeCB	Rb. Trout	Fillets	2	2	16,000-115,000	65,500	NR	Lake Ontario	NR	NR	5	
(118)	Coho Salmon	Whole	2	2	100,000-271,000	185,500	NR	Lake Ontario	NR	NR	5	
(continued)	Coho Salmon	Fillets	2	2	39,000-136,000	87,500	NR	Lake Ontario	NR	NR	5	
	Carp	Whole	1	1	1.35×10^6	1.35×10^6	NR	Saginaw Bay	NR	NR	6	
PeCBs	Various[c]	Mixed[d]	362	314	NR	564,700	Wet	Various, US[b]	Various	86-89	7	composite 3-5 fish
Hexachloro-PCB (MW=360.88)												
3,3',4,4',5,5'-HxCB	Baltic Herring	NR	6	NR	ND-12	4.5	Wet	Finland	Urban	NR	1	
(169)	Rainbow Trout	NR	4	NR	ND-7.4	3.9	Wet	Finland	Urban	NR	1	
	Other Fish	NR	4	NR	0.6-6.5	1.9	Wet	Finland	Urban	NR	1	3 samples of white fish and one pike perch
	Freshwater Fish	NR	NR	NR	NR	<1	Wet	Canada	Urban	86-88	2	
	Ocean Fish	Mixed	NR	NR	NR	0.2	Wet	Various U.S. Locations	Urban	95	3	
	Fresh Fish	Mixed	NR	NR	NR	0.94	Wet	Various U.S. Locations	Urban	95	3	
	Carp	Whole	1	0	ND(5,000)	NA	NR	Saginaw Bay	NR	NR	6	
	White Catfish	Whole	3	3	1.28-4.42	2.82	Wet	San Joaquin River	Industrial	NR	9	
	Channel Catfish	Whole	2	2	1.4-6.1	3.7	Wet	Antioch	Industrial	NR	9	
	White Catfish	Whole	1	1	2.23	2.23	Wet	Sacramento River	Industrial	NR	9	
	Channel Catfish	Whole	1	1	1.64	1.64	Wet	Sacramento River	Industrial	NR	9	
	Yellowfin Goby	Whole	1	1	1.19	1.19	Wet	Sacramento River	Industrial	NR	9	

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Chemical (IUPAC number)	Fish species[a]	Tissue	Number samples	Number positive samples	Concentration range	Conc. mean	Wt. basis	Location	Location description	Samp. year	Ref. no.	Comments
3,3',4,4',5,5'-HxCB (169) (continued)	Yellowfin Goby	Whole	1	1	1.63	1.63	Wet	San Pablo Bay	Industrial	NR	9	
	Staghorn Sculpin	Whole	1	1	1.96	1.96	Wet	San Pablo Bay	Industrial	NR	9	
	Diamond Turbot	Whole	1	1	9.89	9.89	Wet	San Pablo Bay	Industrial	NR	9	
	Starry Flounder	Whole	1	1	3.50	3.50	Wet	San Pablo Bay	Industrial	NR	9	
2,3,3',4,4',5-HxCB (156)	Small Smelt	Whole	1	1	2,700	2,700	Wet	Port Credit, Lake Ontario	NR	86	8	composite 48 samples
	Large Smelt	Whole	1	1	6,100	6,100	Wet	Vineland, Lake Ontario	NR	82	8	composite 20 samples
	Salmonids	Whole	1	1	34,000	34,000	Wet	Lake Ontario	NR	81-82	8	composite 60 samples
	Carp	Whole	1	1	79,000	79,000	NR	Saginaw Bay	NR	NR	6	
2,3,3',4,4',5'-HxCB (157)	Carp	Whole	1	1	76,000	76,000	NR	Saginaw Bay	NR	NR	6	
2,3',4,4',5,5'-HxCB (167)	Carp	Whole	1	1	77,000	77,000	NR	Saginaw Bay	NR	NR	6	
HxCBs	Various[c]	Mixed[d]	362	321	NR	355,930	Wet	Various, US[b]	Various	86-89	7	composite 3-5 fish
Heptachloro-PCB (MW=396.33)												
2,2',3,4,4',5,5-HpCB (180)	Ocean Fish	Mixed	NR	NR	NR	170	NR	Various U.S. Locations	Urban	95	3	
	Fresh Fish	Mixed	NR	NR	NR	810	NR	Various U.S. Locations	Urban	95	3	
2,3,3',4,4',5,5'-HpCB (189)	Carp	Whole	1	1	29,000	29,000	NR	Saginaw Bay	NR	NR	6	
HpCBs	Various[c]	Mixed[d]	362	250	NR	96,700	Wet	Various, US[b]	Various	86-89	7	composite 3-5 fish

Table B-13. Environmental Levels of PCBs in Fish (ppt) (continued)

Footnote References

[a] Blk. = Black; Lg. M. = Large Mouth; Wh. = White; Y. = Yellow; Br. = Brown; Rb. = Rainbow
[b] US = samples taken from 362 sites across the US, including industrial and background sites.
[c] Species were taken from both bottom feeders and open water feeders, and then composited.
[d] Whole fish samples and fillet samples were combined for analysis.

NOTES: Summary statistics provided in or derived from references; when reference did not compute composite, it was computed using one-half the detection limit for non-detects;
NA = not applicable;
ND = non-detected (limit of detection);
NR = not reported;
Descriptions provided were those given by reference or surmised from study description when not given.

Sources:
1. Himberg (1993)
2. Mes and Weber (1989)
3. Schecter et al. (1996)
4. Huckins et al. (1988)
5. Niimi and Oliver (1989b)
6. Smith et al. (1990)
7. U.S. EPA (1991)
8. Oliver and Niimi (1988)
9. Petreas (1991)

Table B-14. Levels of Dioxins in Food Products (ppt)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
Tetrachlorodibenzo-p-dioxins (MW=321.98)											
2,3,7,8-TCDD	Food basket	3	0	ND(0.1-0.4)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	0	ND(.012-.013)	NA	Whole	Switzerland	Background	NR	2	
	Milk	4	3	ND-0.049	0.027	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.2	0.2	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.08	0.08	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.03	0.03	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.01	0.01	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.2	0.2	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	1	1	0.0018	0.0018	Whole	U.S.		NR	4	
	Beef	3	3	0.017-0.062	0.032	Whole	U.S.		NR	4	
	Pork	3	0	ND(0.006)	NA	Whole	U.S.		NR	4	
	Milk	10	NR	ND-1.9	0.4	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Beef	3	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Veal	4	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Sheep	2	0	ND(0.5)	NA	Fat	W. Germany		NR	5	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
2,3,7,8-TCDD	Chicken	2	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
(continued)	Canned meat	2	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Milk	7	NR	ND-0.013	0.009[c]	Whole	England & Wales	Rural	1989	6	
	Cow cream	1	0	ND(0.15)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.03)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.34)	NA	Wet	USSR		88-89	7	
	Pork	1	0	ND(0.72)	NA	Wet	USSR		88-89	7	
	Butter	1	0	ND(0.53)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	0	ND(0.03)	NA	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.57)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	0	ND(0.34)	NA	Wet	South Vietnam		NR	7	
	Pork fat	1	0	ND(0.99)	NA	Wet	South Vietnam		NR	7	
	Chicken fat	1	0	ND(0.95)	NA	Wet	South Vietnam		NR	7	
	Milk	1	1	0.12[d]	0.12[d]	Whole	Vermont, U.S.	Background	87-88	8	
	Cottage cheese	1	0	ND(0.003)	NA	Wet	New York, NY		1990	9	
	Soft blue cheese	1	0	ND(0.05)	NA	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	0	ND(0.04)	NA	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	0.04	0.04	Wet	New York, NY		1990	9	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
2,3,7,8-TCDD	American cheese	1	1	0.07	0.07	Wet	New York, NY		1990	9	
(continued)	Beef	5	0	ND(0.12-0.41)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Beef	3	0	ND(0.16-0.40)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Pork	5	0	ND(0.07-0.52)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Pork	3	0	ND(0.39-0.49)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Chicken	5	2	ND-0.43	0.23	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Chicken	3	1	ND-1.67	0.70	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Eggs	5	0	ND(0.01-0.03)	NA	Whole	Los Angeles	Urban	NR	10	composite 6 samples
	Eggs	3	0	ND(0.01-0.03)	NA	Whole	San Francisco	Urban	NR	10	composite 6 samples
	Beef	3	3	0.005-0.028	0.017	Wet	New York, NY		1990	11	
	Pork	1	1	0.013	0.013	Wet	New York, NY		1990	11	
	Chicken	1	1	0.011	0.011	Wet	New York, NY		1990	11	
	Beef	63	11	ND-0.74	0.05	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Carcass Meat	2	1	ND-0.28	0.15	Whole	United Kingdom		88-91	13	
	Poultry	2	2	0.09-0.11	0.1	Whole	United Kingdom		88-91	13	
	Meat Products	1	1	0.05	0.05	Whole	United Kingdom		88-91	13	
	Milk Products	2	1	ND-0.02	0.035	Whole	United Kingdom		88-91	13	
	Butter	4	NR	0.14-0.16	0.15	Whole	United Kingdom		88-91	13	
	Cheddar Cheese	1	1	0.05	0.05	Whole	United Kingdom		88-91	13	
	Reduced Fat Cheese	1	0	ND	NA	Whole	United Kingdom		88-91	13	
2,3,7,8-TCDD	Fats & Oils	1	1	0.21	0.21	Whole	United Kingdom		88-91	13	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
(continued)	Eggs	2	2	0.05	0.05	Whole	United Kingdom		88-91	13	
	Green Vegetables	2	0	ND	NA	Whole	United Kingdom		88-91	13	
	Potatoes	1	0	ND	NA	Whole	United Kingdom		88-91	13	
	Fresh Fruit	2	0	ND	NA	Whole	United Kingdom		88-91	13	
	Milk	27	NR	ND-0.25	<0.2	Fat	Germany		1992	14	
	Beef	9	NR	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	NR	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	0	ND	NA	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.064	0.004	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Milk	3	3	0.06-0.07	0.06	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	0.05-0.07	0.06	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	0.05-0.09	0.06	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Eggs	3	0	ND(0.03-0.07)	0.04	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken	3	3	0.15-0.19	0.16	Fat	S. Mississippi	NR	1994	18	purchased from grocery store

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
2,3,7,8-TCDD	Chicken Liver	3	3	0.18-0.45	0.29	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
(continued)	Ground Beef	3	3	0.04-0.05	0.04	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	3	0.04-0.11	0.07	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	0.07	Fat	Various U.S. Sites	Background	1996	21	
	Pork	78	3	NR	0.10	Fat	Various U.S. Sites	Background	1995	22	
	Young Chicken	39	26	NR	0.16	Fat	Various U.S. Sites	Background	1996	23	
	Light Fowl	12	3	NR	0.05	Fat	Various U.S. Sites	Background	1996	23	
	Heavy Fowl	12	11	NR	0.43	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	11	NR	0.24	Fat	Various U.S. Sites	Background	1996	23	
	Eggs	3	0	NR	0.02	Whole	Various U.S. Sites		1995	24	
	Milk	538	NR	0 - 1.2	0.71	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0 - 0.26	0.64	Fat	Germany		93-96	25	official food inspection
	Eggs	218	NR	0 - 3.4	2.1	Fat	Germany		93-96	25	official food inspection
	Meat	107	NR	0.04 - 0.85	0.61	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	0.36	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	0.26	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	0.26	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	0.08	Fat	Russia		1996	26	supermarkets
	Goose Fat	NR	NR	NR	0.21	Fat	Russia		1996	26	supermarkets
	Duck Fat	NR	NR	NR	0.26	Fat	Russia		1996	26	supermarkets

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
2,3,7,8-TCDD	Chicken Fat	NR	NR	NR	0.23	Fat	Russia		1996	26	supermarkets
(continued)	Vegetables	2	NR	NR	0.1	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	ND	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	ND	Dry	Spain		1996	27	supermarkets
	Meat	7	NR	NR	0.1	Fat	Spain		1996	27	supermarkets
	Eggs	2	NR	NR	0.1	Fat	Spain		1996	27	supermarkets
	Milk & Dairy	6	NR	NR	ND	Fat	Spain		1996	27	supermarkets
	Fats & Oils	4	NR	NR	0.4	Fat	Spain		1996	27	supermarkets
	Butter	21	15	ND - 1.1	NR	Fat	Spain		NR	28	supermarkets
TCDD	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Eggs	3	0	NR	0.03	Whole	Various U.S. Sites		1995	24	
	Butter	18	11	ND - 1.5	NR	Fat	Spain		NR	28	supermarkets
Pentachlorodibenzo-p-dioxins (MW = 326.44)											
1,2,3,7,8-PeCDD	Food basket	3	0	ND(0.2-0.8)	NA	Fresh	Stockholm, Sweden	Urban	NR	1	
	Milk	2	0	ND(0.04-0.06)	NA	Whole	Switzerland	Background	NR	2	
	Milk	4	2	ND-0.25	0.12	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.7	0.7	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.41	0.41	Fat	Berlin, W. Germany	Urban	NR	3	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8-PeCDD	Beef fat	1	1	0.8	0.8	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
(continued)	Pork	1	1	0.12	0.12	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.5	0.5	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.7	0.7	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.4	0.4	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	NR	ND-2.5	1.2	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	NR	ND-0.8	0.6	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Beef	3	3	0.5-4.6	1.7	Fat	W. Germany		NR	5	
	Veal	4	4	2.5-3.4	3.1	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Sheep	2	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Chicken	2	2	0.9-1.2	1.0	Fat	W. Germany		NR	5	
	Canned meat	2	1	ND-0.9	0.6	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Milk	7	7	0.012-0.023	0.016[c]	Whole	England & Wales	Rural	1989	6	
	Cow cream	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.18)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8-PeCDD	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
(continued)	Butter	1	0	ND(0.26)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.17	0.17	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.50	0.50	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.95	0.95	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.01	0.01	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	0.2	0.2	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	0.11	0.11	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	0.11	0.11	Wet	New York, NY		1990	9	
	American cheese	1	1	0.12	0.12	Wet	New York, NY		1990	9	
	Beef	5	0	ND(0.40-17.50)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Beef	3	0	ND(0.49-1.09)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Pork	5	0	ND(1.00-4.36)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Pork	3	0	ND(1.94-2.70)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Chicken	5	0	ND(0.19-2.19)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Chicken	3	0	ND(0.44-7.40)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Eggs	5	0	ND(0.06-0.40)	NA	Whole	Los Angeles	Urban	NR	10	composite 6 samples
	Eggs	3	0	ND(0.04-0.06)	NA	Whole	San Francisco	Urban	NR	10	composite 6 samples

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8-PeCDD	Beef	3	3	0.01 - 0.208	0.093	Wet	New York, NY		1990	11	
(continued)	Pork	1	1	0.041	0.041	Wet	New York, NY		1990	11	
	Chicken	1	0	ND(0.011)	NA	Wet	New York, NY		1990	11	
	Beef	63	2	ND-3.04	0.35	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Carcass Meat	2	1	ND-0.41	0.22	Whole	United Kingdom		88-91	13	
	Offals	1	0	ND	NA	Whole	United Kingdom		88-91	13	
	Poultry	2	2	0.09-0.11	0.1	Whole	United Kingdom		88-91	13	
	Meat Products	2	1	ND-0.07	0.048	Whole	United Kingdom		88-91	13	
	Milk Products	2	1	ND-0.04	0.06	Whole	United Kingdom		88-91	13	
	Butter	4	NR	ND-0.48	0.32	Whole	United Kingdom		88-91	13	
	Cheddar Cheese	1	1	0.04	0.04	Whole	United Kingdom		88-91	13	
	Reduced Fat Cheese	1	1	0.05	0.05	Whole	United Kingdom		88-91	13	
	Fats & Oils	1	1	0.29	0.29	Whole	United Kingdom		88-91	13	
	Eggs	2	2	0.06-0.09	0.075	Whole	United Kingdom		88-91	13	
	Green Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	13	
	Potatoes	1	0	ND	NA	Whole	United Kingdom		88-91	13	
	Fresh Fruit	1	0	ND	NA	Whole	United Kingdom		88-91	13	
	Milk	9	9	0.34-0.76	0.46	Fat	Switzerland		1990	19	
	Milk	27	NR	0.22-0.56	0.37	Fat	Germany		1992	14	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8-PeCDD	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
(continued)	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-40	< 10	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.168	0.041	Whole	Finland		1991	17	
	Beef	20	NR	ND-0.78	< 0.5	Fat	Finland		1991	17	
	Pork	20	0	< 0.2	< 0.2	Fat	Finland		1991	17	
	Milk	3	3	0.28-0.43	0.38	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	0.03-0.37	0.25	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	0.34-0.49	0.4	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Eggs	3	3	0.13-0.14	0.14	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken	3	3	0.18-0.25	0.22	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken Liver	3	3	0.27-0.46	0.35	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Ground Beef	3	3	0.18-0.35	0.25	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	2	ND-0.21	0.15	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	0.32	Fat	Various U.S. Sites	Background	1996	21	
	Pork	78	3	NR	0.45	Fat	Various U.S. Sites	Background	1995	22	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8-PeCDD	Young Chicken	39	8	NR	0.24	Fat	Various U.S. Sites	Background	1996	23	
(continued)	Light Fowl	12	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	23	
	Heavy Fowl	12	4	NR	0.32	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	5	NR	0.32	Fat	Various U.S. Sites	Background	1996	23	
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1995	24	
	Milk	538	NR	0 - 1.3	0.25	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0 - 0.48	0.21	Fat	Germany		93-96	25	official food inspection
	Eggs	218	NR	0 - 8.2	0.68	Fat	Germany		93-96	25	official food inspection
	Meat	107	NR	0.03 - 2.4	0.3	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	0.41	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	0.20	Fat	Russia		1996	26	supermarkets
	Goose Fat	NR	NR	NR	0.47	Fat	Russia		1996	26	supermarkets
	Duck Fat	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Chicken Fat	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Vegetables	2	NR	NR	0.1	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	ND	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	ND	Dry	Spain		1996	27	supermarkets
	Meat	7	NR	NR	ND	Fat	Spain		1996	27	supermarkets

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8-PeCDD	Eggs	2	NR	NR	0.1	Fat	Spain		1996	27	supermarkets
(continued)	Milk & Dairy	6	NR	NR	ND	Fat	Spain		1996	27	supermarkets
	Fats & Oils	4	NR	NR	0.1	Fat	Spain		1996	27	supermarkets
	Butter	21	19	ND - 1.08	NR	Fat	Spain		NR	28	supermarkets
PeCDDs	Cottage cheese	1	1	0.6	0.6	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	14	14	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	5	5	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	4	4	Wet	New York, NY		1990	9	
	American cheese	1	1	4	4	Wet	New York, NY		1990	9	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1995	24	
	Butter	21	19	ND - 1.23	NR	Fat	Spain		NR	28	supermarkets
Hexachlorodibenzo-p-dioxins (MW = 390.87)											
1,2,3,4,7,8-HxCDD	Food basket	3	0	ND(0.4-1.6)	NA	Fresh	Stockholm, Sweden	Urban	NR	1	
	Milk	2	1	ND-0.068	0.049	Whole	Switzerland	Background	NR	2	
	Milk	4	3	ND-0.23	0.14	Whole	Switzerland	Industrial	NR	2	near incinerators

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,7,8-HxCDD	Milk	1	1	0.3	0.3	Fat	W. Germany		NR	3	composite from 8 trucks
(continued)	Butter	1	1	0.15	0.15	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.21	0.21	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.5	0.5	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	1.3	1.3	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	NR	ND-2.0	0.8	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	10	0.2-0.4	0.3	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Beef	3	3	0.5-4.6	1.9	Fat	W. Germany		NR	5	
	Veal	4	4	1.1-3.0	1.9	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Sheep	2	2	0.7-1.0	0.8	Fat	W. Germany		NR	5	
	Chicken	2	1	ND-0.8	0.6	Fat	W. Germany		NR	5	
	Canned meat	2	1	ND-2.1	1.0	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Cow cream	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.18)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,7,8-HxCDD	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
(continued)	Butter	1	0	ND(0.26)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.012	0.012	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.24	NA	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.60	NA	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.48	NA	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.02	0.02	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	0.29	0.29	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	0.07	0.07	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	9	
	American cheese	1	1	0.017	0.017	Wet	New York, NY		1990	9	
	Eggs	5	0	ND(0.12-0.67)	NA	Whole	Los Angeles	Urban	NR	10	composite 6 samples
	Eggs	3	0	ND(0.08-0.25)	NA	Whole	San Fransisco	Urban	NR	10	composite 6 samples
	Chicken	1	0	ND(0.017)	NA	Wet	New York, NY		1990	11	
	Beef	63	8	ND-4.69	0.64	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Carcass Meat	2	2	0.32-1.1	0.71	Whole	United Kingdom		88-91	13	
	Offals	2	2	0.31-0.37	0.34	Whole	United Kingdom		88-91	13	
	Poultry	2	2	0.45-0.82	0.64	Whole	United Kingdom		88-91	13	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,7,8-HxCDD	Meat Products	2	2	0.17-0.24	0.21	Whole	United Kingdom		88-91	13	
(continued)	Milk Products	2	1	ND-0.11	0.14	Whole	United Kingdom		88-91	13	
	Butter	4	NR	0.7-0.94	0.82	Whole	United Kingdom		88-91	13	
	Cheddar Cheese	1	1	0.1	0.1	Whole	United Kingdom		88-91	13	
	Reduced Fat Cheese	1	1	0.12	0.12	Whole	United Kingdom		88-91	13	
	Fats & Oils	2	1	ND-0.41	0.31	Whole	United Kingdom		88-91	13	
	Eggs	2	2	0.22-0.29	0.26	Whole	United Kingdom		88-91	13	
	Green Vegetables	2	2	0.01-0.02	0.015	Whole	United Kingdom		88-91	13	
	Other Vegetables	2	2	0.11-0.24	0.175	Whole	United Kingdom		88-91	13	
	Potatoes	2	1	ND-0.12	0.07	Whole	United Kingdom		88-91	13	
	Fresh Fruit	1	0	ND	NA	Whole	United Kingdom		88-91	13	
	Milk	9	9	0.16-0.29	0.21	Fat	Switzerland		1990	19	
	Milk	27	NR	ND-0.53	0.29	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	0	ND	NA	Whole	Finland		1991	17	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,7,8-HxCDD	Beef	20	NR	ND-1.52	<0.5	Fat	Finland		1991	17	
(continued)	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Eggs	20	0	ND	NA	Whole	Finland		1991	17	
	Milk	3	3	0.09-0.36	0.26	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	0.22-0.28	0.26	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	0.34-0.51	0.43	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Eggs	3	1	ND-0.18	0.10	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken	3	2	ND-0.19	0.15	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken Liver	3	3	0.19-0.39	0.29	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Ground Beef	3	3	0.15-0.47	0.27	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	3	0.26-1.2	0.59	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	0.39	Fat	Various U.S. Sites	Background	1996	21	
	Pork	78	12	NR	0.52	Fat	Various U.S. Sites	Background	1995	22	
	Young Chicken	39	4	NR	0.18	Fat	Various U.S. Sites	Background	1996	23	
	Light Fowl	12	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	23	
	Heavy Fowl	12	3	NR	0.24	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	2	NR	0.16	Fat	Various U.S. Sites	Background	1996	23	
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1995	24	
	Milk	538	NR	0 - 1.1	0.17	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0 - 0.48	0.14	Fat	Germany		93-96	25	official food inspection

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,7,8-HxCDD	Eggs	218	NR	0 - 8.4	0.56	Fat	Germany		93-96	25	official food inspection
(continued)	Meat	107	NR	0.03 - 2.2	0.23	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	0.44	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	0.65	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	0.1	Fat	Russia		1996	26	supermarkets
	Goose Fat	NR	NR	NR	0.19	Fat	Russia		1996	26	supermarkets
	Duck Fat	NR	NR	NR	0.08	Fat	Russia		1996	26	supermarkets
	Chicken Fat	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Vegetables	2	NR	NR	0.4	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	0.3	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	ND	Dry	Spain		1996	27	supermarkets
	Meat	7	NR	NR	0.4	Fat	Spain		1996	27	supermarkets
	Eggs	2	NR	NR	0.3	Fat	Spain		1996	27	supermarkets
	Milk & Dairy	6	NR	NR	0.1	Fat	Spain		1996	27	supermarkets
	Fats & Oils	4	NR	NR	0.2	Fat	Spain		1996	27	supermarkets
	Butter	21	20	ND - 0.63	NR	Fat	Spain		NR	28	supermarkets
1,2,3,6,7,8-HxCDD	Food basket	3	0	ND(0.4-1.6)	NA	Fresh	Stockholm, Sweden	Urban	NR	1	
	Milk	2	1	ND-0.068	0.049	Whole	Switzerland	Background	NR	2	
	Milk	4	3	ND-0.29	0.18	Whole	Switzerland	Industrial	NR	2	near incinerators

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,6,7,8-HxCDD	Milk	1	1	1.1	1.1	Fat	W. Germany		NR	3	composite from 8 trucks
(continued)	Butter	1	1	0.95	0.95	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	1.9	1.9	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.29	0.29	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	1.5	1.5	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	2.8	2.8	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	1.4	1.4	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	10	0.5-10.0	4.0	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	10	0.4-1.2	0.8	Fat	W. Germany		NR	5	
	Butter	5	NR	ND-1.0	0.7	Fat	W. Germany		NR	5	
	Beef	3	3	1.3-6.0	3.2	Fat	W. Germany		NR	5	
	Veal	4	4	3.3-8.0	5.3	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Sheep	2	2	2.3-3.7	3.0	Fat	W. Germany		NR	5	
	Chicken	2	2	1.7-1.8	1.8	Fat	W. Germany		NR	5	
	Canned meat	2	2	0.9-7.4	3.2	Fat	W. Germany		NR	5	
	Lard	4	NR	ND-0.6	0.3	Fat	W. Germany		NR	5	
	Cow cream	1	1	0.135	0.135	Wet	USSR		88-89	7	
	Beef	1	1	0.018	0.018	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.288	0.288	Wet	USSR		88-89	7	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,6,7,8-HxCDD	Beef fat	1	1	0.340	0.340	Wet	USSR		88-89	7	
(continued)	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
	Butter	1	1	0.318	0.318	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.048	0.048	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.47	0.47	Wet	South Vietnam		NR	7	
	Pork fat	1	1	1.69	1.69	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	3.8	3.8	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.07	0.07	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	1.72	1.72	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	0.7	0.7	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	0.58	0.58	Wet	New York, NY		1990	9	
	American cheese	1	1	0.38	0.38	Wet	New York, NY		1990	9	
	Beef	5	0	ND(0.74-2.72)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Beef	3	0	ND(1.64-4.08)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Pork	5	0	ND(0.64-3.60)	NA	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Pork	3	0	ND(1.06-2.92)	NA	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Chicken	5	1	ND-2.14	0.98	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Chicken	3	1	ND-4.30	1.84	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Eggs	5	0	ND(0.10-0.56)	NA	Whole	Los Angeles	Urban	NR	10	composite 6 samples

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,6,7,8-HxCDD	Eggs	3	0	ND(0.07-0.21)	NA	Whole	San Francisco	Urban	NR	10	composite 6 samples
(continued)	Beef	3	3	0.03-1.981	0.84	Wet	New York, NY		1990	11	
	Pork	1	1	0.282	0.282	Wet	New York, NY		1990	11	
	Chicken	1	1	0.04	0.04	Wet	New York, NY		1990	11	
	Beef	63	21	ND-12.46	1.42	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Milk	9	9	0.37-0.63	0.49	Fat	Switzerland		1990	19	
	Milk	27	NR	0.44-0.84	0.55	Fat	Germany		1992	14	
	Beef	9	NR	NR	4.92	Fat	Various U.S. Sites		NR	15	
	Chicken	7	ND	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	NR	NR	1.81	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	1	0.22	0.22	Whole	U.S.		NR	16	fast food
	Pizza	1	1	0.149	0.149	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-69	47	Whole	Finland		1991	17	
	Beef	20	NR	ND-1.52	<0.5	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Eggs	20	NR	ND-0.472	0.119	Whole	Finland		1991	17	
	Milk	3	3	0.68-2	1.46	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	1.5-1.8	1.67	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	1.7-2.3	1.9	Fat	S. Mississippi	NR	1994	18	purchased from grocery store

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,6,7,8-HxCDD	Eggs	3	3	0.16-0.39	0.26	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
(continued)	Chicken	3	3	0.29-1.3	0.7	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken Liver	3	3	0.42-0.6	0.5	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Ground Beef	3	3	0.95-3.4	2.02	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	3	0.63-1.3	0.97	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	1.87	Fat	Various U.S. Sites	Background	1996	21	
	Pork	78	29	NR	1.10	Fat	Various U.S. Sites	Background	1995	22	
	Young Chicken	39	24	NR	0.39	Fat	Various U.S. Sites	Background	1996	23	
	Light Fowl	12	8	NR	0.34	Fat	Various U.S. Sites	Background	1996	23	
	Heavy Fowl	12	11	NR	0.71	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	13	NR	0.79	Fat	Various U.S. Sites	Background	1996	23	
	Eggs	3	0	NR	0.16	Whole	Various U.S. Sites		1995	24	
	Milk	538	NR	0 - 2.6	0.44	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0 - 1.1	0.36	Fat	Germany		93-96	25	official food inspection
	Eggs	218	NR	0.09 - 35	1.7	Fat	Germany		93-96	25	official food inspection
	Meat	107	NR	0.04 - 5.4	0.42	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	0.36	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	0.11	Fat	Russia		1996	26	supermarkets

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,6,7,8-HxCDD	Goose Fat	NR	NR	NR	0.24	Fat	Russia		1996	26	supermarkets
(continued)	Duck Fat	NR	NR	NR	0.16	Fat	Russia		1996	26	supermarkets
	Chicken Fat	NR	NR	NR	0.59	Fat	Russia		1996	26	supermarkets
	Vegetables	2	NR	NR	0.8	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	0.8	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	ND	Dry	Spain		1996	27	supermarkets
	Meat	7	NR	NR	1.1	Fat	Spain		1996	27	supermarkets
	Eggs	2	NR	NR	1.7	Fat	Spain		1996	27	supermarkets
	Milk & Dairy	6	NR	NR	0.6	Fat	Spain		1996	27	supermarkets
	Fats & Oils	4	NR	NR	0.3	Fat	Spain		1996	27	supermarkets
	Butter	21	20	ND - 1.33	NR	Fat	Spain		NR	28	supermarkets
1,2,3,7,8,9-HxCDD	Food basket	3	0	ND(0.5-1.6)	NA	Fresh	Stockholm, Sweden	Urban	NR	1	
	Milk	2	1	ND-0.068	0.049	Whole	Switzerland	Background	NR	2	
	Milk	4	3	ND-0.17	0.10	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.4	0.4	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.26	0.26	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.06	0.06	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.4	0.4	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8,9-HxCDD	Eggs	1	1	0.5	0.5	Fat	Berlin, W. Germany	Urban	NR	3	
(continued)	Milk	10	NR	ND-3.0	0.8	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	10	0.3-0.9	0.5	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Beef	3	3	0.7-4.5	2.0	Fat	W. Germany		NR	5	
	Veal	4	4	1.2-3.0	1.8	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Sheep	2	NR	ND-1.1	0.7	Fat	W. Germany		NR	5	
	Chicken	2	2	0.5-0.6	0.6	Fat	W. Germany		NR	5	
	Canned meat	2	NR	ND-2.7	1.2	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.5)	NA	Fat	W. Germany		NR	5	
	Milk	7	NR	ND-0.018	0.010[c]	Whole	England & Wales	Rural	1989	6	
	Cow cream	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.18)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
	Butter	1	0	ND(0.26)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.012	0.012	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8,9-HxCDD (continued)	Pork sticks	1	1	0.10	0.10	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.40	0.40	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.67	0.67	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.02	0.02	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	0.29	0.29	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	9	
	American cheese	1	1	0.19	0.19	Wet	New York, NY		1990	9	
	Beef	5	0	ND(0.74-2.72)	NA	Fat	Los Angeles, CA		NR	10	
	Beef	3	0	ND(1.64-4.08)	NA	Fat	San Francisco, CA		NR	10	
	Pork	5	0	ND(0.64-3.6)	NA	Fat	Los Angeles,		NR	10	
	Pork	3	0	ND(1.06-2.92)	NA	Fat	San Francisco, CA		NR	10	
	Chicken	5	1	ND-2.14	NA	Fat	Los Angeles, CA		NR	10	
	Chicken	3	1	ND-4.30	NA	Fat	San Francisco, CA		NR	10	
	Beef	3	3	0.011-0.616	0.238	Wet	New York		1990	11	
	Pork	1	1	0.044	0.044	Wet	New York, NY		1990	11	
	Chicken	1	0	ND(0.014)	NA	Wet	New York, NY		1990	11	
	Beef	63	9	ND-3.68	0.53	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Milk	9	9	0.19-0.46	0.27	Fat	Switzerland		1990	19	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8,9-HxCDD	Milk	27	NR	ND-0.47	0.24	Fat	Germany		1992	14	
(continued)	Beef	9	NR	NR	1.04	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-67	28	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.436	0.082	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Milk	3	3	0.12-0.58	0.4	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	0.32-0.46	0.37	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	0.33-0.57	0.43	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Eggs	3	2	ND-0.1	0.07	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken	3	3	0.11-0.17	0.14	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken Liver	3	3	0.16-0.29	0.21	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Ground Beef	3	3	0.13-0.68	0.35	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	3	0.12-0.19	0.16	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	0.55	Fat	Various U.S. Sites	Background	1996	21	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8,9-HxCDD	Pork	78	5	NR	0.47	Fat	Various U.S. Sites	Background	1995	22	
(continued)	Young Chicken	39	12	NR	0.39	Fat	Various U.S. Sites	Background	1996	23	
	Light Fowl	12	1	NR	0.15	Fat	Various U.S. Sites	Background	1996	23	
	Heavy Fowl	12	5	NR	0.60	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	3	NR	0.17	Fat	Various U.S. Sites	Background	1996	23	
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1995	24	
	Milk	538	NR	0 - 0.82	0.18	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0 - 0.57	0.15	Fat	Germany		93-96	25	official food inspection
	Eggs	218	NR	0 - 16	0.82	Fat	Germany		93-96	25	official food inspection
	Meat	107	NR	0.03 - 1.9	0.20	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	0.71	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	ND	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	0.06	Fat	Russia		1996	26	supermarkets
	Goose Fat	NR	NR	NR	0.15	Fat	Russia		1996	26	supermarkets
	Duck Fat	NR	NR	NR	0.08	Fat	Russia		1996	26	supermarkets
	Chicken Fat	NR	NR	NR	0.7	Fat	Russia		1996	26	supermarkets
	Vegetables	2	NR	NR	0.5	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	0.3	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	ND	Dry	Spain		1996	27	supermarkets

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,7,8,9-HxCDD	Meat	7	NR	NR	0.3	Fat	Spain		1996	27	supermarkets
(continued)	Eggs	2	NR	NR	0.6	Fat	Spain		1996	27	supermarkets
	Milk & Dairy	6	NR	NR	0.1	Fat	Spain		1996	27	supermarkets
	Fats & Oils	4	NR	NR	ND	Fat	Spain		1996	27	supermarkets
	Butter	21	19	ND - 0.67	NR	Fat	Spain		NR	28	supermarkets
HxCDDs	Chicken fat	26	13	ND-67	27	Fat	Canada		1980	20	
	Beef	9	NR	NR	6.23	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	NR	2.39	Fat	Various U.S. Sites		NR	15	
	Pork	7	NR	NR	1.93	Fat	Various U.S. Sites		NR	15	
	Eggs	3	NR	NR	0.17	Whole	Various U.S. Sites		1995	24	
	Butter	20	18	ND - 2.45	NR	Fat	Spain		NR	28	supermarkets
Heptachlorodibenzo-p-dioxins (MW = 425.31)											
1,2,3,4,6,7,8-HpCDD	Food basket	3	0	ND(0.4-1.7)	NA	Fresh	Stockholm, Sweden	Urban	NR	1	
	Milk	2	2	0.064	0.064	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.066-0.42	0.21	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	2	2	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	1.5	1.5	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	18	18	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	2.1	2.1	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	15	15	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8-HpCDD	Chicken	1	1	6.0	6.0	Fat	Berlin, W. Germany	Urban	NR	3	
(continued)	Eggs	1	1	0.4	0.4	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	10	1.0-29.0	6.2	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	10	1.2-4.0	2.3	Fat	W. Germany		NR	5	
	Butter	5	5	0.5-5.0	1.7	Fat	W. Germany		NR	5	
	Beef	3	3	1.8-6.7	3.9	Fat	W. Germany		NR	5	
	Veal	4	4	2.6-43.7	14.4	Fat	W. Germany		NR	5	
	Pork	3	NR	ND-1.6	0.7	Fat	W. Germany		NR	5	
	Sheep	2	2	10.9-11.8	11.4	Fat	W. Germany		NR	5	
	Chicken	2	2	4.5-5.0	4.5	Fat	W. Germany		NR	5	
	Canned meat	2	2	2.5-33.0	13.2	Fat	W. Germany		NR	5	
	Lard	4	4	2.0-3.0	2.8	Fat	W. Germany		NR	5	
	Milk	7	NR	ND-0.066	0.046[c]	Whole	England & Wales	Rural	1989	6	
	Cow cream	1	1	0.450	0.450	Wet	USSR		88-89	7	
	Beef	1	1	0.156	0.156	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.720	0.720	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	1	1.44	1.44	Wet	USSR		88-89	7	
	Butter	1	1	0.530	0.530	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.240	0.240	Wet	USSR		88-89	7	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8-HpCDD	Sausage	1	1	0.57	0.57	Wet	Moscow, USSR		88-89	7	
(continued)	Pork sticks	1	1	2.84	2.84	Wet	South Vietnam		NR	7	
	Pork fat	1	1	7.44	7.44	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	13.3	13.3	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.18	0.18	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	5.88	5.88	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	2.11	2.11	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	1.51	1.51	Wet	New York, NY		1990	9	
	American cheese	1	1	1.13	1.13	Wet	New York, NY		1990	9	
	Beef	5	4	ND-6.71	4.48	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Beef	3	3	4.56-8.95	6.28	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Pork	5	5	3.32-45.50	14.74	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Pork	3	3	3.04-15.30	10.15	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Chicken	5	4	ND-35.20	9.64	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Chicken	3	3	1.10-11.40	4.62	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Eggs	5	0	ND(0.10-0.42)	NA	Whole	Los Angeles	Urban	NR	10	composite 6 samples
	Eggs	3	0	ND(0.08-0.24)	NA	Whole	San Francisco	Urban	NR	10	composite 6 samples
	Beef	3	3	0.117-12.065	4.45	Wet	New York, NY		1990	11	
	Pork	1	1	8.197	8.2	Wet	New York, NY		1990	11	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8-HpCDD	Chicken	1	1	0.133	0.13	Wet	New York, NY		1990	11	
(continued)	Beef	63	45	ND-47.56	4.48	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Carcass Meat	2	2	0.8-7.7	4.25	Whole	United Kingdom		88-91	13	
	Offals	2	2	2.6-8.1	5.35	Whole	United Kingdom		88-91	13	
	Poultry	2	2	1.3-3.7	2.5	Whole	United Kingdom		88-91	13	
	Meat Products	2	2	1.2-2.2	1.7	Whole	United Kingdom		88-91	13	
	Milk Products	2	2	0.21-0.60	0.4	Whole	United Kingdom		88-91	13	
	Butter	4	NR	0.98-2.9	1.9	Whole	United Kingdom		88-91	13	
	Cheddar Cheese	1	1	0.47	0.47	Whole	United Kingdom		88-91	13	
	Reduced Fat Cheese	1	1	0.48	0.48	Whole	United Kingdom		88-91	13	
	Fats & Oils	2	2	2.1-4.5	3.3	Whole	United Kingdom		88-91	13	
	Eggs	2	2	0.74-0.95	0.85	Whole	United Kingdom		88-91	13	
	Green Vegetables	2	2	0.12-0.13	0.125	Whole	United Kingdom		88-91	13	
	Other Vegetables	2	2	0.44-1.0	0.72	Whole	United Kingdom		88-91	13	
	Potatoes	2	2	0.18-1.2	0.69	Whole	United Kingdom		88-91	13	
	Fresh Fruit	2	2	1.3-3.6	2.45	Whole	United Kingdom		88-91	13	
	Milk	9	9	0.61-1.25	0.98	Fat	Switzerland		1990	19	
	Milk	27	NR	0.45-1.00	0.66	Fat	Germany		1992	14	
	Beef	9	NR	NR	20.9	Fat	Various U.S. Sites		NR	15	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8-HpCDD	Chicken	7	NR	NR	8.09	Fat	Various U.S. Sites		NR	15	
(continued)	Pork	7	NR	NR	17.1	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	1	0.862	0.862	Whole	U.S.		NR	16	fast food
	Pizza	1	1	0.936	0.936	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	1	0.454	0.454	Whole	U.S.		NR	16	fast food
	Milk	20	NR	12-82	53	Whole	Finland		1991	17	
	Eggs	20	NR	0.002-0.876	0.184	Whole	Finland		1991	17	
	Beef	20	NR	ND-10	1.5	Fat	Finland		1991	17	
	Pork	20	NR	ND-4.13	0.63	Fat	Finland		1991	17	
	Milk	3	3	1.4-4.9	3.67	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	4.1-4.9	4.53	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	4.5-6.9	5.4	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Eggs	3	3	1.2-1.8	1.4	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken	3	3	1.5-8.2	4.37	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken Liver	3	3	5.3-6.8	5.97	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Ground Beef	3	3	2.9-12	6.97	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	3	8.8-15	11.6	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	5.03	Fat	Various U.S. Sites	Background	1996	21	
	Pork	78	43	NR	10.2	Fat	Various U.S. Sites	Background	1995	22	
	Young Chicken	39	39	NR	1.53	Fat	Various U.S. Sites	Background	1996	23	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8-HpCDD	Light Fowl	12	12	NR	0.93	Fat	Various U.S. Sites	Background	1996	23	
(continued)	Heavy Fowl	12	11	NR	2.04	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	13	NR	0.54	Fat	Various U.S. Sites	Background	1996	23	
	Eggs	3	NR	NR	2.74	Whole	Various U.S. Sites		1995	24	
	Milk	538	NR	0 - 12	0.89	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0.22 - 2.1	0.69	Fat	Germany		93-96	25	official food inspection
	Eggs	218	NR	0.55 - 277	10.2	Fat	Germany		93-96	25	official food inspection
	Meat	107	NR	0.18 - 50	2.3	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	0.18	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	0.75	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	1.04	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	0.43	Fat	Russia		1996	26	supermarkets
	Goose Fat	NR	NR	NR	0.71	Fat	Russia		1996	26	supermarkets
	Duck Fat	NR	NR	NR	0.06	Fat	Russia		1996	26	supermarkets
	Chicken Fat	NR	NR	NR	0.93	Fat	Russia		1996	26	supermarkets
	Vegetables	2	NR	NR	10.3	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	5.6	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	0.2	Dry	Spain		1996	27	supermarkets
	Meat	7	NR	NR	16.6	Fat	Spain		1996	27	supermarkets
	Eggs	2	NR	NR	10.2	Fat	Spain		1996	27	supermarkets

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8-HpCDD	Milk & Dairy	6	NR	NR	2.6	Fat	Spain		1996	27	supermarkets
(continued)	Fats & Oils	4	NR	NR	1.9	Fat	Spain		1996	27	supermarkets
	Butter	21	21	0.58 - 3.09	1.32	Fat	Spain		NR	28	supermarkets
HpCDDs	Chicken fat	26	16	ND-142	52	Fat	Canada		1980	20	
	Beef	9	NR	NR	20.9	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	NR	8.09	Fat	Various U.S. Sites		NR	15	
	Pork	7	NR	NR	17.1	Fat	Various U.S. Sites		NR	15	
	Eggs	3	NR	NR	6.04	Whole	Various U.S. Sites		1995	24	
	Butter	21	21	0.58 - 5.51	1.65	Fat	Spain		NR	28	supermarkets
Octachlorodibenzo-p-dioxin (MW=460.76)											
1,2,3,4,6,7,8,9-OCDD	Food basket	3	3	1.0-2.1	1.47	Fresh	Stockholm, Sweden	Urban	NR	1	
	Milk	2	2	0.12-0.16	0.14	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.16-0.59	0.32	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	10	10	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	3.4	3.4	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	25	25	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	19	19	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	68	68	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	52	52	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	12	12	Fat	Berlin, W. Germany	Urban	NR	3	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8,9-OCDD	Milk	10	10	4.3-25.0	11.0	Fat	W. Germany		NR	5	samples not randomly selected
(continued)	Cheese	10	10	5.0-17.0	10.5	Fat	W. Germany		NR	5	
	Butter	5	5	2.0-35.0	11.6	Fat	W. Germany		NR	5	
	Beef	3	3	4.7-6.0	5.4	Fat	W. Germany		NR	5	
	Veal	4	4	3.1-69.0	22.3	Fat	W. Germany		NR	5	
	Pork	3	3	5.4-12.3	8.2	Fat	W. Germany		NR	5	
	Sheep	2	2	14.4-24.4	19.3	Fat	W. Germany		NR	5	
	Chicken	2	2	14.0-19.0	16.5	Fat	W. Germany		NR	5	
	Canned meat	2	2	17.0-122	53.0	Fat	W. Germany		NR	5	
	Lard	4	4	10.0-23.0	16.0	Fat	W. Germany		NR	5	
	Chicken fat	26	12	ND-238	90	Fat	Canada		1980	20	
	Milk	7	7	0.215-0.323	0.230[c]	Whole	England & Wales	Rural	1989	6	
	Cow cream	1	1	3.15	3.15	Wet	USSR		88-89	7	
	Beef	1	1	0.63	0.63	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	5.40	5.40	Wet	USSR		88-89	7	
	Beef fat	1	1	3.40	3.40	Wet	USSR		88-89	7	
	Pork	1	1	11.5	11.5	Wet	USSR		88-89	7	
	Butter	1	1	9.01	9.01	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.660	0.660	Wet	USSR		88-89	7	
	Sausage	1	1	5.70	5.70	Wet	Moscow, USSR		88-89	7	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8,9-OCDD	Pork sticks	1	1	9.46	9.46	Wet	South Vietnam		NR	7	
(continued)	Pork fat	1	1	29.8	29.8	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	22.8	22.8	Wet	South Vietnam		NR	7	
	Swiss cheese	1	1	0.66	0.66	Wet	USSR		88-89	7	
	Sausage	1	1	5.7	5.7	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	9.46	9.46	Wet	South Vietnam		NR	7	
	Pork fat	1	1	29.8	29.8	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	22.8	22.8	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.34	0.34	Wet	New York, NY		1990	9	
	Soft blue cheese	1	1	5.93	5.93	Wet	New York, NY		1990	9	
	Heavy cream cheese	1	1	1.54	1.54	Wet	New York, NY		1990	9	
	Soft cream cheese	1	1	1.5	1.5	Wet	New York, NY		1990	9	
	American cheese	1	1	1.6	1.6	Wet	New York, NY		1990	9	
	Beef	5	4	ND-11.40	8.58	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Beef	3	3	8.03-11.90	9.43	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Pork	5	5	13.70-254.00	77.20	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Pork	3	3	24.90-125.00	72.43	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Chicken	5	4	ND-64.00	28.97	Fat	Los Angeles	Urban	NR	10	composite 6 samples
	Chicken	3	3	2.61-96.20	35.01	Fat	San Francisco	Urban	NR	10	composite 6 samples
	Eggs	5	0	ND(0.80-1.60)	NA	Whole	Los Angeles	Urban	NR	10	composite 6 samples

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8,9-OCDD	Eggs	3	1	ND-1.30	0.63	Whole	San Francisco	Urban	NR	10	composite 6 samples
(continued)	Beef	3	3	0.414-15.825	6.167	Wet	New York, NY		1990	11	
	Pork	1	1	50.742	50.7	Wet	New York, NY		1990	11	
	Chicken	1	1	0.74	0.74	Wet	New York, NY		1990	11	
	Beef	63	13	ND-71.84	4.78	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	12	statistically-based survey
	Carcass Meat	2	2	4.6-13	8.8	Whole	United Kingdom		88-91	13	
	Offals	1	1	21	21	Whole	United Kingdom		88-91	13	
	Poultry	2	2	2.8-4.2	3.5	Whole	United Kingdom		88-91	13	
	Meat Products	2	2	13-20	16.5	Whole	United Kingdom		88-91	13	
	Milk Products	2	2	1.9-3.1	2.5	Whole	United Kingdom		88-91	13	
	Butter	4	NR	1.9-5.5	3.7	Whole	United Kingdom		88-91	13	
	Cheddar Cheese	1	1	2.4	2.4	Whole	United Kingdom		88-91	13	
	Reduced Fat Cheese	1	1	1.8	1.8	Whole	United Kingdom		88-91	13	
	Milk	9	9	1.79-3.06	2.5	Fat	Switzerland		1990	19	
	Milk	27	NR	0.41-1.05	0.63	Fat	Germany		1992	14	
	Beef	9	NR	NR	32.7	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	NR	20.2	Fat	Various U.S. Sites		NR	15	
	Pork	7	NR	NR	87.1	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	1	1.59	1.59	Whole	U.S.		NR	16	fast food

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8,9-OCDD	Pizza	1	1	4.04	4.04	Whole	U.S.		NR	16	fast food
(continued)	Fried Chicken	1	1	2.55	2.55	Whole	U.S.		NR	16	fast food
	Milk	20	NR	67-181	120	Whole	Finland		1991	17	
	Eggs	20	NR	0.087-2.38	0.677	Whole	Finland		1991	17	
	Beef	20	NR	ND-1.0	3.0	Fat	Finland		1991	17	
	Pork	20	NR	ND-8.9	2.53	Fat	Finland		1991	17	
	Milk	3	3	2.8-5.7	4.13	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Cheddar Cheese	3	3	3.7-3.9	3.77	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Butter	3	3	5.1-6.7	5.67	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Eggs	3	3	7.3-20	14.10	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken	3	3	17-54	35	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Chicken Liver	3	3	18-53	40.33	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Ground Beef	3	3	4.4-20	11.33	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Sausage	3	3	56-92	75.67	Fat	S. Mississippi	NR	1994	18	purchased from grocery store
	Milk	8	8	NR	4.89	Fat	Various U.S. Sites	Background	1996	21	
	Pork	78	49	NR	52.8	Fat	Various U.S. Sites	Background	1995	22	
	Young Chicken	39	38	NR	5.31	Fat	Various U.S. Sites	Background	1996	23	
	Light Fowl	12	12	NR	2.07	Fat	Various U.S. Sites	Background	1996	23	
	Heavy Fowl	12	12	NR	7.67	Fat	Various U.S. Sites	Background	1996	23	
	Young Turkeys	15	11	NR	0.78	Fat	Various U.S. Sites	Background	1996	23	

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Chemical	Sample Type[a]	Number Samples	Number Positive Samples	Concentration Range	Conc. Mean[b]	Wt. Basis	Location	Location Description	Sample Year	Ref. No.	Comments
1,2,3,4,6,7,8,9-OCDD	Eggs	3	NR	NR	33.10	Whole	Various U.S. Sites		1995	24	
(continued)	Milk	538	NR	0.09 - 13	1.8	Fat	Germany		93-96	25	official food inspection
	Butter	222	NR	0.75 - 4.8	1.4	Fat	Germany		93-96	25	official food inspection
	Eggs	218	NR	2.3 - 1924	72	Fat	Germany		93-96	25	official food inspection
	Meat	107	NR	1.1 - 213	11	Fat	Germany		93-96	25	official food inspection
	Beef	NR	NR	NR	1.58	Fat	Russia		1996	26	supermarkets
	Smoked Sausage	NR	NR	NR	2.78	Fat	Russia		1996	26	supermarkets
	Chicken	NR	NR	NR	2.49	Fat	Russia		1996	26	supermarkets
	Pork	NR	NR	NR	2.6	Fat	Russia		1996	26	supermarkets
	Goose Fat	NR	NR	NR	4.4	Fat	Russia		1996	26	supermarkets
	Duck Fat	NR	NR	NR	3.26	Fat	Russia		1996	26	supermarkets
	Chicken Fat	NR	NR	NR	2.63	Fat	Russia		1996	26	supermarkets
	Vegetables	2	NR	NR	111.5	Dry	Spain		1996	27	supermarkets
	Pulses & Cereals	4	NR	NR	51.7	Dry	Spain		1996	27	supermarkets
	Fruits	2	NR	NR	1.7	Dry	Spain		1996	27	supermarkets
	Meat	7	NR	NR	224.6	Fat	Spain		1996	27	supermarkets
	Eggs	2	NR	NR	61.6	Fat	Spain		1996	27	supermarkets
	Milk & Dairy	6	NR	NR	26.7	Fat	Spain		1996	27	supermarkets
	Fats & Oils	4	NR	NR	17.8	Fat	Spain		1996	27	supermarkets
1,2,3,4,6,7,8,9-OCDD	Butter	21	21	1.35 - 26.6	6.57	Fat	Spain		NR	28	supermarkets

Table B-14. Levels of Dioxins in Food Products (ppt) (continued)

Footnote references

[a] Samples were obtained from grocery stores unless stated otherwise. Milk samples were obtained from dairies or transport trucks. No cooked samples from the references were used.
[b] For ND values 1/2 LOD was used in calculating the mean. Therefore, it is possible to have mean concentrations greater than the range (e.g., reported detection limit for nondetects greater than the positive sample).
[c] For ND values the detection limit was used in calculating the mean.
[d] Value in reference was reported as total 2,3,7,8-TCDD toxic equivalents.

NR = not reported
NA = not applicable

Sources:
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3. Beck et al. (1989)
4. LaFleur et al. (1990)
5. Furst et al. (1990)
6. Startin et al. (1990)
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12. Winters et al. (1994)
13. MAFF (1992)
14. Mayer (1995)
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16. Schecter et al. (1995)
17. Vartiainen and Hallikainen (1994)
18. Fiedler et al. (1997)
19. Schmid and Schlatter (1992)
20. Ryan et al. (1985)
21. Lorber et al. (1998)
22. Lorber et al. (1997)
23. Ferrario et al. (1997)
24. Schecter et al. (1997)
25. Malisch (1998)
26. Amirova et al. (1997)
27. Domingo et al. (1999)
28. Ramos et al. (1999)

Table B-15. Levels of Dibenzofurans in Food Products (ppt)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
Tetrachlorodibenzofurans (MW=305.98)											
2,3,7,8-TCDF	Food basket	3	3	0.1-0.4	2.3	Fresh	Sweden	Urban	NR	1	
	Milk	2	2	0.021-0.028	0.024	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.022-0.035	0.029	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.7	0.7	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.15	0.15	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.11	0.11	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	2.1	2.1	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	1.1	1.1	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	1	0	ND(0.001)	NA	Whole	U.S.		NR	4	
	Beef	3	1	ND-0.005	0.0032	Whole	U.S.		NR	4	
	Pork	3	3	0.013-0.020	0.015	Whole	U.S.		NR	4	
	Milk	10	NR	ND-10.0	4.1	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	NR	ND-2.6	1.1	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Beef	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Veal	4	NR	ND-0.5	0.2	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Chicken	2	2	1.2-4.0	2.6	Fat	W. Germany		NR	5	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,7,8-TCDF	Canned meat	2	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
(continued)	Lard	4	NR	ND-1.0	0.5	Fat	W. Germany		NR	5	
	Milk	7	NR	ND-0.011	0.008[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	1	0.285	0.285	Wet	USSR		88-89	7	
	Beef	1	1	0.027	0.027	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.108	0.108	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	1	0.288	0.288	Wet	USSR		88-89	7	
	Butter	1	1	0.212	0.212	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.021	0.021	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.17)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.34	0.34	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.50	0.50	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	1.9	1.9	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.02	0.02	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	0.15	0.15	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	1	0.07	0.07	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	0.07	0.07	Wet	New York, NY		1990	8	
	American cheese	1	1	0.1	0.1	Wet	New York, NY		1990	8	
	Beef	5	1	ND-0.84	0.28	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	2	ND-1.56	0.78	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(0.22-0.49)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Pork	3	0	ND(0.35-0.54)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,7,8-TCDF	Chicken	5	0	ND(0.19-0.58)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
(continued)	Chicken	3	1	ND-0.67	0.33	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.01-0.03)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	1	ND-0.01	0.01	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	3	0.01-0.051	0.029	Wet	New York, NY		1990	10	
	Pork	1	1	0.065	0.065	Wet	New York, NY		1990	10	
	Chicken	1	1	0.032	0.032	Wet	New York, NY		1990	10	
	Beef	63	0	ND	NA	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Fats & Oils	1	1	0.24	0.24	Whole	United Kingdom		88-91	12	
	Eggs	2	2	0.10-0.11	0.15	Whole	United Kingdom		88-91	12	
	Green Vegetables	2	2	0.02	0.02	Whole	United Kingdom		88-91	12	
	Other Vegetables	2	1	ND-0.13	0.14	Whole	United Kingdom		88-91	12	
	Potatoes	1	1	0.03	0.03	Whole	United Kingdom		88-91	12	
	Fresh Fruit	1	1	0.1	0.1	Whole	United Kingdom		88-91	12	
	Carcass Meat	2	2	0.13-0.32	0.23	Whole	United Kingdom		88-91	12	
	Offals	2	2	0.06	0.06	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.15-0.22	0.19	Whole	United Kingdom		88-91	12	
	Meat Products	2	2	0.07-0.14	0.11	Whole	United Kingdom		88-91	12	
	Milk Products	2	1	ND-0.02	0.04	Whole	United Kingdom		88-91	12	
	Butter	4	0	ND	NA	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.04	0.04	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	0	ND	NA	Whole	United Kingdom		88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,7,8-TCDF	Milk	9	9	0.18-0.31	0.24	Fat	Switzerland		1990	13	
(continued)	Milk	27	0	ND	NA	Fat	Germany		1992	14	
	Beef	9	NR	NR	0.488	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	NR	1.97	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	1	0.0734	0.0734	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-90	19	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.346	0.064	Whole	Finland		1991	17	
	Beef	20	NR	ND-1.42	<0.5	Fat	Finland		1991	17	
	Pork	20	NR	ND-3.02	0.74	Fat	Finland		1991	17	
	Milk	3	3	0.09-0.14	0.12	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.04-0.08	0.06	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.04-0.07	0.06	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	3	0.08-0.11	0.10	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	3	0.74-0.83	0.77	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	3	0.4-0.99	0.78	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.06-0.08	0.07	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	0.06-0.25	0.17	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	8	NR	0.08	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	1	NR	0.09	Fat	Various U.S. Sites	Background	1995	20	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Young Chickens	39	35	NR	0.28	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	9	NR	0.25	Fat	Various U.S. Sites	Background	1996	21	
2,3,7,8-TCDF	Heavy Fowl	12	11	NR	0.48	Fat	Various U.S. Sites	Background	1996	21	
(continued)	Young Turkeys	15	12	NR	0.57	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	NR	NR	0.03	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-0.62	0.08	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0-0.66	0.04	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0-32	1.5	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0.04-3.0	0.30	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	0.35	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	0.64	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	1.32	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.30	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.89	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.46	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.25	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	0.6	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	0.1	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	1.0	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	1.8	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	2.1	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	2.1	Fat	Spain		1996	25	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Fats & Oils	4	NR	NR	0.3	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-0.75	NR	Fat	Spain		NR	26	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
TCDF	Beef	9	NR	NR	0.949	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	NR	42.2	Fat	Various U.S. Sites		NR	15	
	Pork	7	NR	NR	4.7	Fat	Various U.S. Sites		NR	15	
	Eggs	3	NR	NR	0.11	Whole	Various U.S. Sites		1995	22	
	Butter	21	21	ND-3.10	1.1	Fat	Spain		1996	26	supermarkets
Pentachlorodibenzofurans (MW=340.42)											
1,2,3,7,8-PeCDF	Food basket	3	0	ND(0.1-0.4)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	2	0.020-0.021	0.020	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.020-0.036	0.028	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.2	0.2	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.09	0.09	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.01	0.01	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.01	0.01	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.01	0.01	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.01	0.01	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	NR	ND-1.3	0.3	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	NR	ND-0.3	0.2	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Beef	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Veal	4	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Sheep	2	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Chicken	2	1	ND-1.2	0.7	Fat	W. Germany		NR	5	
1,2,3,7,8-PeCDF	Canned meat	2	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
(continued)	Lard	4	NR	ND-0.3	0.2	Fat	W. Germany		NR	5	
	Milk	7	0	ND(.002-.017)	0.005[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	1	0.165	0.165	Wet	USSR		88-89	7	
	Beef	1	1	0.006	0.006	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	1	0.144	0.144	Wet	USSR		88-89	7	
	Butter	1	1	0.212	0.212	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.006	0.006	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.17)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.14	0.14	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.20	0.20	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.48	0.48	Wet	South Vietnam		NR	7	
	Cottage cheese	1	0	ND(0.003)	NA	Wet	New York, NY		1990	8	
	Soft blue cheese	1	0	ND(0.05)	NA	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	0	ND(0.04)	NA	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	0.04	0.04	Wet	New York, NY		1990	8	
	American cheese	1	0	ND(0.05)	NA	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.25-0.86)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Beef	3	0	ND(0.10-1.44)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(0.37-1.40)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	0	ND(0.28-0.58)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	0	ND(0.16-0.67)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
1,2,3,7,8-PeCDF	Chicken	3	0	ND(0.12-0.15)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
(continued)	Eggs	5	0	ND(0.03-0.10)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.01-0.02)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	1	ND-0.01	NA	Wet	New York, NY		1990	10	
	Pork	1	1	0.009	0.009	Wet	New York, NY		1990	10	
	Chicken	1	0	ND(0.006)	NA	Wet	New York, NY		1990	10	
	Beef	3	1	ND-0.01	NA	Wet	New York, NY		1990	10	
	Pork	1	1	0.009	0.009	Wet	New York, NY		1990	10	
	Chicken	1	0	ND(0.006)	NA	Wet	New York, NY		1990	10	
	Beef	63	0	ND	NA	Fat	Various U.S. SItes	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Fats & Oils	1	1	0.11	0.11	Whole	United Kingdom		88-91	12	
	Eggs	2	2	0.01-0.03	0.02	Whole	United Kingdom		88-91	12	
	Green Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Other Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Potatoes	2	0	ND	NA	Whole	United Kingdom		88-91	12	
	Fresh Fruit	2	0	ND	NA	Whole	United Kingdom		88-91	12	
	Carcass Meat	2	2	0.01-0.24	0.125	Whole	United Kingdom		88-91	12	
	Offals	1	1	0.02	0.02	Whole	United Kingdom		88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Poultry	2	2	0.03-0.04	0.035	Whole	United Kingdom		88-91	12	
	Meat Products	2	1	ND-0.01	0.0125	Whole	United Kingdom		88-91	12	
	Milk Products	2	0	ND	NA	Whole	United Kingdom		88-91	12	
	Butter	4	NR	ND-0.04	0.035	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.01	0.01	Whole	United Kingdom		88-91	12	
1,2,3,7,8-PeCDF	Reduced Fat Cheese	1	1	0.01	0.01	Whole	United Kingdom		88-91	12	
(continued)	Milk	9	9	0.06-0.16	0.09	Fat	Switzerland		1990	13	
	Milk	27	0	ND	NA	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-28	< 10	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.254	0.061	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Milk	3	0	ND(0.02)	0.02	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.02-0.03	0.03	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	1	ND-0.05	0.02	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	0	ND(0.02)	0.02	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken	3	3	0.14-0.25	0.20	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	3	0.09-0.14	0.12	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.01-004	0.02	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	0.03-0.08	0.05	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	0	NR	0.05	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	0	NR	0.45	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	5	NR	0.21	Fat	Various U.S. Sites	Background	1996	21	
1,2,3,7,8-PeCDF	Light Fowl	12	1	NR	0.18	Fat	Various U.S. Sites	Background	1996	21	
(continued)	Heavy Fowl	12	2	NR	0.14	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	4	NR	0.36	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-0.32	0.04	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0-0.66	0.03	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0-9.5	0.65	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0-1.4	0.11	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	0.31	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	0.55	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	1.62	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.27	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.56	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.44	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.98	Fat	Russia		1996	24	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Vegetables	2	NR	NR	0.6	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	0.2	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.6	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	0.9	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	1.0	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	1.5	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	0.4	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-0.32	NR	Fat	Spain		NR	26	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,4,7,8-PeCDF	Food basket	3	0	ND(0.1-0.5)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	2	0.069-0.084	0.076	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.066-0.43	0.24	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	1.4	1.4	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.45	0.45	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	1.5	1.5	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.08	0.08	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.9	0.9	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	1.5	1.5	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.8	0.8	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	10	1.7-4.6	2.7	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	10	0.9-2.5	1.7	Fat	W. Germany		NR	5	
	Butter	5	NR	ND-2.0	1.1	Fat	W. Germany		NR	5	
	Beef	3	3	1.7-3.9	2.7	Fat	W. Germany		NR	5	
	Veal	4	4	6.5-8.2	7.4	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	2	0.7-2.8	1.7	Fat	W. Germany		NR	5	
	Chicken	2	2	0.7-2.0	1.3	Fat	W. Germany		NR	5	
	Canned meat	2	2	0.3-1.3	0.8	Fat	W. Germany		NR	5	
	Lard	4	NR	ND-0.4	0.3	Fat	W. Germany		NR	5	
	Milk	7	7	0.028-0.038	0.032[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	1	1.10	1.10	Wet	USSR		88-89	7	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Beef	1	1	0.177	0.177	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.108	0.108	Wet	USSR		88-89	7	
2,3,4,7,8-PeCDF	Beef fat	1	1	0.204	0.204	Wet	USSR		88-89	7	
(continued)	Pork	1	1	0.504	0.504	Wet	USSR		88-89	7	
	Butter	1	1	1.43	1.43	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.015	0.015	Wet	USSR		88-89	7	
	Sausage	1	1	0.171	0.171	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.27	0.27	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.99	0.99	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.02	0.02	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	0.25	0.25	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	0.18	0.18	Wet	New York, NY		1990	8	
	American cheese	1	1	0.07	0.07	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.22-0.78)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.28-1.31)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(0.33-1.28)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	0	ND(0.26-0.53)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	0	ND(0.15-0.60)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.11-0.14)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.01-0.07)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.02-0.02)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Beef	3	3	0.03-1.783	0.626	Wet	New York, NY		1990	10	
	Pork	1	1	0.039	0.039	Wet	New York, NY		1990	10	
	Chicken	1	1	0.01	0.01	Wet	New York, NY		1990	10	
2,3,4,7,8-PeCDF (continued)	Beef	63	4	ND-1.09	0.36	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	2	2	0.18-0.39	0.29	Whole	United Kingdom		88-91	12	
	Offals	2	2	0.09-0.71	0.40	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.05-0.08	0.065	Whole	United Kingdom		88-91	12	
	Meat Products	2	2	0.09-0.12	0.105	Whole	United Kingdom		88-91	12	
	Milk Products	2	2	0.04-0.15	0.095	Whole	United Kingdom		88-91	12	
	Butter	4	NR	0.78-0.99	0.89	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.1	0.1	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	1	0.07	0.07	Whole	United Kingdom		88-91	12	
	Fats & Oils	2	1	ND-0.55	0.37	Whole	United Kingdom	Rural	88-91	12	
	Eggs	2	1	0.05-0.10	0.075	Whole	United Kingdom		88-91	12	
	Green Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Other Vegetables	2	1	ND-0.04	0.0275	Whole	United Kingdom		88-91	12	
	Potatoes	1	1	0.02	0.02	Whole	United Kingdom		88-91	12	
	Fresh Fruit	2	1	ND-0.02	0.0175	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.69-1.54	1.13	Fat	Switzerland		1990	13	
	Milk	27	NR	0.4-0.88	0.66	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	NR	2.6	Fat	Various U.S. Sites		NR	15	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
2,3,4,7,8-PeCDF	Milk	20	NR	ND-81	14	Whole	Finland		1991	17	
(continued)	Eggs	20	NR	ND-0.112	0.016	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	NR	NR	0.3	Fat	Finland		1991	17	
	Milk	3	3	0.1-0.08	0.15	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.23-0.36	0.31	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.17-0.34	0.25	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	1	ND-0.08	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	3	0.18-0.24	0.22	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	3	0.23-0.35	0.27	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.17-0.26	0.21	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	0.08-0.18	0.12	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	8	NR	0.28	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	7	NR	0.56	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	5	NR	0.25	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	3	NR	0.22	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	4	NR	0.18	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	9	NR	0.53	Fat	Various U.S. Sites	Background	1996	21	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0.22-3.1	0.62	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0.18-2.5	0.59	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0.09-17	1.1	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0.02-2.0	0.40	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	0.48	Fat	Russia		1996	24	supermarkets
2,3,4,7,8-PeCDF	Smoked Sausage	NR	NR	NR	0.51	Fat	Russia		1996	24	supermarkets
(continued)	Chicken	NR	NR	NR	0.68	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.39	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.71	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.63	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	1.3	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	0.7	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	0.2	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.5	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	0.7	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	0.5	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	1.5	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	0.1	Fat	Spain		1996	25	supermarkets
	Butter	21	20	ND-2.06	0.86	Fat	Spain		NR	26	supermarkets
PeCDFs	Cottage cheese	1	1	0.3	0.03	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	5	5	Wet	New York, NY		1990	8	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Heavy Cream cheese	1	1	2	2	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	2	2	Wet	New York, NY		1990	8	
	American cheese	1	1	2	2	Wet	New York, NY		1990	8	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	NR	NR	30.8	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Eggs	3	0	NR	0.12	Whole	Various U.S. Sites		1996	22	
	Butter	21	21	0.50-9.58	1.72	Fat	Spain		NR	26	supermarkets
Hexachlorodibenzofurans (MW=374.87)											
1,2,3,4,7,8-HxCDF	Milk	2	2	0.017-0.020	0.018	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.026-0.13	0.075	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.9	0.9	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.43	0.43	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.8	0.8	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.15	0.15	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.9	0.9	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.4	0.4	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	10	0.7-3.0	1.7	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	NR	ND-2.6	0.8	Fat	W. Germany		NR	5	
	Butter	5	NR	ND-1.0	0.7	Fat	W. Germany		NR	5	
	Beef	3	NR	ND-1.1	0.7	Fat	W. Germany		NR	5	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Veal	4	4	1.8-6.0	2.9	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	1	ND-1.4	0.8	Fat	W. Germany		NR	5	
	Chicken	2	1	ND-1.9	1.0	Fat	W. Germany		NR	5	
	Canned meat	2	2	0.6-0.9	0.8	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Milk	7	7	0.013-0.026	0.017[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	1	1.05	1.05	Wet	USSR		88-89	7	
	Beef	1	1	0.141	0.141	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.108	0.108	Wet	USSR		88-89	7	
1,2,3,4,7,8-HxCDF (continued)	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	1	0.432	0.432	Wet	USSR		88-89	7	
	Butter	1	1	2.01	2.01	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.009	0.009	Wet	USSR		88-89	7	
	Sausage	1	1	0.171	0.171	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.27	0.27	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.79	0.79	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.48	0.48	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.06	0.06	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	0.93	0.93	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	1	0.47	0.47	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	0.43	0.43	Wet	New York, NY		1990	8	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	American cheese	1	1	0.36	0.36	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.38-1.19)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.35-0.79)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(0.49-3.40)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	0	ND(0.40-3.33)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	0	ND(0.35-0.59)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.51-0.71)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.14-0.25)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.04-0.09)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	3	0.066-4.846	1.69	Wet	New York, NY		1990	10	
	Pork	1	1	0.108	0.108	Wet	New York, NY		1990	10	
	Chicken	1	1	0.009	0.009	Wet	New York, NY		1990	10	
1,2,3,4,7,8-HxCDF (continued)	Beef	63	8	ND-4.29	0.55	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	2	2	0.1-0.37	0.235	Whole	United Kingdom		88-91	12	
	Offals	2	1	ND-0.40	0.22	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.06-0.08	0.07	Whole	United Kingdom		88-91	12	
	Meat Products	2	2	0.06-0.14	0.1	Whole	United Kingdom		88-91	12	
	Milk Products	2	1	ND-0.02	0.0125	Whole	United Kingdom		88-91	12	
	Butter	4	NR	0.43-0.48	0.455	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.5	0.5	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	1	0.5	0.5	Whole	United Kingdom		88-91	12	
	Fats & Oils	2	1	ND-0.21	0.17	Whole	United Kingdom	Rural	88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Eggs	2	2	0.04-0.09	0.065	Whole	United Kingdom		88-91	12	
	Green Vegetables	2	1	ND-0.01	0.0075	Whole	United Kingdom		88-91	12	
	Other Vegetables	2	1	ND-0.05	0.04	Whole	United Kingdom		88-91	12	
	Potatoes	1	1	0.01	0.01	Whole	United Kingdom		88-91	12	
	Fresh Fruit	2	1	ND-0.03	0.02	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.42-0.73	0.56	Fat	Switzerland		1990	13	
	Milk	27	NR	0.22-0.47	0.31	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
1,2,3,4,7,8-HxCDF (continued)	Milk	20	NR	ND-63	21	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.302	0.083	Whole	Finland		1991	17	
	Beef	20	NR	ND	NA	Fat	Finland		1991	17	
	Pork	20	NR	ND-0.9	0.27	Fat	Finland		1991	17	
	Milk	3	3	0.12-0.35	0.25	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.45-0.48	0.52	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.28-0.57	0.46	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	1	ND-0.14	0.07	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	3	0.21-0.22	0.21	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken Liver	3	3	0.32-0.5	0.4	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.38-0.81	0.55	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	0.14-1.2	0.62	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	8	NR	0.39	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	15	NR	0.98	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	5	NR	0.23	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	2	NR	0.16	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	3	NR	0.17	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	8	NR	0.32	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	0	NR	0.67	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0.10-1.9	0.32	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0.06-0.76	0.29	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0.08-10	0.91	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0.03-2.1	0.28	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	24	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8-HxCDF (continued)	Smoked Sausage	NR	NR	NR	0.7	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	1.24	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.28	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.47	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.49	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.74	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	3.3	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	1.0	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.5	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	2.1	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	2.0	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	2.0	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	0.6	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-0.93	NR	Fat	Spain		NR	26	supermarkets
1,2,3,6,7,8-HxCDF	Food basket	3	0	ND(0.1-0.8)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	2	0.021-0.028	0.024	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.018-0.19	0.090	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.8	0.8	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.44	0.44	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.07	0.07	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	1.2	1.2	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken	1	1	0.4	0.4	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	3	
1,2,3,6,7,8-HxCDF	Milk	10	10	0.5-2.0	1.1	Fat	W. Germany		NR	5	samples not randomly selected
(continued)	Cheese	10	NR	ND-0.9	0.5	Fat	W. Germany		NR	5	
	Butter	5	NR	ND-1.0	0.7	Fat	W. Germany		NR	5	
	Beef	3	NR	ND-0.9	0.5	Fat	W. Germany		NR	5	
	Veal	4	4	1.3-5.0	2.4	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	1	ND-1.0	0.6	Fat	W. Germany		NR	5	
	Chicken	2	2	0.3-0.8	0.5	Fat	W. Germany		NR	5	
	Canned meat	2	1	ND-0.7	0.5	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Milk	7	7	0.009-0.017	0.012[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	1	0.240	0.240	Wet	USSR		88-89	7	
	Beef	1	1	0.030	0.030	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.108	0.108	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	1	0.144	0.144	Wet	USSR		88-89	7	
	Butter	1	1	0.424	0.424	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.009	0.009	Wet	USSR		88-89	7	
	Sausage	1	1	0.171	0.171	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.14	0.14	Wet	South Vietnam		NR	7	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Pork fat	1	1	0.40	0.40	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.38	0.38	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.02	0.02	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	0.34	0.34	Wet	New York, NY		1990	8	
1,2,3,6,7,8-HxCDF	Heavy Cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	8	
(continued)	Soft cream cheese	1	1	0.18	0.18	Wet	New York, NY		1990	8	
	American cheese	1	1	0.1	0.1	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.37-1.17)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.35-0.77)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(0.48-0.81)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	0	ND(0.39-0.84)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	0	ND(0.35-0.56)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.14-0.70)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.14-0.31)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.04-0.05)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	3	ND-0.199	NA	Wet	New York	1990	1990	10	
	Pork	1	1	0.031	0.031	Wet	New York		1990	10	
	Chicken	1	1	0.008	0.008	Wet	New York		1990	10	
	Beef	63	7	ND-1.96	0.40	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	2	2	0.05-0.36	0.205	Whole	United Kingdom		88-91	12	
	Offals	2	1	ND-0.42	0.23	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.03-0.05	0.04	Whole	United Kingdom		88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Meat Products	2	2	0.02-0.08	0.05	Whole	United Kingdom		88-91	12	
	Milk Products	1	1	0.02	0.02	Whole	United Kingdom		88-91	12	
	Butter	4	NR	0.4-0.5	0.45	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	1	0.04	0.04	Whole	United Kingdom		88-91	12	
	Fats & Oils	2	1	ND-0.2	0.148	Whole	United Kingdom	Rural	88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,6,7,8-HxCDF	Eggs	2	2	0.02-0.05	0.035	Whole	United Kingdom		88-91	12	
(continued)	Green Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Other Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Potatoes	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Fresh Fruit	2	1	ND-0.01	0.008	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.35-0.81	0.51	Fat	Switzerland		1990	13	
	Milk	27	NR	0.20-0.54	0.26	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-65	22	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.295	0.087	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	NR	ND-1.0	0.28	Fat	Finland		1991	17	
	Milk	3	3	0.12-0.34	0.23	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.26-0.39	0.32	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.28-0.42	0.34	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	1	ND-0.08	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	3	0.05-0.08	0.07	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken Liver	3	3	0.09-0.22	0.17	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,6,7,8-HxCDF	Ground Beef	3	3	0.2-0.39	0.28	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
(continued)	Sausage	3	3	0.08-0.21	0.16	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	8	NR	0.25	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	12	NR	0.58	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	5	NR	0.20	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	2	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	1	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	1	NR	0.17	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	0	NR	0.77	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-1.3	0.26	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0.06-0.69	0.25	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0.05-5.5	0.53	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0.02-1.7	0.17	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	0.38	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	0.81	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.17	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.25	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.24	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.51	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	0.9	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	0.5	Dry	Spain		1996	25	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Fruits	2	NR	NR	0.4	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	0.7	Fat	Spain		1996	25	supermarkets
1,2,3,6,7,8-HxCDF	Eggs	2	NR	NR	0.4	Fat	Spain		1996	25	supermarkets
(continued)	Milk & Dairy	6	NR	NR	0.8	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	0.4	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-0.94	NR	Fat	Spain		NR	26	supermarkets
1,2,3,7,8,9-HxCDF	Food basket	3	0	ND(0.1-0.3)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	7	0	ND(.002-.012)	0.008[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	0	ND(0.04)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.01)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.11)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	0	ND(0.14)	NA	Wet	USSR		88-89	7	
	Butter	1	0	ND(0.16)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	0	ND(0.01)	NA	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.11)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	0	ND(0.1)	NA	Wet	South Vietnam		NR	7	
	Pork fat	1	0	ND(0.2)	NA	Wet	South Vietnam		NR	7	
	Chicken fat	1	0	ND(0.19)	NA	Wet	South Vietnam		NR	7	
	Cottage cheese	1	0	ND(0.006)	NA	Wet	New York, NY		1990	8	
	Soft blue cheese	1	0	ND(0.1)	NA	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	0	ND(0.04)	NA	Wet	New York, NY		1990	8	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Soft cream cheese	1	0	ND(0.04)	NA	Wet	New York, NY		1990	8	
	American cheese	1	0	ND(0.05)	NA	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.48-1.51)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.45-1.01)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
1,2,3,7,8,9-HxCDF	Pork	5	0	ND(0.62-1.06)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
(continued)	Pork	3	0	ND(0.51-1.09)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	0	ND(0.45-0.75)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.18-0.91)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.18-0.58)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.05-0.06)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.002-0.01)	NA	Wet	New York, NY		1990	10	
	Pork	1	0	ND(0.007)	NA	Wet	New York, NY		1990	10	
	Chicken	1	0	ND(0.012)	NA	Wet	New York, NY		1990	10	
	Beef	63	0	ND	NA	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	1	1	0.36	0.36	Whole	United Kingdom		88-91	12	
	Offals	1	1	0.01	0.01	Whole	United Kingdom		88-91	12	
	Butter	4	NR	ND-0.02	0.02	Whole	United Kingdom		88-91	12	
	Fats & Oils	2	0	ND	NA	Whole	United Kingdom	Rural	88-91	12	
	Eggs	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.02-0.06	0.03	Fat	Switzerland		1990	13	
	Milk	27	0	ND	NA	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,7,8,9-HxCDF	Milk	20	0	ND	NA	Whole	Finland		1991	17	
(continued)	Eggs	20	0	ND	NA	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Milk	3	0	ND(0.03)	0.03	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	0	ND(0.01-0.02)	0.01	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	0	ND(0.01-0.02)	0.02	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	0	ND(0.03-0.04)	0.03	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	1	ND-0.07	0.05	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	0	ND(0.03-0.04)	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.01-0.02	0.02	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	0.06-0.15	0.1	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	0	NR	0.05	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	0	NR	0.45	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	0	NR	0.63	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-0.11	0.01	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0-0.29	0.01	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0-0.62	0.03	Fat	Germany		93-96	23	official food inspection

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Meat	107	NR	0-0.12	0.02	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	24	supermarkets
1,2,3,7,8,9-HxCDF	Smoked Sausage	NR	NR	NR	0.42	Fat	Russia		1996	24	supermarkets
(continued)	Chicken	NR	NR	NR	0.94	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.16	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.20	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.17	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.44	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	0.9	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	0.3	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.06	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	0.1	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	0.1	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	0.2	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	ND	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-3.1	NR	Fat	Spain		NR	26	supermarkets
2,3,4,6,7,8-HxCDF	Food basket	3	0	ND(0.1-0.5)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	1	ND-0.020	0.015	Whole	Switzerland	Background	NR	2	
	Milk	4	4	0.018-0.28	0.12	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.7	0.7	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.31	0.31	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	1.3	1.3	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Pork	1	1	0.05	0.05	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	1.5	1.5	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	1.7	1.7	Fat	Berlin, W. Germany	Urban	NR	3	
2,3,4,6,7,8-HxCDF	Milk	10	10	0.7-2.2	1.3	Fat	W. Germany		NR	5	samples not randomly selected
(continued)	Cheese	10	NR	ND-1.1	0.7	Fat	W. Germany		NR	5	
	Butter	5	NR	ND-1.0	0.7	Fat	W. Germany		NR	5	
	Beef	3	NR	ND-1.5	0.9	Fat	W. Germany		NR	5	
	Veal	4	4	1.7-5.0	2.8	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	1	ND-0.9	0.5	Fat	W. Germany		NR	5	
	Chicken	2	1	ND-1.2	0.7	Fat	W. Germany		NR	5	
	Canned meat	2	1	ND-0.6	0.4	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Milk	7	7	0.007-0.017	0.012[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	1	0.060	0.060	Wet	USSR		88-89	7	
	Beef	1	1	0.009	0.009	Wet	USSR		88-89	7	
	Cheese w/butter	1	1	0.072	0.072	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	1	0.144	0.144	Wet	USSR		88-89	7	
	Butter	1	1	0.159	0.159	Wet	USSR		88-89	7	
	Swiss cheese	1	1	0.006	0.006	Wet	USSR		88-89	7	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Sausage	1	1	0.114	0.114	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.10	0.10	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.20	0.20	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.19	0.19	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.01	0.01	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	0.15	0.15	Wet	New York, NY		1990	8	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,4,6,7,8-HxCDF	Heavy Cream cheese	1	1	0.11	0.11	Wet	New York, NY		1990	8	
(continued)	Soft cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	8	
	American cheese	1	1	0.07	0.07	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.44-1.39)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.41-0.92)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(0.57-0.97)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	0	ND(0.47-1.00)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	0	ND(0.41-0.69)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.17-0.84)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.16-0.52)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.04-0.05)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	3	0.01-0.177	0.075	Wet	New York, NY		1990	10	
	Pork	1	1	0.019	0.019	Wet	New York, NY		1990	10	
	Chicken	1	0	ND(0.01)	NA	Wet	New York, Ny		1990	10	
	Beef	63	5	ND-1.75	0.39	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	2	2	0.07-0.38	0.225	Whole	United Kingdom		88-91	12	
	Offals	1	1	0.42	0.42	Whole	United Kingdom		88-91	12	
	Poultry	2	1	ND-0.05	0.035	Whole	United Kingdom		88-91	12	
	Meat Products	2	0	ND	NA	Whole	United Kingdom		88-91	12	
	Milk Products	2	1	ND-0.01	0.02	Whole	United Kingdom		88-91	12	
	Butter	4	NR	0.38-0.47	0.43	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.04	0.04	Whole	United Kingdom		88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,4,6,7,8-HxCDF	Reduced Fat Cheese	1	1	0.03	0.03	Whole	United Kingdom		88-91	12	
(continued)	Fats & Oils	2	0	ND	NA	Whole	United Kingdom	Rural	88-91	12	
	Eggs	2	2	0.02-0.04	0.03	Whole	United Kingdom		88-91	12	
	Green Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Potatoes	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.39-0.98	0.61	Fat	Switzerland		1990	13	
	Milk	27	NR	ND-0.33	0.22	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-69	20	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.4	0.127	Whole	Finland		1991	17	
	Beef	20	NR	ND	NA	Fat	Finland		1991	17	
	Pork	20	NR	ND	NA	Fat	Finland		1991	17	
	Milk	3	3	0.11-0.28	0.19	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.09-0.4	0.21	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.18-0.25	0.22	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	1	ND-0.06	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	2	ND-0.08	0.07	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken Liver	3	2	ND-0.29	0.2	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
2,3,4,6,7,8-HxCDF	Ground Beef	3	3	0.18-0.3	0.24	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
(continued)	Sausage	3	3	0.08-0.45	0.22	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	8	NR	0.28	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	9	NR	0.57	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	6	NR	0.21	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	2	NR	0.14	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	2	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	2	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	0	NR	0.56	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-1.4	0.24	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0-0.63	0.23	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0.04-5.8	0.47	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0.02-0.72	0.15	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	ND	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	0.66	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	1.22	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.19	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.28	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.22	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.62	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	ND	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	ND	Dry	Spain		1996	25	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Fruits	2	NR	NR	0.05	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	ND	Fat	Spain		1996	25	supermarkets
2,3,4,6,7,8-HxCDF	Eggs	2	NR	NR	ND	Fat	Spain		1996	25	supermarkets
(continued)	Milk & Dairy	6	NR	NR	ND	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	ND	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-1.27	NR	Fat	Spain		NR	26	supermarkets
HxCDF	Beef	9	NR	NR	1.13	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Eggs	3	0	NR	0.62	Whole	Various U.S. Sites		1995	22	
	Butter	21	21	ND-5.56	NR	Dry	Spain		NR	26	supermarkets
Heptachlorodibenzofuran(MW=409.31)											
1,2,3,4,6,7,8-HpCDF	Food basket	3	0	ND(0.2-0.9)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	1	ND-0.12	0.08	Whole	Switzerland	Background	NR	2	
	Milk	4	3	ND-0.49	0.25	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	0.5	0.5	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.34	0.34	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	2.2	2.2	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	1.1	1.1	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	8.1	8.1	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.8	0.8	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Milk	10	10	0.2-6.0	1.5	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	NR	ND-1.1	0.5	Fat	W. Germany		NR	5	
	Butter	5	NR	ND-1.0	0.3	Fat	W. Germany		NR	5	
	Beef	3	NR	ND-5.1	2.0	Fat	W. Germany		NR	5	
1,2,3,4,6,7,8-HpCDF	Veal	4	4	0.7-4.0	1.7	Fat	W. Germany		NR	5	
(continued)	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	2	0.6-1.4	1.0	Fat	W. Germany		NR	5	
	Chicken	2	2	0.5-0.5	0.5	Fat	W. Germany		NR	5	
	Canned meat	2	2	0.9-1.9	1.2	Fat	W. Germany		NR	5	
	Lard	4	NR	ND-0.5	0.2	Fat	W. Germany		NR	5	
	Milk	7	0	ND(.007-.067)	0.020[c]	Whole	England & Wales	Rural	89	6	
	Cow cream	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.18)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
	Butter	1	0	ND(0.26)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.10	0.10	Wet	South Vietnam		NR	7	
	Pork fat	1	1	0.40	0.40	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.38	0.38	Wet	South Vietnam		NR	7	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Cottage cheese	1	1	0.1	0.1	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	1.76	1.76	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	1	0.6	0.6	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	0.58	0.58	Wet	New York, NY		1990	8	
	American cheese	1	1	0.52	0.52	Wet	New York, NY		1990	8	
	Beef	5	3	ND-1.15	0.96	Fat	Los Angeles	Urban	NR	9	composite 6 samples
1,2,3,4,6,7,8-HpCDF	Beef	3	1	ND-0.67	0.74	Fat	San Francisco	Urban	NR	9	composite 6 samples
(continued)	Pork	5	4	ND-10.60	4.05	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	3	2.09-5.68	3.55	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	5	1.57-24.60	7.00	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	1	ND-1.01	0.51	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Eggs	5	0	ND(0.06-0.77)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	1	ND-0.07	0.05	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	3	0.018-2.702	1	Wet	New York, NY		1990	10	
	Pork	1	1	1.251	1.251	Wet	New York, NY		1990	10	
	Chicken	1	1	0.024	0.024	Wet	New York, NY		1990	10	
	Beef	63	14	ND-10.11	1.00	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	2	2	0.12-0.5	0.31	Whole	United Kingdom		88-91	12	
	Offals	2	2	2.5-5.2	3.9	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.72-1.5	1.1	Whole	United Kingdom		88-91	12	
	Meat Products	2	2	0.1-0.34	0.22	Whole	United Kingdom		88-91	12	
	Milk Products	2	1	ND-0.04	0.098	Whole	United Kingdom		88-91	12	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Butter	4	NR	0.32-0.33	0.325	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.10	0.10	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	1	0.06	0.06	Whole	United Kingdom		88-91	12	
	Fats & Oils	2	1	ND-0.61	0.55	Whole	United Kingdom		88-91	12	
	Eggs	2	2	0.10-0.12	0.11	Whole	United Kingdom		88-91	12	
	Green Vegetables	2	2	0.03-0.04	0.035	Whole	United Kingdom		88-91	12	
	Other Vegetables	2	2	0.16-0.26	0.21	Whole	United Kingdom		88-91	12	
1,2,3,4,6,7,8-HpCDF	Potatoes	2	2	0.03-0.15	0.09	Whole	United Kingdom		88-91	12	
(continued)	Fresh Fruit	2	2	0.03-0.09	0.06	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.20-0.53	0.36	Fat	Switzerland		1990	13	
	Milk	27	NR	ND-0.23	<0.02	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-390	50	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.282	0.069	Whole	Finland		1991	17	
	Beef	20	NR	ND	NA	Fat	Finland		1991	17	
	Pork	20	NR	ND	NA	Fat	Finland		1991	17	
	Milk	3	0	ND(0.29-1.00)	0.73	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Cheddar Cheese	3	3	0.55-0.93	0.68	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.74-1.3	1.01	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	3	0.18-0.33	0.25	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	3	0.21-2.9	1.25	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	3	0.63-0.99	0.78	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.88-2.7	1.63	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	3.3-4.3	3.83	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	8	NR	0.83	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	45	NR	3.56	Fat	Various U.S. Sites	Background	1995	20	
1,2,3,4,6,7,8-HpCDF	Young Chickens	39	19	NR	0.27	Fat	Various U.S. Sites	Background	1996	21	
(continued)	Light Fowl	12	4	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	4	NR	0.20	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	2	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	NR	NR	0.28	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-2.9	0.20	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0.02-0.45	0.17	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0.06-36	1.5	Fat	Germany		93-96	23	official food inspection
	Meat	107	NR	0.03-7.2	0.45	Fat	Germany		93-96	23	official food inspection
	Beef	NR	NR	NR	1.32	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	0.87	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	1.92	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.42	Fat	Russia		1996	24	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Goose Fat	NR	NR	NR	0.54	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.47	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	1.15	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	23.5	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	5.6	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.2	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	1.9	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	0.9	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	1.1	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	0.8	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-1.33	NR	Fat	Spain		NR	26	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
1,2,3,4,7,8,9-HpCDF	Food basket	3	0	ND(0.3-1.6)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	7	0	ND(0.01-.067)	0.026[c]	Whole	England & Wales	Rural	1989	6	
	Cow cream	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Cheese w/butter	1	0	ND(0.18)	NA	Wet	USSR		88-89	7	
	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
	Butter	1	0	ND(0.26)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	0	ND(0.07)	NA	Wet	South Vietnam		NR	7	
	Pork fat	1	0	ND(0.3)	NA	Wet	South Vietnam		NR	7	
	Chicken fat	1	0	ND(0.19)	NA	Wet	South Vietnam		NR	7	
	Cottage cheese	1	0	ND(0.03)	NA	Wet	New York, NY		1990	8	
	Soft blue cheese	1	0	ND(0.34)	NA	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	1	0.14	0.14	Wet	New York, NY		1990	8	
	Soft cream cheese	1	0	ND(0.18)	NA	Wet	New York, NY		1990	8	
	American cheese	1	0	ND(0.12)	NA	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.37-3.28)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.78-2.37)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	0	ND(2.22-5.40)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	0	ND(1.63-3.12)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken	5	0	ND(0.47-4.10)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.45-0.75)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
1,2,3,4,7,8,9-HpCDF	Eggs	5	0	ND(0.09-1.10)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
(continued)	Eggs	3	0	ND(0.04-0.18)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	2	ND-0.118	NA	Wet	New York, NY		1990	10	
	Pork	1	1	0.097	0.097	Wet	New York, NY		1990	10	
	Chicken	1	0	ND(0.01)	NA	Wet	New York, NY		1990	10	
	Beef	63	0	ND	NA	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	1	1	0.41	0.41	Whole	United Kingdom		88-91	12	
	Offals	2	2	0.1-0.13	0.115	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.02-0.1	0.06	Whole	United Kingdom		88-91	12	
	Meat Products	1	1	0.03	0.03	Whole	United Kingdom		88-91	12	
	Milk Products	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Butter	2	0	ND	NA	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	1	0.02	0.02	Whole	United Kingdom		88-91	12	
	Fats & Oils	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Other Vegetables	1	0	ND	NA	Whole	United Kingdom		88-91	12	
	Potatoes	2	0	ND	NA	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.04-0.09	0.05	Fat	Switzerland		1990	13	
	Milk	27	0	ND	NA	Fat	Germany		1992	14	
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
1,2,3,4,7,8,9-HpCDF	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
(continued)	Fried Chicken	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Milk	20	NR	ND-97	25	Whole	Finland		1991	17	
	Eggs	20	0	ND	NA	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Milk	3	0	ND(0.03-0.04)	0.03	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.04-0.09	0.05	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	1	ND-0.07	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	0	ND(0.03-0.07)	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	2	ND-0.04	0.04	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	3	0.1-0.15	0.13	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.04-0.09	0.07	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	0.06-0.2	0.12	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	0	NR	0.05	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	10	NR	0.57	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	4	NR	0.17	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Heavy Fowl	12	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Young Turkeys	15	0	NR	0.15	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	NR	NR	0.12	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-0.61	0.02	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0-0.21	0.02	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0-5.8	0.19	Fat	Germany		93-96	23	official food inspection
1,2,3,4,7,8,9-HpCDF	Meat	107	NR	0-0.71	0.06	Fat	Germany		93-96	23	official food inspection
(continued)	Beef	NR	NR	NR	ND	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	0.54	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	0.74	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.13	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.15	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.13	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	0.48	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	2.2	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	0.6	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.2	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	0.5	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	0.5	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	0.4	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	ND	Fat	Spain		1996	25	supermarkets
	Butter	21	21	ND-0.63	NR	Fat	Spain		NR	26	supermarkets
HpCDF	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Eggs	3	NR	NR	1.1	Whole	Various U.S. Sites		1995	22	
	Butter	21	21	0.36-8.85	1.72	Fat	Spain		NR	26	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
Octachlorodibenzofurans (MW=444.76)											
1,2,3,4,6,7,8,9-OCDF	Food basket	3	0	ND(0.4-2.1)	NA	Fresh	Sweden	Urban	NR	1	
	Milk	2	1	ND-0.20	0.12	Whole	Switzerland	Background	NR	2	
	Milk	4	1	ND-0.52	0.19	Whole	Switzerland	Industrial	NR	2	near incinerators
	Milk	1	1	1	1	Fat	W. Germany		NR	3	composite from 8 trucks
	Butter	1	1	0.25	0.25	Fat	Berlin, W. Germany	Urban	NR	3	
	Beef fat	1	1	0.2	0.2	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Pork	1	1	0.41	0.41	Fat	Berlin, W. Germany	Urban	NR	3	
	Sheep fat	1	1	0.3	0.3	Fat	Berlin, W. Germany	Urban	NR	3	from slaughterhouse
	Chicken	1	1	0.6	0.6	Fat	Berlin, W. Germany	Urban	NR	3	
	Eggs	1	1	0.2	0.2	Fat	Berlin, W. Germany	Urban	NR	3	
	Milk	10	NR	ND-4.3	1.2	Fat	W. Germany		NR	5	samples not randomly selected
	Cheese	10	10	0.4-4.2	1.2	Fat	W. Germany		NR	5	
	Butter	5	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Beef	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Veal	4	NR	ND-5.0	1.4	Fat	W. Germany		NR	5	
	Pork	3	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Sheep	2	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Chicken	2	2	0.6-1.5	1.0	Fat	W. Germany		NR	5	
	Canned meat	2	2	0.3-2.7	1.3	Fat	W. Germany		NR	5	
	Lard	4	0	ND(0.3)	NA	Fat	W. Germany		NR	5	
	Milk	7	7	0.023-0.071	0.041[c]	Whole	England & Wales	Rural	89	6	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Cow cream	1	0	ND(0.07)	NA	Wet	USSR		88-89	7	
	Beef	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
1,2,3,4,6,7,8,9-OCDF	Cheese w/butter	1	0	ND(0.18)	NA	Wet	USSR		88-89	7	
(continued)	Beef fat	1	0	ND(0.17)	NA	Wet	USSR		88-89	7	
	Pork	1	0	ND(0.36)	NA	Wet	USSR		88-89	7	
	Butter	1	0	ND(0.26)	NA	Wet	USSR		88-89	7	
	Swiss cheese	1	0	ND(0.02)	NA	Wet	USSR		88-89	7	
	Sausage	1	0	ND(0.29)	NA	Wet	Moscow, USSR		88-89	7	
	Pork sticks	1	1	0.10	0.10	Wet	South Vietnam		NR	7	
	Pork fat	1	0	ND(0.3)	NA	Wet	South Vietnam		NR	7	
	Chicken fat	1	1	0.57	0.57	Wet	South Vietnam		NR	7	
	Cottage cheese	1	1	0.06	0.06	Wet	New York, NY		1990	8	
	Soft blue cheese	1	1	1.08	1.08	Wet	New York, NY		1990	8	
	Heavy Cream cheese	1	1	0.29	0.29	Wet	New York, NY		1990	8	
	Soft cream cheese	1	1	0.29	0.29	Wet	New York, NY		1990	8	
	American cheese	1	1	0.3	0.03	Wet	New York, NY		1990	8	
	Beef	5	0	ND(0.48-5.31)	NA	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Beef	3	0	ND(0.45-2.15)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Pork	5	4	ND-9.36	2.90	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Pork	3	1	ND-1.89	1.20	Fat	San Francisco	Urban	NR	9	composite 6 samples
	Chicken	5	2	ND-26.00	6.64	Fat	Los Angeles	Urban	NR	9	composite 6 samples
	Chicken	3	0	ND(0.64-0.77)	NA	Fat	San Francisco	Urban	NR	9	composite 6 samples

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Eggs	5	0	ND(0.10-1.30)	NA	Whole	Los Angeles	Urban	NR	9	composite 6 samples
	Eggs	3	0	ND(0.05-0.21)	NA	Whole	San Francisco	Urban	NR	9	composite 6 samples
	Beef	3	3	0.018-1.073	0.381	Wet	New York, NY		1990	10	
	Pork	1	1	0.821	0.821	Wet	New York, NY		1990	10	
1,2,3,4,6,7,8,9-OCDF	Chicken	1	1	0.034	0.034	Wet	New York, NY		1990	10	
(continued)	Beef	63	0	ND	NA	Fat	Various U.S. Sites	Federally-Inspected Slaughter Houses	1994	11	statistically-based survey
	Carcass Meat	2	2	0.16-11.0	5.58	Whole	United Kingdom		88-91	12	
	Offals	1	1	1.2	1.2	Whole	United Kingdom		88-91	12	
	Poultry	2	2	0.51-0.52	0.515	Whole	United Kingdom		88-91	12	
	Meat Products	2	2	1.5-3.8	2.65	Whole	United Kingdom		88-91	12	
	Milk Products	2	1	ND-0.46	0.275	Whole	United Kingdom		88-91	12	
	Butter	4	NR	ND-0.16	0.103	Whole	United Kingdom		88-91	12	
	Cheddar Cheese	1	1	0.1	0.1	Whole	United Kingdom		88-91	12	
	Reduced Fat Cheese	1	1	0.07	0.07	Whole	United Kingdom		88-91	12	
	Fats & Oils	2	1	ND-2.3	1.34	Whole	United Kingdom		88-91	12	
	Eggs	2	2	0.03-0.05	0.04	Whole	United Kingdom		88-91	12	
	Green Vegetables	2	2	0.04	0.04	Whole	United Kingdom		88-91	12	
	Other Vegetables	2	2	0.17-0.27	0.22	Whole	United Kingdom		88-91	12	
	Potatoes	2	2	0.13-0.47	0.30	Whole	United Kingdom		88-91	12	
	Fresh Fruit	2	2	0.15-0.18	0.165	Whole	United Kingdom		88-91	12	
	Milk	9	9	0.10-0.32	0.18	Fat	Switzerland		1990	13	
	Milk	27	NR	ND-0.29	<0.02	Fat	Germany		1992	14	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Beef	9	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Chicken	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Pork	7	0	ND	NA	Fat	Various U.S. Sites		NR	15	
	Hamburger	1	0	ND	NA	Whole	U.S.		NR	16	fast food
	Pizza	1	0	ND	NA	Whole	U.S.		NR	16	fast food
1,2,3,4,6,7,8,9-OCDF	Fried Chicken	1	1	0.385	0.385	Whole	U.S.		NR	16	fast food
(continued)	Milk	20	NR	ND-38	16	Whole	Finland		1991	17	
	Eggs	20	NR	ND-0.105	0.032	Whole	Finland		1991	17	
	Beef	20	0	ND	NA	Fat	Finland		1991	17	
	Pork	20	0	ND	NA	Fat	Finland		1991	17	
	Milk	3	0	ND(0.06-0.07)	0.06	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Cheddar Cheese	3	3	0.18-0.59	0.36	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Butter	3	3	0.23-0.61	0.42	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Eggs	3	3	0.25-0.42	0.31	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken	3	3	0.3-1.5	0.68	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Chicken Liver	3	3	0.39-1.3	0.83	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Ground Beef	3	3	0.26-0.86	0.51	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Sausage	3	3	1.2-2.3	1.63	Fat	S. Mississippi	NR	1994	18	purchased from a grocery store
	Milk	8	0	NR	0.05	Fat	Various U.S. Sites	Background	1996	19	
	Pork	78	41	NR	2.30	Fat	Various U.S. Sites	Background	1995	20	
	Young Chickens	39	5	NR	0.34	Fat	Various U.S. Sites	Background	1996	21	
	Light Fowl	12	0	NR	0.29	Fat	Various U.S. Sites	Background	1996	21	

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Chemical	Sample type[a]	Number samples	Number positive samples	Concentration range	Conc. mean[b]	Wt. basis	Location	Location description	Sample year	Ref. no.	Comments
	Heavy Fowl	12	1	NR	0.31	Fat	Various U.S. Sites	Background	1996	21	
	Young Turkeys	15	0	NR	0.29	Fat	Various U.S. Sites	Background	1996	21	
	Eggs	3	NR	NR	1.34	Whole	Various U.S. Sites		1995	22	
	Milk	538	NR	0-2.5	0.11	Fat	Germany		93-96	23	official food inspection
	Butter	222	NR	0-0.67	0.09	Fat	Germany		93-96	23	official food inspection
	Eggs	218	NR	0-46	1.8	Fat	Germany		93-96	23	official food inspection
1,2,3,4,6,7,8,9-OCDF	Meat	107	NR	0.05-6.0	0.32	Fat	Germany		93-96	23	official food inspection
(continued)	Beef	NR	NR	NR	2.5	Fat	Russia		1996	24	supermarkets
	Smoked Sausage	NR	NR	NR	1.99	Fat	Russia		1996	24	supermarkets
	Chicken	NR	NR	NR	1.57	Fat	Russia		1996	24	supermarkets
	Pork	NR	NR	NR	0.48	Fat	Russia		1996	24	supermarkets
	Goose Fat	NR	NR	NR	0.83	Fat	Russia		1996	24	supermarkets
	Duck Fat	NR	NR	NR	0.52	Fat	Russia		1996	24	supermarkets
	Chicken Fat	NR	NR	NR	1.07	Fat	Russia		1996	24	supermarkets
	Vegetables	2	NR	NR	119.5	Dry	Spain		1996	25	supermarkets
	Pulses & Cereals	4	NR	NR	42.5	Dry	Spain		1996	25	supermarkets
	Fruits	2	NR	NR	0.8	Dry	Spain		1996	25	supermarkets
	Meats	7	NR	NR	8.2	Fat	Spain		1996	25	supermarkets
	Eggs	2	NR	NR	3.7	Fat	Spain		1996	25	supermarkets
	Milk & Dairy	6	NR	NR	3.5	Fat	Spain		1996	25	supermarkets
	Fats & Oils	4	NR	NR	1.8	Fat	Spain		1996	25	supermarkets
	Butter	21	16	ND-3.18	NR	Fat	Spain		NR	26	supermarkets

Table B-15. Levels of Dibenzofurans in Food Products (ppt) (continued)

Footnote references

[a] Samples were obtained from grocery stores unless stated otherwise. Milk samples were obtained from dairies or transport trucks. No cooked samples from the references were used.
[b] For ND values 1/2 LOD was used in calculating the mean. Therefore, it is possible to have mean concentrations greater than the range (e.g., reported detection limit for nondetects greater than the positive sample).
[c] For ND values the detection limit was used in calculating the mean.

NR = not reported.
NA = not applicable.

Sources:
1. De Wit et al. (1990)
2. Rappe et al. (1987)
3. Beck et al. (1989)
4. LaFleur et al. (1990)
5. Furst et al. (1990)
6. Startin et al. (1990)
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Table B-16. Environmental Levels of PCBs in Food (ppt)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
Tetrachloro-PCB (MW=291.99)											
77	3,3',4,4'-TCB	Beef	6	NR	0.6-38	13	Finland	Urban	NR	1	
		Pork	3	NR	1.0-24	13	Finland	Urban	NR	1	
		Poultry	2	NR	NR	8.2	Finland	Urban	NR	1	
		Inner Organs	5	NR	ND-7.9	3.2	Finland	Urban	NR	1	
		Eggs	2	NR	NR	4.1	Finland	Urban	NR	1	
		Fish Liver Oil	2	NR	NR	2,700	Finland	Urban	NR	1	
		Milk	17	NR	NR	4.0	The Netherlands	Agricultural	NR	2	
		Milk	5	NR	NR	3.3	The Netherlands	Industrial	NR	2	
		Milk	7	NR	NR	8.9	The Netherlands	Near Waste Incinerator	NR	2	
		Milk	10	NR	NR	8.4	The Netherlands	Outlying Land of Main Rivers	NR	2	
		Beef	NR	NR	NR	1	Canada	Urban	86-88	3	
		Butter	NR	NR	NR	6	Canada	Urban	86-88	3	
		Canned Fish	NR	NR	NR	8	Canada	Urban	86-88	3	
		Cheese	NR	NR	NR	7	Canada	Urban	86-88	3	
		Cream	NR	NR	NR	<1	Canada	Urban	86-88	3	
		Eggs	NR	NR	NR	1	Canada	Urban	86-88	3	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
77	3,3',4,4'-TCB	Organ Meats	NR	NR	NR	2	Canada	Urban	86-88	3	
	(continued)	Poultry	NR	NR	NR	2	Canada	Urban	86-88	3	
		Beef	NR	NR	NR	3.83	Various U.S. Locations	Urban	95	4	
		Chicken	NR	NR	NR	10.7	Various U.S. Locations	Urban	95	4	
		Pork	NR	NR	NR	10.6	Various U.S. Locations	Urban	95	4	
		Beef Back Fat	63	12	ND-7.97	0.98	Various U.S. Locations	U.S. Slaughterhouses	94	5	
		Milk	8	8	NR	10.6	Various U.S. Sites	Background	96	7	
		Pork	78	13	NR	1.57	Various U.S. Sites	Background	95	8	
		Young Chickens	39	39	NR	9.3	Various U.S. Sites	Background	96	9	
		Light Fowl	12	12	NR	12.2	Various U.S. Sites	Background	96	9	
		Heavy Fowl	12	12	NR	10.6	Various U.S. Sites	Background	96	9	
		Young Turkeys	15	12	NR	5.6	Various U.S. Sites	Background	96	9	
		Butter	21	21	0.03-1.83	0.41	Spain		NR	11	supermarket

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
Pentachloro-PCB (MW=326.44)											
105	2,3,3',4,4'-PeCB	Steak	1	1	NR	19	Canada	Urban	86-88	6	
		Roast Beef	3	3	NR	10	Canada	Urban	86-88	6	
		Ground Beef	2	2	NR	32	Canada	Urban	86-88	6	
		Pork	1	1	NR	54	Canada	Urban	86-88	6	
		Poultry	4	4	NR	25	Canada	Urban	86-88	6	
		Eggs	4	4	NR	34	Canada	Urban	86-88	6	
		Cream	3	3	NR	17	Canada	Urban	86-88	6	
		Ice cream	4	4	NR	16	Canada	Urban	86-88	6	
		Yogurt	1	1	NR	10	Canada	Urban	86-88	6	
		Cheese	5	5	NR	61	Canada	Urban	86-88	6	
		Cottage cheese	3	3	NR	13	Canada	Urban	86-88	6	
		Processed cheese	5	5	NR	49	Canada	Urban	86-88	6	
		Butter	4	4	NR	116	Canada	Urban	86-88	6	
		Rainbow Trout	4	NR	410-2,100	1,200	Finland	Urban	NR	1	
		Beef	6	NR	5.3-38	22	Finland	Urban	NR	1	
		Pork	3	NR	11-47	24	Finland	Urban	NR	1	
		Poultry	2	NR	NR	68	Finland	Urban	NR	1	
105	2,3,3',4,4'-PeCB	Inner Organs	5	NR	8.1-11	45	Finland	Urban	NR	1	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	(continued)	Eggs	2	NR	NR	98	Finland	Urban	NR	1	
		Fish Liver Oil	2	NR	NR	30,000	Finland	Urban	NR	1	
		Beef	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Chicken	NR	NR	NR	78	Various U.S. Locations	Urban	95	4	
		Pork	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Hot Dog/ Bologna	NR	NR	NR	400	Various U.S. Locations	Urban	95	4	
		Eggs	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Vegan Diet	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Butter	NR	NR	NR	220	Various U.S. Locations	Urban	95	4	
		Cheese	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Beef Back Fat	63	55	ND-437	92.7	Various U.S. Locations	U.S. Slaughterhouses	94	5	
		Milk	8	8	NR	170.3	Various U.S. Sites	Background	96	7	
		Pork	78	15	NR	33.4	Various U.S. Sites	Background	95	8	
		Young Chickens	39	39	NR	132	Various U.S. Sites	Background	96	9	
105	2,3,3',4,4'-PeCB	Light Fowl	12	12	NR	171	Various U.S. Sites	Background	96	9	
	(continued)	Heavy Fowl	12	12	NR	165	Various U.S. Sites	Background	96	9	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
		Young Turkeys	15	12	NR	307	Various U.S. Sites	Background	96	9	
		Eggs	3	0	ND	NA	Various U.S. Sites	Background	95	10	
		Butter	21	21	0.02-0.31	0.098	Spain		NR	11	supermarket
114	2,3,4,4',5-PeCB	Beef	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Chicken	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Pork	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Hot Dog/ Bologna	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Eggs	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Vegan Diet	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Butter	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Cheese	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Eggs	3	0	ND	NA	Various U.S. Sites		95	10	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
118	2,3',4,4',5-PeCB	Steak	5	5	NR	56	Canada	Urban	86-88	6	
		Roast Beef	5	5	NR	38	Canada	Urban	86-88	6	
		Ground Beef	5	5	NR	119	Canada	Urban	86-88	6	
		Pork	4	4	NR	55	Canada	Urban	86-88	6	
		Poultry	4	4	NR	81	Canada	Urban	86-88	6	
		Eggs	5	5	NR	99	Canada	Urban	86-88	6	
		Margarine	1	1	NR	19	Canada	Urban	86-88	6	
		Cream	5.00	5	NR	72	Canada	Urban	86-88	6	
		Ice cream	5	5	NR	53	Canada	Urban	86-88	6	
		Yogurt	5	5	NR	24	Canada	Urban	86-88	6	
		Cheese	5	5	NR	251	Canada	Urban	86-88	6	
		Cottage cheese	5	5	NR	33	Canada	Urban	86-88	6	
		Processed cheese	5	5	NR	184	Canada	Urban	86-88	6	
		Butter	5	5	NR	487	Canada	Urban	86-88	6	
		Beef	NR	NR	NR	94	Various U.S. Locations	Urban	95	4	
		Chicken	NR	NR	NR	200	Various U.S. Locations	Urban	95	4	
		Pork	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
118	`2,3',4,4',5-PeCB	Hot Dog/ Bologna	NR	NR	NR	1,100	Various U.S. Locations	Urban	95	4	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	(continued)	Eggs	NR	NR	NR	64	Various U.S. Locations	Urban	95	4	
		Vegan Diet	NR	NR	NR	15	Various U.S. Locations	Urban	95	4	
		Butter	NR	NR	NR	930	Various U.S. Locations	Urban	95	4	
		Cheese	NR	NR	NR	240	Various U.S. Locations	Urban	95	4	
		Beef Back Fat	63	63	61-2,294	448.6	Various U.S. Locations	U.S. Slaughterhouses	94	5	
		Milk	8	8	NR	685.3	Various U.S. Sites	Background	96	7	
		Pork	78	24	NR	95.5	Various U.S. Sites	Background	95	8	
		Young Chickens	39	39	NR	522	Various U.S. Sites	Background	96	9	
		Light Fowl	12	12	NR	599	Various U.S. Sites	Background	96	9	
		Heavy Fowl	12	12	NR	663	Various U.S. Sites	Background	96	9	
		Young Turkeys	15	12	NR	1,116	Various U.S. Sites	Background	96	9	
		Eggs	3	NR	NR	64	Various U.S. Sites	Background	95	10	
		Butter	21	21	0.05-1.17	0.37	Spain		NR	11	supermarket

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
126	3,3',4,4',5-PeCB	Beef	6	NR	0.3-7.3	3.2	Finland	Urban	NR	1	
		Pork	3	NR	0.5-3.7	1.5	Finland	Urban	NR	1	
		Poultry	2	NR	NR	1.2	Finland	Urban	NR	1	
		Inner Organs	5	NR	0.4-6.0	2.6	Finland	Urban	NR	1	
		Eggs	2	NR	NR	2.9	Finland	Urban	NR	1	
		Fish Liver Oil	2	NR	NR	620	Finland	Urban	NR	1	
		Milk	17	NR	NR	16.5	The Netherlands	Agricultural	NR	2	
		Milk	5	NR	NR	20.5	The Netherlands	Industrial	NR	2	
		Milk	7	NR	NR	35.8	The Netherlands	Near Waste Incinerator	NR	2	
		Milk	10	NR	NR	30.3	The Netherlands	Outlying Land of Main Rivers	NR	2	
		Beef	NR	NR	NR	1	Canada	Urban	86-88	3	
		Butter	NR	NR	NR	12	Canada	Urban	86-88	3	
		Canned Fish	NR	NR	NR	3	Canada	Urban	86-88	3	
		Cheese	NR	NR	NR	3	Canada	Urban	86-88	3	
		Cream	NR	NR	NR	< 1	Canada	Urban	86-88	3	
		Eggs	NR	NR	NR	1	Canada	Urban	86-88	3	
		Organ Meats	NR	NR	NR	1	Canada	Urban	86-88	3	
		Poultry	NR	NR	NR	< 1	Canada	Urban	86-88	3	
126	3,3',4,4',5-PeCB	Beef	NR	NR	NR	0.39	Various U.S. Locations	Urban	95	4	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	(continued)	Chicken	NR	NR	NR	0.38	Various U.S. Locations	Urban	95	4	
		Pork	NR	NR	NR	0.10	Various U.S. Locations	Urban	95	4	
		Hot Dog/ Bologna	NR	NR	NR	0.71	Various U.S. Locations	Urban	95	4	
		Eggs	NR	NR	NR	0.29	Various U.S. Locations	Urban	95	4	
		Vegan Diet	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Butter	NR	NR	NR	3.38	Various U.S. Locations	Urban	95	4	
		Cheese	NR	NR	NR	1.04	Various U.S. Locations	Urban	95	4	
		Milk	NR	NR	NR	0.16	Various U.S. Locations	Urban	95	4	
		Ice Cream	Nr	NR	NR	0.86	Various U.S. Locations	Urban	95	4	
		Beef Back Fat	63	63	0.7-21.2	4.1	Various U.S. Locations	U.S. Slaughterhouses	94	5	
		Milk	8	8	NR	3.6	Various U.S. Sites	Background	96	7	
		Pork	78	24	NR	0.33	Various U.S. Sites	Background	95	8	
		Young Chickens	39	39	NR	1.8	Various U.S. Sites	Background	96	9	
		Light Fowl	12	12	NR	1.6	Various U.S. Sites	Background	96	9	
126	3,3',4,4',5-PeCB	Heavy Fowl	12	12	NR	2.2	Various U.S. Sites	Background	96	9	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	(continued)	Young Turkeys	15	12	NR	4.4	Various U.S. Sites	Background	96	9	
		Eggs	3	NR	NR	0.29	Various U.S. Sites	Background	95	10	
		Butter	21	16	ND-0.62	NR	Spain		NR	11	supermarket
		Hexachloro-PCB (MW=360.88)									
156	2,3,3',4,4',5-HxCB	Steak	2	2	NR	8	Canada	Urban	86-88	6	
		Ground Beef	4	4	NR	14	Canada	Urban	86-88	6	
		Pork	2	2	NR	9	Canada	Urban	86-88	6	
		Poultry	3	3	NR	16	Canada	Urban	86-88	6	
		Eggs	3	3	NR	24	Canada	Urban	86-88	6	
		Cream	2	2	NR	9	Canada	Urban	86-88	6	
		Ice cream	2	2	NR	9	Canada	Urban	86-88	6	
		Yogurt	1	1	NR	7	Canada	Urban	86-88	6	
		Cheese	5	5	NR	28	Canada	Urban	86-88	6	
		Cottage cheese	1	1	NR	13	Canada	Urban	86-88	6	
		Processed cheese	5	5	NR	22	Canada	Urban	86-88	6	
		Butter	5	5	NR	63	Canada	Urban	86-88	6	
156	2,3,3',4,4',5-HxCB	Beef Back Fat	63	63	4.9-426	60.7	Various U.S. Locations	Urban	94	5	
	(Continued)	Milk	8	8	NR	60.1	Various U.S. Sites	Background	96	7	
		Pork	78	30	NR	21.6	Various U.S. Sites	Background	95	8	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
		Young Chickens	39	39	NR	41	Various U.S. Sites	Background	96	9	
		Light Fowl	12	11	NR	58	Various U.S. Sites	Background	96	9	
		Heavy Fowl	12	12	NR	54	Various U.S. Sites	Background	96	9	
		Young Turkeys	15	12	NR	108	Various U.S. Sites	Background	96	9	
		Butter	21	15	ND-0.21	NR	Spain		NR	11	supermarket
157	2,3,3',4,4',5'-HxCB	Beef Back Fat	63	62	ND-91.7	13.8	Various U.S. Locations	Urban	94	5	
		Milk	8	8	NR	13.8	Various U.S. Sites	Background	96	7	
		Pork	78	32	NR	5.1	Various U.S. Sites	Background	95	8	
		Young Chickens	39	39	NR	10.5	Various U.S. Sites	Background	96	9	
		Light Fowl	12	11	NR	12.5	Various U.S. Sites	Background	96	9	
		Heavy Fowl	12	12	NR	13.3	Various U.S. Sites	Background	96	9	
		Young Turkeys	15	12	NR	26.2	Various U.S. Sites	Background	96	9	
167	2,3',4,4',5,5'-HxCB	Butter	21	20	ND-0.49	NR	Spain	--	NR	11	supermarkets

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
169	3,3',4,4',5,5'-HxCB	Beef	6	NR	ND-1.0	0.5	Finland	Urban	NR	1	
		Pork	3	NR	ND-2.2	0.8	Finland	Urban	NR	1	
		Poultry	2	NR	ND	NA	Finland	Urban	NR	1	
		Inner Organs	5	NR	ND-0.6	0.3	Finland	Urban	NR	1	
		Eggs	2	NR	NR	0.1	Finland	Urban	NR	1	
		Fish Liver Oil	2	NR	NR	130	Finland	Urban	NR	1	
		Milk	17	NR	NR	2.6	The Netherlands	Agricultural	NR	2	
		Milk	5	NR	NR	4.0	The Netherlands	Industrial	NR	2	
		Milk	7	NR	NR	8.4	The Netherlands	Near Waste Incinerator	NR	2	
		Milk	10	NR	NR	4.2	The Netherlands	Outlying Land of Main Rivers	NR	2	
		Beef	NR	NR	NR	< 1	Canada	Urban	86-88	3	
		Butter	NR	NR	NR	6	Canada	Urban	86-88	3	
		Canned Fish	NR	NR	NR	< 1	Canada	Urban	86-88	3	
		Cheese	NR	NR	NR	1	Canada	Urban	86-88	3	
		Cream	NR	NR	NR	< 1	Canada	Urban	86-88	3	
		Eggs	NR	NR	NR	1	Canada	Urban	86-88	3	
		Organ Meats	NR	NR	NR	1	Canada	Urban	86-88	3	
		Poultry	NR	NR	NR	< 1	Canada	Urban	86-88	3	
169	3,3',4,4',5,5'-HxCB	Beef	NR	NR	NR	0.12	Various U.S. Locations	Urban	95	4	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
	(continued)	Chicken	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Pork	NR	NR	NR	0.14	Various U.S. Locations	Urban	95	4	
		Hot Dog/ Bologna	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Eggs	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Vegan Diet	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Butter	NR	NR	NR	0.39	Various U.S. Locations	Urban	95	4	
		Cheese	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Milk	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Ice Cream	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Beef Back Fat	63	59	ND-2.4	0.70	Various U.S. Locations	U.S. Slaughterhouses	94	5	
		Milk	8	8	NR	0.5	Various U.S. Sites	Background	96	7	
		Pork	78	29	NR	0.26	Various U.S. Sites	Background	95	8	
		Young Chickens	39	31	NR	0.20	Various U.S. Sites	Background	96	9	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
169	3,3',4,4',5,5'-HxCB (continued)	Light Fowl	12	8	NR	0.20	Various U.S. Sites	Background	96	9	
		Heavy Fowl	12	11	NR	0.40	Various U.S. Sites	Background	96	9	
		Young Turkeys	15	12	NR	0.60	Various U.S. Sites	Background	96	9	
		Eggs	3	0	NR	0.10	Various U.S. Sites	Background	95	10	
		Butter	21	0	ND	NA	Spain		NR	11	supermarket
Heptachloro-PCB (MW=396.33)											
170	2,2',3,3',4,4',5-HpCB	Butter	21	21	0.07-0.27	0.16	Spain	--	NR	11	supermarkets
180	2,2',3,4,4',5,5-HpCB	Beef	NR	NR	NR	280	Various U.S. Locations	Urban	95	4	
		Chicken	NR	NR	NR	230	Various U.S. Locations	Urban	95	4	
		Pork	NR	0	ND	NA	Various U.S. Locations	Urban	95	4	
		Hot Dog/ Bologna	NR	NR	NR	140	Various U.S. Locations	Urban	95	4	
		Eggs	NR	NR	NR	16	Various U.S. Locations	Urban	95	4	
		Vegan Diet	NR	NR	NR	7	Various U.S. Locations	Urban	95	4	
		Butter	NR	NR	NR	250	Various U.S. Locations	Urban	95	4	
		Cheese	NR	NR	NR	32	Various U.S. Locations	Urban	95	4	

Table B-16 Environmental Levels of PCBs in Food Products (ppt) (continued)

IUPAC number	Chemical	Sample Type	Number samples	Number positive samples	Concentration range	Conc. mean	Location	Location description	Sample year	Ref. no.	Comments
180	2,2',3,4,4',5,5-HpCB	Eggs	3	NR	NR	16	Various U.S. Sites	--	95	10	
	(continued)	Butter	21	21	0.12-1.26	0.61	Spain	--	NR	11	supermarkets
189	2,3,3',4,4',5,5'-HpCB	Roast beef	1	1	NR	10	Canada	Urban	86-88	6	
		Cream	1	1	NR	10	Canada	Urban	86-88	6	
		Butter	1	1	NR	7	Canada	Urban	86-88	6	

Footnote References

NR= Not Reported

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APPENDIX C. BIOAVAILABILITY OF DIOXIN

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C.1 Bioavailability Data

Umbreit et al. (1985, 1986a,b) conducted experiments in guinea pigs, administering 2,3,7,8-TCDD in corn oil, 2,3,7,8-TCDD added to chemically decontaminated soil, or soil from two industrial sites in Newark, New Jersey (a manufacturing site and a salvage site) contaminated with CDDs. 2,3,7,8-TCDD was the principal lower chlorinated isomer (dioxin or furan) present in the soil from the manufacturing site (for which a chemical analysis was presented). Soil from the manufacturing site was found to have 1,500 to 2,500 ppb 2,3,7,8-TCDD under soxhlet extraction; release under ambient temperature manual solvent extraction was much lower, reported as "$>$2.5 ppb." The soil from the salvage site was reported as approximately 180 ppb 2,3,7,8-TCDD under soxhlet extraction.

In this study, groups of two or four male and two or four female guinea pigs received single gavage doses of the test materials and were observed until death or sacrifice at 60 days. 2,3,7,8-TCDD in corn oil or in recontaminated soil (6 g/kg in both) proved highly toxic, without similar toxicity being observed in animals treated with up to twice this dose of 2,3,7,8-TCDD in the soil from the manufacturing site. The limited data on 2,3,7,8-TCDD levels in the liver showed much higher levels following administration of recontaminated soil versus contaminated soil from the manufacturing site.

Umbreit et al. (1986a) thus demonstrated that gavaged 2,3,7,8-TCDD containing soil from the manufacturing site was substantially less toxic than equivalent doses of 2,3,7,8-TCDD in corn oil. However, quantitative comparison of the effective doses in this study is difficult. Approaches to a quantitative comparison are outlined below.

(1) Guinea pigs receiving 12 ug/kg 2,3,7,8-TCDD in contaminated soil experienced no deaths, while five out of eight guinea pigs receiving 6 ug/kg 2,3,7,8-TCDD in corn oil died, with no groups tested having lower doses in corn oil. Other authors have provided data on the toxic effects of 2,3,7,8-TCDD in corn oil which could aid in the comparison.

McConnell et al. (1984) observed one out of six animals dying at 1 ug/kg and six out of six animals dying at 3 ug/kg. Silkworth et al. (1982) observed three out of six animals dying at 2.5 ug/kg and no deaths out of six at 0.5 ug/kg. Comparing these data directly with the Umbreit et al. results would suggest that the 2,3,7,8-TCDD in the Newark manufacturing site soil was less effective, by a factor of 10 or greater, in producing

toxicity than 2,3,7,8-TCDD in corn oil.

(2) Umbreit et al. reported a "slightly reduced" weight gain in guinea pigs receiving 6 ug/kg of 2,3,7,8-TCDD in Newark manufacturing site soil, and a "greater reduction" at the 12 ug/kg dose. No other signs of toxicity were noted in these groups. The animals receiving 6 ug/kg 2,3,7,8-TCDD in corn oil, in contrast, exhibited a marked loss of body weight and showed toxicity and mortality. Silkworth et al. (1982) also provided data on weights of guinea pigs receiving 2,3,7,8-TCDD in corn oil. Those receiving 2.5 ug/kg exhibited a marked reduction in weight gain among three out of six survivors, while those receiving 0.5 ug/kg showed a weight gain comparable to vehicle controls. Comparison of this weight data with that of Umbreit et al. suggests that the 2,3,7,8-TCDD in corn oil was more than 5 times but less than 25 times as potent as 2,3,7,8-TCDD in the Newark soil. This comparison assumes that the effect of the Newark manufacturing site soil on weight gain was due to 2,3,7,8-TCDD as opposed to other compounds in the soil. Numerous other dioxin and furan compounds and other chemicals have been identified in this soil (Umbreit et al., 1987a). It has not been established that 2,3,7,8-TCDD is the sole or prime source of toxicity in the soil.

(3) Umbreit et al. presented liver concentrations of 2,3,7,8-TCDD after death or sacrifice at 60 days following gavage. Much lower concentrations of 2,3,7,8-TCDD were found in the livers of animals receiving soil from the manufacturing site compared with those receiving the dose in corn oil. There are, however, two factors that limit the conclusions than can be drawn from this comparison.

First, the corn oil group experienced major toxicity and weight loss, particularly complete loss of body fat. These changes may have affected the partitioning of 2,3,7,8-TCDD within the body, leading to a higher concentration in the livers of the animals experiencing toxicity. Second, the animals gavaged with corn oil died early--half were dead by 26 days, while all of the guinea pigs treated with soil survived to 60 days (with the exception of one gavage death). The U.S. EPA (1985c) reported a half-life for 2,3,7,8-TCDD elimination of 30 $\pm$ 6 or 22 to 43 days from two studies in guinea pigs. Additionally, the U.S. EPA (1985c) stated that elimination in the guinea pig may follow zero-order kinetics. Differences in elimination due to differences in periods of survival are likely to have affected the relative quantities of 2,3,7,8-TCDD found in the livers of the test groups.

Perhaps a more appropriate comparison can be made with the four animals receiving 0.32 ug/kg of 2,3,7,8-TCDD in contaminated soil from the Newark salvage site. These animals experienced no reported toxic signs (weight data not presented) and survived the full 60-day experiment. Approximately 6% of the gavage dose was found in the liver of these animals, while only about 0.06% of the gavage dose was found in the livers of guinea pigs in the 12 ug/kg group receiving the Newark manufacturing site soil. This would suggest that the 2,3,7,8-TCDD in the manufacturing site soil was 100 times less bioavailable. However, given the different doses used and the fact that only a single pooled sample was analyzed for 2,3,7,8-TCDD in each group, caution must be used in interpreting this comparison.

The 2,3,7,8-TCDD in soil from the salvage site was substantially bioavailable, based on the single liver tissue analysis. Approximately 6% of the administered dose was recovered from the livers of these animals at 60 days. This can be compared with data on hamsters given 2,3,7,8-TCDD in corn oil by McConnell et al. (1984), where approximately 8% of the 2,3,7,8-TCDD could be recovered in the 1 ug/kg dose group among survivors at 30 days.

McConnell et al. (1984) treated Hartley guinea pigs (2.5 weeks old) with single gavage doses of either 2,3,7,8-TCDD or dioxin contaminated soil from two sites in Missouri. The 2,3,7,8-TCDD concentrations from the two sites were reported at 700 and 880 ppb respectively; total tetrachlorodibenzofurans (TCDF) concentrations in the soil were 40 to 80 ppb, and polychlorinated biphenyls (PCB) concentrations were 3 to 4 ppm. Taking into account the relative toxicities, the authors concluded that toxicity from the other compounds was likely to be small compared with that from 2,3,7,8-TCDD. Livers were analyzed for 2,3,7,8-TCDD at death or sacrifice at 30 days following treatment. Treatment deaths occurred between 5 and 21 days post-gavage.

Guinea pigs that died exhibited severe loss of body fat, markedly reduced thymus and testicle size, and adrenal hemorrhage. No adverse affects were noted in animals treated with decontaminated soil. For 2,3,7,8-TCDD in corn oil and for both contaminated soils, there were clear dose-responses in mortality. The calculated LD_{50} values for the two soil types were lower than the LD_{50} for 2,3,7,8-TCDD in corn oil by a factor of three to four.

There was a dose-response between the liver concentration of 2,3,7,8-TCDD and the gavage dose; the details of this relationship are complex. Animals dying during the experiment had liver concentrations a factor of 1.4 to 3.2 higher than animals in the same dose groups who survived 30 days. This observation makes quantification of the dose-response relationships difficult (all or most of the animals in the low-dose groups

survived the experiment, while all of the animals in the high-dose groups died). When the liver concentrations of 2,3,7,8-TCDD in animals dying early at the middle and high-dose groups are compared, there appears to be a greater-than-linear increase in liver concentration with dose for the Times Beach and Minker Stout soil groups, with a 3.3-fold increase in dose producing a 10- to 13-fold increase in liver concentration.

Liver concentrations of animals in the different dosing groups can best be compared among groups that experienced similar mortality.

(1) Animals in dose groups in which all animals died within 30 days: 2,3,7,8-TCDD in corn oil, approximately 20% of the administered dose was in the liver. For the soil-treated groups, 13% and 11% of the doses, respectively, were in the liver. Comparison of these data suggest that 2,3,7,8-TCDD was approximately twice as available through corn oil as through soil.

(2) Animals surviving the 30-day experiment (in groups where at least 4 out of 6 survived): For 2,3,7,8-TCDD in corn oil, 7.5% of the administered dose was in the liver. For soil-treated animals < 3.6, 1.3, < 4.2, and 2.0% of the doses, respectively, were in the liver. Comparison here would suggest that 2,3,7,8-TCDD was approximately four times as available through corn oil as through soil.

The authors note that the differences in liver concentrations observed in the study may reflect varying partitioning of the 2,3,7,8-TCDD among internal organs, since dying animals suffered major loss of body weight and fat content. In addition, surviving animals would have had greater opportunity to metabolize and excrete 2,3,7,8-TCDD due to a longer lifetime.

Umbreit et al. (1986a) reported additional chemical analyses of the Times Beach soil. Soxhlet extraction of the Times Beach soil yielded a similar quantity of 2,3,7,8-TCDD to the solvent extraction reported by McConnell et al. (1984). This is in contrast to the Newark manufacturing site soil used in the Umbreit et al. (1987a) experiments, where only a small fraction of soxhlet-extractable 2,3,7,8-TCDD was extractable by the solvent extraction methodology used by McConnell et al. (1984).

McConnell et al. (1984) also reported an experiment in which groups of six Sprague-Dawley rats were given single gavage doses of 2,3,7,8-TCDD in corn oil or dioxin-contaminated soil from the Minker site. Induction of aryl hydrocarbon hydroxylase (AHH) in the rat livers was measured at sacrifice 6 days after dosing. Experimental doses ranged from 0.4 to 5.0 ug/kg 2,3,7,8-TCDD. Measured AHH induction was similar for groups receiving 2,3,7,8-TCDD in corn oil or receiving contaminated soil containing nearly equal doses of 2,3,7,8-TCDD. For example (based on the rate of formation of 3-

hydroxybenzo[a]pyrene), AHH activity was measured at 1,269 pmole min^{-1} mg^{-1} for the group receiving 5 ug/kg 2,3,7,8-TCDD in corn oil and at 1,230 pmole min^{-1} mg^{-1} for the group receiving 5.5 ug/kg 2,3,7,8-TCDD in contaminated soil. For the five dose groups, the AHH activity for the soil group ranged from 50% to 110% of the activity in the corn oil group.

The McConnell et al. (1984) rat data indicate that the bioavailability of 2,3,7,8-TCDD from the Minker site soil was at least 50% of that of equivalent doses of 2,3,7,8-TCDD in corn oil.

Lucier et al. (1986) provided additional information on the induction of hepatic enzymes in rats by the 2,3,7,8-TCDD contaminated soil from the Minker site tested by McConnell et al. (1984). AHH induction was similar for the groups of rats receiving 2,3,7,8-TCDD in corn oil and contaminated soil (within a factor of two) over a broader range of doses (0.015 ug/kg to 5 ug/kg) than reported by McConnell et al. (1984). In a second enzyme assay using the same animals, UDP glucuronyltransferase activity was found to be slightly higher in groups receiving 2,3,7,8-TCDD in corn oil than groups receiving equal doses in contaminated soil.

Liver concentrations of 2,3,7,8-TCDD for the rats were also reported. For the corn oil vehicle the liver concentrations were 40.8 $\pm$ 6.5 ppb at the 5 ug/kg dose and 7.6 $\pm$ 2.5 ppb at the 1 ug/kg dose. Assuming that the liver comprises 4.0% of body weight, the retention rates for the 5 and 1 ug/kg doses were 33% and 30%, respectively. In rats receiving 2,3,7,8-TCDD in contaminated soil, the 5.5 ug/kg group had liver concentrations of 20.3 $\pm$ 12.9 ppb, and the 1.1 ug/kg group had concentrations of 1.8 $\pm$ 0.3. Thus, retention rates for the 5.5 and 1.1 ug/kg groups are estimated at 14% and 7%, respectively. These data indicate that liver retention in the soil group was 20% to 40% of that in the corn oil vehicle groups.

Umbreit et al (1986b) report additional studies of mortality in guinea pigs treated with soil containing 2,3,7,8-TCDD from Newark (manufacturing site) and Missouri (Times Beach) previously tested by Umbreit et al (1985, 1986a) and McConnell et al. (1984), respectively. Guinea pigs received a single gavage dose of a soil suspension and were observed for 60 days. After autopsy, deaths were classified as whether or not they appeared to be due to TCDD toxicity. Substantial mortality (25% overall) from conditions not attributed to TCDD was observed across all groups.

The data for both the Newark and Missouri sites are similar in trend for the previous data on these sites; and clearly indicate the greater toxicity of the Newark soil for given equal administered doses of 2,3,7,8-TCDD. With larger groups of guinea pig studied, a toxicity-related death was observed in both the 5 and 10 mg/kg dose groups for

Newark soil while no deaths were observed in corresponding dose groups (6 and 12 mg/kg) with fewer animals in Umbreit et al. (1986a).

Comparing groups within this study, similar mortality (1 or 2 deaths in 10 to 16 animals) was seen in both the 5 and 10 ug/kg Newark groups and the 1 and 3 ug/kg Missouri groups. These results suggest that the toxicity of these materials differs by an order of magnitude or less. As noted above, the degree to which toxicity from these soils can be attributed to 2,3,7,8-TCDD in the presence of numerous other related toxic compounds is not known. 2,3,7,8-TCDD tissue concentrations were not reported in this work.

In another comparative study Umbreit et al. (1987b) compared the Newark manufacturing site and Times Beach soils in the induction of aryl hydrocarbon hydroxylase (AHH) in rats. While the use of only single dose levels prevents detailed analysis, the two soils proved quite similar in their ability to induce AHH. The explanation for the difference in this finding from those observed in the toxicity studies discussed above is not clear, but may relate to the presence of other toxic and/or AHH inducing compounds.

Umbreit et al. (1987a) report a reproductive toxicity study with soils from the Newark manufacturing site and salvage yard previously studied by Umbreit et al. (1986a). Female mice were treated thrice weekly with soil from these sites, with treatment continuing through fertilization to weaning of pups. The total doses of 2,3,7,8-TCDD received by the mice were 720 ug/kg in manufacturing site soil, and 86 ug/kg in salvage yard soil. A corn oil vehicle group and a recontaminated soil group received a total of 225 ug/kg.

Deaths in animals showing "classic signs" of TCDD toxicity were observed in the corn oil and recontaminated soil groups, and indicate appreciable bioavailability of 2,3,7,8-TCDD. Deaths were also observed in animals receiving manufacturing site soil but the authors did not observe "classic signs" of TCDD toxicity. Fewer live pups born and fewer pups surviving until weaning were observed in the manufacturing site soil group compared with those receiving decontaminated soil. TCDD completely blocked reproduction in the corn oil and recontaminated soil groups. The results of this study demonstrate acute and reproductive effects occurred in animals receiving manufacturing site soil. However, these effects were of a lesser magnitude than those seen in animals treated with 2,3,7,8-TCDD in corn oil at a dose three fold lower. The authors note the presence of substantial quantities of other toxic substances in the manufacturing site soil (chemical analyses presented). No toxic effects were noted in animals treated with salvage site soil, who received a much smaller 2,3,7,8-TCDD dose. The data does not allow a quantitative evaluation of the bioavailability of 2,3,7,8-TCDD.

Kaminski et al. (1985) and Silkworth et al. (1982) reported the results of a series of studies on the toxicity of soot containing dioxin and furan compounds from a fire involving transformer fluid containing PCBs. Hartley guinea pigs (500 to 600 g) received single oral doses of soot in an aqueous vehicle, a soxhlet extract of the soot in the same vehicle, or 2,3,7,8-TCDD in either an aqueous vehicle or corn oil.

The soot was reported to contain 2.8 to 2.9 ppm 2,3,7,8-TCDD and 124 to 273 ppm 2,3,7,8-TCDF. The total polychlorinated dibenzofuran content was estimated at 5,000 ppm. Animal weights and mortality were recorded for 42 days, at which point the survivors were sacrificed and LD_{50} values were calculated. Blood chemistry and a pathologic examination were performed at sacrifice.

Silkworth et al. (1982) noted that the LD_{50}s for contaminated soot and soot extract were similar at 410 and 327 equivalent ug/kg, indicating that the matrix had only a small effect on toxicity. If expressed in terms of the content of 2,3,7,8-TCDD, the LD_{50} from soot is 2.5 ug/kg, which is a factor of seven below the LD_{50} for 2,3,7,8-TCDD in an aqueous vehicle, suggesting that other compounds contributed to the toxicity of the soot and soot extract.

The authors stated that they adopted an aqueous vehicle in these experiments because it was nontoxic and provided a stable suspension of soot; they regarded this vehicle as more appropriate for modeling of human exposure conditions than an oil vehicle. The data from these experiments also demonstrate that use of an oil vehicle leads to substantially greater 2,3,7,8-TCDD toxicity than does an aqueous vehicle.

Comparison of mortality and weight loss in groups of female guinea pigs receiving 500 ug/kg of soot or the equivalent amount of soot extract suggests that the extract may be somewhat more toxic; however, all six animals died in the 1,000 ug/kg soot group, while four out of five died in the 500 ug/kg extract group. Taken together, these data indicate that the soxhlet extract of soot in an aqueous vehicle was between one and two times as toxic as the soot itself. It is likely that a larger difference in toxicity would have been observed if the soot extract was in an oil vehicle.

Van den Berg et al. (1983) fed small groups of male Wistar rats fly ash from a municipal incinerator (pretreated with HCl) containing dioxins and furans, a soxhlet extract of the fly ash, or a purified extract of the ash that was obtained using column chromatography. 2,3,7,8-TCDD was present as 3.3% of the TCDD isomer group in the fly ash extract. (The authors did not specify whether this reference was to crude or purified extract.) 2,3,7,8-TCDF was present as 17.9% of the tetra-CDF isomer group in the extract. The rats were fed 2 g/d fly ash mixed with diet or the residual from 2 mL/d extract after the extract was mixed with diet and the solvent was evaporated. The animals

were exposed to the treated diet for 19 days, and then sacrificed, and the liver tissue was analyzed for the presence of dioxins and furans.

Approximately 1% of the 2,3,7,8-TCDD dose from fly ash was retained in the liver, and approximately 4% of the dose of this isomer from fly ash extract was so retained. The corresponding percentages for 2,3,7,8-TCDF are 0.3 and 1.0. Data on the retention of isomer groups in adipose tissue were presented for the extract-treated groups but not for the fly ash-treated group. The concentrations of the various isomers in adipose tissue are comparable to, or less than, the concentrations in liver tissue.

The U.S. EPA (1985b) reported a half-life for elimination of 2,3,7,8-TCDD in the rat of 20 days at high dose. If a similar half-life is assumed in this experiment, the quantities of 2,3,7,8-TCDD in the animals at the end of the 19-day feeding experiment would be significantly less than the absorbed dose, but still of the same order of magnitude. However, the recovery percentages in this study are low for both the fly ash and fly ash extract groups in comparison with other studies in which 2,3,7,8-TCDD was administered to rats. Fries and Marrow (1975) fed rats diets containing 7 or 20 ppb of 2,3,7,8-TCDD for a period of up to 42 days. After 14 days of feeding, the rat livers contained an average of 32% of the cumulative administered dose; at 28 days, 21% of the dose; and at 42 days, 18% of the dose. Thus, in the van den Berg et al. (1983) study, the liver retention of 2,3,7,8-TCDD for the fly ash extract group is a factor of five to eight below what could be anticipated for the Fries and Marrow (1975) data, and the liver retention in the van den Berg et al. (1983) group fed soot is a factor of 20 to 30 lower than that seen by Fries and Marrow (1975). Data from Kociba et al. (1976), Rose et al. (1976), and Kociba et al. (1978) lead to similar conclusions to those from the Fries and Marrow (1975) data regarding the fraction of cumulative 2,3,7,8-TCDD dose retained in the rat liver.

An explanation of the low level of recovery for the animals receiving the soxhlet extract of soot is not apparent. It is possible that the presence of multiple compounds affected absorption or metabolism in the rats fed soot and soot extract.

A second approach to the van den Berg et al. (1983) data is to compare the ratios of liver concentrations for dioxins in fly-ash-treated animals to the concentrations in extract-treated animals. These ratios, based on measurements in small numbers of animals, indicate a substantial bioavailability of dioxin and furan compounds from the tested fly ash. This availability varied among the different isomers with the value of 0.3 for 2,3,7,8-TCDD, indicating that this isomer was three times as available from fly ash extract as from fly ash.

Van den Berg et al. (1985) fed fly ash (pre-treated with HCl) to Wistar rats, guinea pigs, and Syrian golden hamsters. Fly ash was mixed with standard laboratory diet at

2.5% by weight, and animals were allowed to eat ad libitum. The amount of fly ash consumed by each group of five rodents was determined by the authors. For each species there were three groups of animals each fed fly ash for approximately 32 days (group I), 60 days (group II), or 94 days (group III). Concentrations of dioxin and furan isomer groups in the food were presented, and include 1.4 ng/g TCDD compounds and 2.1 ng/g TCDF compounds.

The authors presented calculated recovery percentages for the cumulative dose of specific isomers in the rodent liver. For 2,3,7,8-TCDD in guinea pigs, 3.7%, 0.9%, and 1.4% of the administered dose was recovered in the liver in groups I, II, and III, respectively. The 32-day (group I) recovery percentage is somewhat higher than seen in the lower dose groups receiving 2,3,7,8-TCDD contaminated soil in McConnell et al. (1984). The value in hamsters was approximately 2% (only reported for group II), and analytical problems prevented this determination in rats. No other TCDD compounds were quantified. Similarly, for 2,3,7,8-TCDF, guinea pigs showed retention of 4.7%, 2.2%, 2.5% of the administered dose in groups I, II, and III, respectively. For both 2,3,7,8-TCDD and 2,3,7,8-TCDF the recovery percentages in guinea pigs at 32 days were approximately a factor of 4 to 15 higher than that observed in the van den Berg et al. (1983) study in rats.

Other TCDD compounds that were present showed comparable or somewhat lower retention, averaging 1% to 2% over the animals groups. No TCDD or TCDF compounds were detected in hamster liver or analyzed for in rat liver. Higher chlorinated congeners most typically showed retention in the range of 2% to 5% in rat liver and 1% to 3% in guinea pig liver, with the exception of 2,3,4,7,8-PeCDF (9.8%, 8.3%, and 11.3% in the hamster groups). Few other compounds were found in hamster liver, but 2,3,4,7,8-PeCDF was found with a recovery of 5% to 8% and 2,3,4,7,8-HxCDD was found at 3% to 7%.

As with other experiments in which the retention of dioxins in the liver has been determined, these percentages place a lower bound on the bioavailability of the dioxins but, because not all dioxin is localized in the liver, do not permit bioavailability to be estimated without knowledge of the elimination of the administered dose over time and the quantity of dioxins in the remainder of the organism. No positive control group receiving 2,3,7,8-TCDD was included for comparison.

Poiger and Schlatter (1980) conducted several experiments in Sprague-Dawley rats (180 to 220 g) in which liver concentrations of tritium label from 2,3,7,8-TCDD were determined using various doses and vehicles. All experiments consisted of a single gastric intubation of 2,3,7,8-TCDD-containing material, followed by animal sacrifice at

predetermined times. The doses used were well below the LD_{50} in the rat (the maximum dose applied was 5 ug/kg), and no deaths or toxic effects were reported.

In a preliminary experiment, rats were treated with 14.7 ng/rat 2,3,7,8-TCDD in ethanol. The results indicate substantial localization of 2,3,7,8-TCDD in the rat liver, with a decrease of a factor of two in the fraction of the dose in the liver between 1 and 4 days. Poiger and Schlatter (1980) conducted all further studies with sacrifice at 24 hours to maximize the recovery of 2,3,7,8-TCDD from the liver.

In a second experiment, the authors administered 2,3,7,8-TCDD doses in ethanol ranging from 15 to 1,070 ng/rat to groups of six rats. They found a graded increase in percentage retained in the liver from 37% $\pm$ 1% at the 15 ng dose to 51% $\pm$ 4% at 280 ng. At the high-dose point, the percentage may have fallen (42% $\pm$ 10% at 1,070 ng).

In a further experiment, 2,3,7,8-TCDD was administered at low dose in a series of vehicles. These data demonstrate that administration of 2,3,7,8-TCDD in soil reduced the retention of the dose in the liver to 66%, or 44% of the retention seen with 2,3,7,8-TCDD
in ethanol. The lower value, 44%, was obtained for soil that was aged for 8 days at 30-40 °C following addition of 2,3,7,8-TCDD. This observation is consistent with the findings of other studies reported here that 2,3,7,8-TCDD from environmental soil (naturally aged) was generally less available than 2,3,7,8-TCDD freshly added to clean samples of these soils. The aqueous suspension of 2,3,7,8-TCDD in activated carbon showed little evidence of bioavailability; this is supported by the authors' measurements showing that 2,3,7,8-TCDD was only slightly extractable from the activated carbon matrix by various solvents. In contrast, 58% to 70% of 2,3,7,8-TCDD could be recovered from soil samples by washing with hexane/acetone (4:1 v/v).

Poiger and Schlatter (1980) also presented results from several skin application experiments with TCDD-containing materials using rats and rabbits (not reviewed here).

Bonaccorsi et al. (1984) reported the results of a study of gut absorption of 2,3,7,8-TCDD from soil taken from the Seveso, Italy accident site. Soil containing 81 $\pm$ 8 ppb 2,3,7,8-TCDD from the "highly contaminated" area in Seveso was administered to albino male rabbits (2.6 $\pm$ 0.3 kg) in daily gavage doses for seven days. Additional samples of clean soil were spiked with 2,3,7,8-TCDD in the laboratory to yield 10 and 40 ppb contamination levels and were administered to rabbits following the same protocol. For comparison, rabbits were also treated with 2,3,7,8-TCDD in solution in acetone-vegetable oil (1:6) or alcohol-water (1:1). Rabbits were sacrificed on the day after treatment stopped and liver concentrations of 2,3,7,8-TCDD were measured. The authors did not remark on the presence or absence of toxicity in the treated rabbits. EPA (1985a)

reports values for the single dose LD_{50} of 2,3,7,8-TCDD in rabbits of 115 and 275 ug/kg. The total doses received by the rabbits in this study were approximately 54, 107, and 215 ug/kg over seven days. Based on this comparison, there is a likelihood that toxic effects occurred in the Bonaccorsi work, and as noted above, toxicity has the potential to affect the tissue concentrations of 2,3,7,8-TCDD. For this reason, the most appropriate comparisons among these data are between groups showing similar liver concentrations of 2,3,7,8-TCDD, which may then be inferred to have experienced similar toxic effects.

That this method of comparison is desirable can also be seen from the Bonaccorsi et al. (1984) data, where both solvent vehicle groups and the spiked soil groups show an increase of the fraction of the dose in the liver at the higher administered doses. However, it should be mentioned that use of two different solvent vehicles complicates interpretation. Similar liver concentrations of 2,3,7,8-TCDD were seen in the 40 ug/d solvent vehicle and 80 ug/d Seveso soil groups. Comparing the percentage of liver retention in these two groups indicates absorption from Seveso soil was 40% of that from the solvent vehicle. Using the same approach, comparison of the 80 ug/d solvent vehicle and 160 ug/d Seveso soil groups indicates that absorption from the soil was 41% of that from the solvent.

The same approach can be used to compare absorption from the solvent vehicle and from the spiked soil. In this case the 40 ug/d solvent vehicle group had the liver concentrations closest to either the 40 or 80 ug/d spiked soil groups. Comparison of the percentage of dose in the liver indicates absorption from spiked soil is 68-73% of that from the solvent vehicle. Bonaccorsi et al. (1984) conducted work with either aged or non-aged spiked soil but do not present data to allow a comparison of these groups.

Shu et al. (1987, as cited by Leung and Paustenbach, 1987) studied 2,3,7,8-TCDD from the Missouri site tested by McConnell et al. (1984). Their paper reports an oral bioavailability of approximately 43% in the rat dosed with environmentally contaminated soil from Times Beach, Missouri. This figure did not change significantly over a 500-fold dose range of 2 to 1450 ng 2,3,7,8-TCDD per kg of body weight for soil contaminated with approximately 2, 30 or 60 ppb of 2,3,7,8-TCDD. The data from this study is not now available to the Exposure Assessment Group of EPA for review.

C.2 Summary of Bioavailability

Table C-1

summarizes data that are pertinent to the bioavailability of 2,3,7,8-TCDD from environmental matrices. Studies of bioavailability, which examined soil samples, soot, and fly ash, have utilized three methodologies: measuring acute toxicity, retention of 2,3,7,8-TCDD in the liver, and induction of hepatic enzymes.

Among the five samples of soil from contaminated sites that have been tested, three have shown substantial bioavailability, e.g., 25% to 50%, when compared with 2,3,7,8-TCDD in corn oil gavage. A fourth soil sample was compared with 2,3,7,8-TCDD administered in a solvent vehicle, and fell in this range. The fifth soil, tested by Umbreit et al. (1986a,b; 1987a,b) showed bioavailability substantially less than the other soils tested. While difficult to gauge quantitatively, dioxin from this fifth soil may be an order of magnitude less available than from the other soils.

Additionally, three samples of soil spiked with 2,3,7,8-TCDD have been tested for bioavailability, including one sample in which the 2,3,7,8-TCDD was incubated with soil at

an elevated temperature. The 2,3,7,8-TCDD added to these soil samples proved to be highly available (e.g., 40% to 70%).

In one study, soot from a transformer fire containing dioxins and furans proved similarly toxic to a soxhlet extract of the soot in an aqueous vehicle. However, the soot extract may have proved more toxic if delivered in corn oil, as was 2,3,7,8-TCDD in the soil studies. The availability of 2,3,7,8-TCDD and other dioxins and furans from incinerator fly ash have been addressed by van den Berg et al. (1983, 1985) in extended feeding studies. In these studies, liver retention of 2,3,7,8-TCDD from either fly ash or fly ash extract proved low, with availability from fly ash being approximately 25% of that from the extract.

The individual studies reviewed have a variety of limitations, as discussed in the preceding text. A notable limitation was that some experiments were conducted using highly toxic doses of 2,3,7,8-TCDD, so that determination of bioavailability was complicated by wasting and early death of the test animals. It should also be noted that, while the relative retention of 2,3,7,8-TCDD in the liver can serve as an appropriate indication of differences in bioavailability between samples, the percentage of dose found in the liver only places a lower bound on absorption. This is particularly relevant to experiments where animals have been maintained for many weeks after dosing and an undetermined quantity of 2,3,7,8-TCDD has been excreted.

Finally, toxicity data for mixtures for which both toxicity and bioavailability of individual compounds may vary are difficult to interpret quantitatively in terms of bioavailability.

As presented in U.S. EPA (1985c), Rose et al. (1976) determined gut absorption of 2,3,7,8-TCDD in a 1:25 mixture of acetone to corn oil (by volume) in the rat. In both single dose and multiple dose experiments, measured absorption was approximately 85%. Assuming that absorption from pure corn oil is similar to that from this mixture, and assuming that absorption in other species for which data are not available is similar, the 85% factor can be applied to the data presented here to obtain an approximate range for typical 2,3,7,8-TCDD absorption from soil. Using this factor, the estimated relative bioavailability of 2,3,7,8-TCDD from soil is 25% to 50% and, when compared with corn oil, provides an estimate of gut absorption of 20% to 40% of ingested 2,3,7,8-TCDD in soil. This estimate is comparable with the 20% to 26% absorption from 2,3,7,8-TCDD treated soil from the work of Poiger and Schlatter (1980).

Recognizing these limitations, the weight of evidence indicates that 2,3,7,8-TCDD is often highly available from environmental materials. However, in one tested soil sample the compound was substantially less bioavailable. While the data are too sparse to allow

a prediction as to whether a particular environmental sample will prove more or less bioavailable, one important suggestion has emerged. In the two samples that have proved least bioavailable (the Umbreit et al. (1986a) manufacturing site soil sample, and 2,3,7,8-TCDD on activated carbon tested by Poiger and Schlatter (1980)) the 2,3,7,8-TCDD was largely resistant to solvent extraction. This was not the case for more bioavailable materials.

Further research, using short-term experiments in which animals are handled under identical conditions and are fed dioxins in different media, is needed for an improved comparison of absorption between different environmental samples. Acutely toxic doses should be avoided to ensure that tissue concentrations are directly interpretable. Experiments studying both tissue retention and enzyme induction should prove valuable for this research. Whole-body levels of 2,3,7,8-TCDD need to be related to liver concentrations, and the effects of metabolism need to be addressed. The vehicle of administration has been shown to affect acute 2,3,7,8-TCDD toxicity, and vehicle effects need to be considered in designing experiments.

C.3 Distribution

Ryan et al. (1985) examined the distribution of 2,3,7,8-TCDD in two humans at autopsy. On a weight basis, there were 6 ppt of TCDD in fat, 2 ppt in liver and below levels of detection in kidney and muscle. They reported that on a per lipid basis the levels were similar between tissues. It is important to note that one of these subjects suffered from a fatty liver syndrome, possibly resulting in higher levels in the liver than might normally be found in healthy individuals.

Poiger and Schlatter (1986) estimated that about 90% of the total body burden of 2,3,7,8-TCDD was sequestered in fat. Levels of 2,3,7,8-TCDD averaging 5-10 ppt have been reported for background populations in St. Louis, MO, by Graham et al. (1986), and in Atlanta, GA, and Utah by Patterson et al. (1986). These data are consistent with the lipid bioconcentrations assumptions made in calculations of daily intakes (*vidae supra*).

Patterson et al. (1987) developed a high resolution gas chromatographic/high resolution mass spectrometric analysis for 2,3,7,8-TCDD in human serum. A high correlation was reported between adipose tissue and serum concentrations when adjusted for total lipid content. The reader is referred to other documents (U.S/ EPA, 1993; Schlatter, 1991; Schecter, 1991) for more details on the distribution and elimination.

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Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

Part I: Estimating Exposure to Dioxin-Like Compounds

Volume 3: Site-Specific Assessment Procedures

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FIGURES

FIGURES (continued)

1. BACKGROUND AND SUMMARY

1.1. BACKGROUND

This reassessment is comprised of three reports:

Part 1. *Estimating Exposure to Dioxin-Like Compounds* (EPA, 2000a) (which expanded upon a 1988 draft exposure report titled, *Estimating Exposure to 2,3,7,8-TCDD* [EPA, 1988]);
Part 2. *Health Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (EPA, 1994; EPA, 2000b); and
Part 3. *Dioxin: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (EPA, 2000c).

Throughout the remainder of this document, these three parts as a whole will be abbreviated as the Reassessment Documents, and the individual parts will be referred to as the Exposure Reassessment Document, the Health Reassessment Document, and the Risk Characterization. The Exposure Reassessment Document has expanded to three volumes, as discussed below. Volumes 1 and 2 of the Exposure Reassessment Document are summarized in Section 4 of the Risk Characterization.

The process for developing the Reassessment Documents has been open and participatory. Each of the documents has been developed in collaboration with scientists from inside and outside the Federal Government. Each document has undergone extensive internal and external review, including review by EPA's Science Advisory Board (SAB). In September 1994, drafts of each document were made available for public review and comment. This included a 150-day comment period and 11 public meetings around the country to receive oral and written comments. These comments, along with those of the SAB (EPA, 1995a), have been considered in the drafting of this final document. The Dose-Response Chapter of the Health Document underwent peer review in 1997 (EPA, 1997a); an earlier version of the Integrated Summary and Risk Characterization underwent development and review in 1997 and 1998, and comments have been incorporated. In 1998, EPA released a workshop review version of the sources inventory (EPA, 1998), one of the three volumes of the Exposure Reassessment Document. In addition, as requested by the SAB, a chapter on Toxic Equivalency has been developed and underwent external peer review in parallel with the Integrated Summary and Risk Characterization in July, 2000. The November, 2000, review by the SAB of the Dose-Response Chapter, the Toxic Equivalency Chapter and the Integrated Summary and Risk Characterization

was the final step in this open and participatory process of reassessment. The full set of background documents and the integrative summary and risk characterization replace the previous dioxin assessments as the scientific basis for EPA decision-making.

The final Exposure Reassessment Document reflects changes made as a result of both review comments and analyses of a variety of other types of information that has come available. These include relevant information obtained from published peer-reviewed literature, EPA program offices, and other Federal agencies. This version of the Exposure Reassessment Document is current in this regard through 2000.

The purpose of the Exposure Reassessment Document is threefold: 1) to inventory the known sources of release of dioxins into the environment, 2) to develop an understanding of dioxins in the environment, including fate and transport properties, environmental and exposure media concentrations, background as well as elevated exposures, and temporal trends in exposure, and 3) provide site-specific procedures for evaluating the incremental exposures due to specific sources of dioxin-like compounds. Following this structure, the Exposure Reassessment Document is presented in three volumes:

Volume I - Sources of Dioxin-Like Compounds in the United States

This volume presents a comprehensive review of known sources of environmental releases of dioxin-like compounds in the United States. It includes an inventory of known source activity in terms of estimates of annual releases of dioxin-like compounds into the U.S. environment (i.e., air, water and land). This inventory is specific for two reference years, 1987 and 1995. From these data, it is possible to compare and contrast releases of dioxin-like compounds among the sources and between the reference years.

Volume II - Properties, Environmental Levels, and Background Exposures

This volume presents and evaluates information on the physical-chemical properties, environmental fate, environmental and exposure media levels, background and elevated human exposures, and temporal trends of dioxin-like compounds in the U.S. environment during the 20^{th} century.

Volume III - Site-Specific Assessment Procedures

This volume presents procedures for evaluating the incremental impact from sources of dioxin release into the environment. The sources covered include contaminated soils, stack emissions, and point discharges into surface water. This volume includes sections on: exposure parameters and exposure scenario development; stack emissions and atmospheric transport modeling; aquatic and terrestrial fate, and food chain modeling; demonstration of methodologies; and uncertainty evaluations including exercises on

sensitivity analysis and model validation, review of Monte Carlo assessments conducted for dioxin-like compounds, and other discussions.

The primary technical resource supporting the development of the inventory of sources of dioxin-like compounds discussed in Volume I (above) is the Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States (EPA/600/C-01/012. March, 2001). This database includes congener-specific CDD and CDF emissions data extracted from original engineering test reports. It has been published independently from the Reassessment and is available on Compact Disk -Read only Memory (CD-ROM), without cost, from EPA's National Service Center for Environmental Publications (NSCEP) in Cincinnati, Ohio (telephone: 1-800-490-9198, or 513-489-8190; fax: 513-489-8695). In addition, it can be downloaded from the web page of the National Center for Environmental Assessment, www.epa.gov/ncea/dioxin.htm.

1.2. DEFINITION OF DIOXIN-LIKE COMPOUNDS

This assessment addresses specific compounds in the following chemical classes: polychlorinated dibenzo-*p*-dioxins (PCDDs or CDDs), polychlorinated dibenzofurans (PCDFs or CDFs), polybrominated dibenzo-*p*-dioxins (PBDDs or BDDs), polybrominated dibenzofurans (PBDFs or BDFs), and polychlorinated biphenyls (PCBs), and describes this subset of chemicals as "dioxin-like." Dioxin-like refers to the fact that these compounds have similar chemical structure, similar physical-chemical properties, and invoke a common battery of toxic responses. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. The CDDs include 75 individual compounds; CDFs include 135 different compounds. These individual compounds are referred to technically as congeners. Likewise, the BDDs include 75 different congeners and the BDFs include an additional 135 congeners. Only 7 of the 75 congeners of CDDs, or of BDDs, are thought to have dioxin-like toxicity; these are ones with chlorine/bromine substitutions in, at a minimum, the 2, 3, 7, and 8 positions. Only 10 of the 135 possible congeners of CDFs or of BDFs are thought to have dioxin-like toxicity; these also are ones with substitutions in the 2, 3, 7, and 8 positions. This suggests that 17 individual CDDs/CDFs, and an additional 17 BDDs/BDFs, exhibit dioxin-like toxicity. The database on many of the brominated compounds regarding dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment.

There are 209 PCB congeners. Only 12 of the 209 congeners are thought to have dioxin-like toxicity; these are PCBs with 4 or more lateral chlorines with 1 or no substitution in the

ortho position. These compounds are sometimes referred to as coplanar, meaning that they can assume a flat configuration with rings in the same plane. Similarly configured polybrominated biphenyls (PBBs) are likely to have similar properties. However, the database on these compounds with regard to dioxin-like activity has been less extensively evaluated, and these compounds have not been explicitly considered in this assessment. Mixed chlorinated and brominated congeners of dioxins, furans, and biphenyls also exist, increasing the number of compounds potentially considered dioxin-like within the definitions of this assessment. The physical/chemical properties of each congener vary according to the degree and position of chlorine and/or bromine substitution. Very little is known about occurrence and toxicity of the mixed (chlorinated and brominated) dioxin, furan, and biphenyl congeners. Again, these compounds have not been explicitly considered in this assessment. Generally speaking, this assessment focuses on the 17 CDDs/CDFs and a few of the coplanar PCBs that are frequently encountered in source characterization or environmental samples. While recognizing that other "dioxin-like" compounds exist in the chemical classes discussed above (e.g., brominated or chlorinated/brominated congeners) or in other chemical classes (e.g., halogenated naphthalenes or benzenes, azo- or azoxybenzenes), the evaluation of less than two dozen chlorinated congeners is generally considered sufficient to characterize environmental "dioxin."

The chlorinated dibenzodioxins and dibenzofurans are tricyclic aromatic compounds with similar physical and chemical properties. Certain of the PCBs (the so-called coplanar or mono-ortho coplanar congeners) are also structurally and conformationally similar. The most widely studied of this general class of compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This compound, often called simply "dioxin," represents the reference compound for this class of compounds. The structure of TCDD and several related compounds is shown in Figure 1-1 . Although sometimes confusing, the term "dioxin" is often also used to refer to the complex mixtures of TCDD and related compounds emitted from sources, or found in the environment or in biological samples. It can also be used to refer to the total TCDD "equivalents" found in a sample. This concept of toxic equivalency is discussed below.

1.3. TOXIC EQUIVALENCY FACTORS

CDDs, CDFs, and PCBs are commonly found as complex mixtures when detected in environmental media and biological tissues, or when measured as environmental releases from specific sources. Humans are likely to be exposed to variable distributions of CDDs, CDFs, and dioxin-like PCB congeners that vary by source and pathway of exposures. This complicates the human health risk assessment that may be associated with exposures to variable mixtures of dioxin-like compounds. In order to address this problem, the concept of toxic equivalency has

been considered and discussed by the scientific community, and TEFs have been developed and introduced to facilitate risk assessment of exposure to these chemical mixtures.

On the most basic level, TEFs compare the potential toxicity of each dioxin-like compound comprising the mixture to the well-studied and understood toxicity of TCDD, the most toxic member of the group. The background and historical perspective regarding this procedure is described in detail in Part II, Chapter 9, Section 9.1, 9.2, and in Agency documents (EPA 1987, 1989a,b, 1991). This procedure involves assigning individual TEFs to the 2,3,7,8-substituted CDD/CDF congeners and "dioxin-like" PCBs. To accomplish this, scientists have reviewed the toxicological databases along with considerations of chemical structure, persistence, and resistance to metabolism, and have agreed to ascribe specific, "order of magnitude" TEFs for each dioxin-like congener relative to TCDD, which is assigned a TEF of 1.0. The other congeners have TEF values ranging from 1.0 to 0.00001. Thus, these TEFs are the result of scientific judgment of a panel of experts using all of the available data and are selected to account for uncertainties in the available data and to avoid underestimating risk. In this sense, they can be described as "public health conservative" values. To apply this TEF concept, the TEF of each congener present in a mixture is multiplied by the respective mass concentration and the products are summed to represent the 2,3,7,8-TCDD Toxic Equivalence (TEQ) of the mixture, as determined by Equation (1-1):

The TEF values for PCDDs and PCDFs were originally adopted by international convention (EPA, 1989a). Subsequent to the development of the first international TEFs for CDD/CDFs, these values were further reviewed and/or revised and TEFs were also developed for PCBs (Ahlborg et al., 1994; van den Berg et al., 1998). A problem arises in that past and present quantitative exposure and risk assessments may not have clearly identified which of three TEF schemes was used to estimate the TEQ. This reassessment introduces a new uniform TEQ

$$TEQ \cong \sum_{i-n}\left(Congener_i \times TEF_i\right) + \left(Congener_j \times TEF_j\right) + ...\left(Congener_n \times TEF_n\right) \quad (1\text{-}1)$$

nomenclature that clearly distinguishes between the different TEF schemes and identifies the congener groups included in specific TEQ calculations. The nomenclature uses the following abbreviations to designate which TEF scheme was used in the TEQ calculation:

1. I-TEQ refers to the International TEF scheme adopted by EPA in 1989 (EPA, 1989a). See Table 1-1.
2. TEQ-WHO_{94} refers to the 1994 WHO extension of the I-TEF scheme to include 13 dioxin-like PCBs (Ahlborg et al., 1994). See Table 1-2.

3. TEQ-WHO_{98} refers to the 1998 WHO update to the previously established TEFs for dioxins, furans, and dioxin-like PCBs (van den Berg et al., 1998). See Table 1-3.

The nomenclature also uses subscripts to indicate which family of compounds is included in any specific TEQ calculation. Under this convention, the subscript D is used to designate dioxins, the subscript F to designate furans and the subscript P to designate PCBs. As an example, "TEQ_{DF}-WHO_{98}" would be used to describe a mixture for which only dioxin and furan congeners were determined and where the TEQ was calculated using the WHO_{98} scheme. If PCBs had also been determined, the nomenclature would be "TEQ_{DFP}-WHO_{98}." Note that the designations TEQ_{DF}-WHO_{94} and I-TEQ_{DF} are interchangeable, as the TEFs for dioxins and furans are the same in each scheme. Note also that in this document, I-TEQ sometimes appears without the D and F subscripts. This indicates that the TEQ calculation includes both dioxins and furans.

This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxic equivalency to complex environmental mixtures for assessment and regulatory purposes. Sections in the Health Reassessment Document, and summarized in the Risk Characterization, describe the mode(s) of action by which dioxin-like chemicals mediate biochemical and toxicological actions. These data provide the scientific basis for the TEF/TEQ methodology. In its 20-year history, the approach has evolved, and decision criteria supporting the scientific judgment and expert opinion used in assigning TEFs has become more transparent. Numerous states, countries, and several international organizations have evaluated and adopted this approach to evaluating complex mixtures of dioxin and related compounds. It has become the accepted methodology, although the need for research to explore alternative approaches is widely endorsed. Clearly, basing risk on TCDD alone or assuming all chemicals are equally potent to TCDD is inappropriate on the basis of available data. Although uncertainties in the use of the TEF methodology have been identified (which are described in detail in the Health Reassessment Document, Chapter 9, Section 9.5), one must examine the use of this method in the broader context of the need to evaluate the potential public health impact of complex mixtures of persistent, bioaccumulative chemicals. It can be generally concluded that the use of TEF methodology for evaluating complex mixtures of dioxin-like compounds decreases the overall uncertainties in the risk assessment process as compared to alternative approaches. Use of the latest consensus values for TEFs assures that the most recent scientific information informs this "useful, interim approach" (EPA, 1989a; Kutz et al., 1990) to dealing with complex environmental mixtures of dioxin-like compounds. As stated by the U.S. EPA Science Advisory Board (EPA, 1995a), "The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the

TEFs and the availability of representative and reliable exposure data." EPA will continue to work with the international scientific community to update these TEF values to assure that the most up-to-date and reliable data are used in their derivation and to evaluate their use on a periodic basis.

A chemical is assigned a TEF value based on all the available data comparing the chemical to either TCDD or PCB 126. In addition, there are weighting criteria that place more emphasis on chronic and subchronic studies examining toxic endpoints (van den Berg et al., 1998). There is a broad range in the quantity and quality of the data available for individual congeners. For example, the TEF for PCB 126 is based on over 60 in vivo endpoints examining responses as diverse as enzyme induction, developmental toxicity, immunotoxicity, hepatic toxicity, alterations in hormones and tumor promotion, while the TEF for 3,4,4',5-tetrachlorobiphenyl (PCB 81) is based on in vitro CYP1A induction and QSAR calculations. Fortunately, PCB 81 does not significantly contribute to human TEQ exposures. There are 5 congeners that contribute approximately 80% of the total TEQ in humans: 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PCDF, and PCB 126 (See Part I, Volume 3 and Section 4.4.3 of this document). With the exception of 1,2,3,6,7,8-HxCDD, the TEFs for these chemicals are based on a number of different endpoints from multiple studies performed in different laboratories. The TEF for 1,2,3,6,7,8-HxCDD is based on a two-year bioassay in which rats were exposed to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD. The TEFs for 2,3,4,7,8-PCDF and PCB 126 are similar to the mean REP value for all in vivo endpoints and are similar to their REPs for tumor promotion. The TEF for 12378-PCDD is based largely on its REP for tumor promotion in rats. From these data, it is clear that the chemicals that contribute approximately 80% to the total human TEQ are well studied and the assigned TEFs provide reasonable estimates of the relative potency of these chemicals. In contrast, while there are some chemicals in the TEF methodology which have minimal data sets to reliably assess their relative potency, these chemicals do not contribute substantially to the human blood TEQ.

The ability of the TEF methodology to predict the biological effects of mixtures containing dioxin-like chemicals has been evaluated in a number of experimental systems. These studies generally demonstrate that the assumption of additivity provides a reasonable estimate of the dioxin-like potential of a mixture (described in the Health Reassessment Document, Chapter 9, Section 9.4). In addition, there are examples of non-additive interactions between dioxins and non-dioxins. Both greater than additive and less than additive interactions have been observed in these studies. In general the non-additive interactions between the dioxins and non-dioxins have been observed at doses that are considerably higher than present background human exposures.

There are a number of natural chemicals that bind and activate the AhR and induce some dioxin-like effects. It has been proposed by some scientists that these chemicals contribute significantly to the total TEQ exposures and that these exposures far out weigh those from PCDDs, PCDFs and PCBs (Safe, 1995). While this hypothesis is intriguing, there are several limitations to these analyses. The in vivo data on the natural AhR ligands is limited to enzyme induction and a single developmental study. Few, if any, toxicology studies demonstrating clear dioxin-like toxicities have been published. The natural AhR ligands are rapidly metabolized and result in both transient tissue concentrations and transient effects. The natural ligands also have significant biological effects that are independent of the AhR and it is not clear as to the role of the AhR in the biological effects of these chemicals. Clearly this issue requires further research in order to better understand the relative potential health effect of dioxin and related chemicals as compared to natural AhR ligands.

One of the limitations of the use of the TEF methodology in risk assessment of complex environmental mixtures is that the risk from non-dioxin-like chemicals is not evaluated in concert with that of dioxin-like chemicals. Another limition of the TEF methodology is their application to non-biological samples. The fate and distribution of PCDDs, PCDFs and PCBs are not necessarily related to their TEF. Thus, the use of the TEF for non-biological media must be done cautiously. Future approaches to the assessment of environmental mixtures should focus on the development of methods that will allow risks to be predicted when multiple mechanisms are present from a variety of contaminants.

1.4. OVERALL COMMENTS ON THE USE OF VOLUME III OF THE DIOXIN EXPOSURE DOCUMENT

Users of the dioxin exposure document should recognize the following:

1. This document does not present detailed procedures for evaluating multiple sources of release. However, it can be used in two ways to address this issue. Incremental impacts estimated with procedures in Volume III can be compared to background exposure estimates which are presented in Volume II. This would be a way of comparing the incremental impact of a specific source to an individual's total exposure otherwise. Assuming the releases from multiple sources behave independently, it is possible to model them individually and then add the impacts. For example, if several stack emission sources are identified and their emissions quantified, and it is desired to evaluate the impact of all sources simultaneously, then it is possible with ISCST3 to model each stack emission source individually and then sum the concentrations and depositions at points of interest in the surrounding area.

2. The demonstration of the site-specific procedures presented in this exposure document best serve as general examples for evaluating exposures to dioxin-like compounds, rather than specific assessments. This demonstration scenarios in Chapter 5 of this document were not generated for purposes of supporting any specific regulation. Rather, they were only intended to demonstrate the procedure described earlier in Chapters 2 through 4. Certainly, the goal of developing “high end” and “central” is consistent with Agency policy, and even assignment of many of the exposure and fate parameters can be adopted for other assessments. Therefore, assessors may find even the specifics of the demonstration scenarios useful for other purposes.

3. The understanding of the exposure to dioxin-like compounds continues to expand. Despite being one of the most studied groups of organic enivronmental contaminants, new information is generated almost daily about dioxin-like compounds. This document is considered to be current through 2000.

Numerous parameter values are used in this document and it is important to understand their degree of "endorsement" by EPA. The parameters can be divided into the following four classes for purposes of addressing this issue:

1) **First Order Defaults:** As defaults, these parameters are independent of site specific characteristics and can be used for any assessment. Also, as first order defaults, it is felt that the values selected for the demonstration scenarios carry a sufficient weight of evidence from current literature such that these values are recommended for other assessments. Several of the chemical specific parameters, such as the Henry's Constant, H, and the organic carbon partition coefficient, Koc, fall into this category. The qualifier above, "current literature", indicates that new information could lead to changes in these values.

2) **Second Order Defaults:** Like the above category, these parameters are judged to be independent of site specific characteristics. However, unlike the above category, the current scientific weight of evidence is judged insufficient to describe values selected for demonstration purposes as first order defaults. Parameters of principal note in this category are the bioconcentration parameters specific to the chemicals, such the Biota Sediment Accumulation Factor, or BSAF. This parameter translates a bottom sediment concentration to a fish tissue concentration. The science is evolving for this parameter, including thought on the extent to which BSAFs generated for one species at one site can be generalized to other sites and/or species, the differences in BSAF between column and bottom feeders, the differences between past and ongoing contamination, and so on. Users should carefully review the justification for the SOD values selected for the demonstration scenarios before using the same values.

3) **Site Specific:** These parameters should or can be assigned values based on site-specific information. The information provided on their assignment for the demonstration of methodologies in this document can be useful where site specific information is unavailable. A key class of site specific are the source strength terms - the soil concentrations, effluent discharge rates, and stack emission rates. Others include physical properties (organic carbon contents of soil and sediment, climate variables, areas, distances, and volumes) and parameters for bioconcentration algorithms (yields of vegetation, cattle raising practices, fish lipid contents).
4) **Exposure Parameters:** The exposure parameters have not been categorized as have the contaminant fate and transport/transfer parameters. Assignment of these values are critical as Lifetime Average Daily Dose (LADD) estimates are linearly related to parameter assignments - doubling exposure duration assumptions double LADDs, and so on. Some exposure parameters are appropriately described as first order defaults. These include: lifetime, body weights, water ingestion rates, inhalation rates, and an exposure duration for a childhood pattern of soil ingestion. All of the other exposure parameters are better described as either second order defaults or site specific parameters. All exposure parameters were developed based on information and recommendations in EPA's *Exposure Factors Handbook* (EPA, 1997b) and *Dermal Exposure Assessment: Principles and Applications* (EPA, 1992a).

The end products of the exposure assessment procedures presented in this document are estimates of potential dose expressed in mass (pg, ng, etc.) of dioxin-like compound/body weight (usually kg)-day. The procedures for converting these dose estimates to risk estimates, both cancer and non-cancer, are described in Chapter 2 and demonstrated in Chapter 5.

The scope of each chapter in Volume III is summarized below.

Chapter 2, Estimating Exposure and Risks, presents overall framework for conducting exposure assessments. It provides procedures for identifying exposure pathways, estimating contact rates and resulting exposure levels. Approaches for defining exposure scenarios are presented. Procedures for converting exposure dose to lifetime cancer risk estimates are provided, and procedures for evaluating non-cancer risk are also discussed.

Chapter 3, Evaluating Atmospheric Releases of Dioxin-Like Compounds from Combustion Sources, provides procedures to estimate the emission rates of dioxin-like compounds from combustion processes and further atmospheric transport modeling procedures from the stack to the surrounding land surface. This chapter describes and demonstrates the use of the ISCST3 model on a hypothetical incinerator and lists the associated atmospheric dispersion and deposition estimates from that model exercise.

Chapter 4, Estimating Exposure Media Concentrations, provides procedures for estimating concentrations of the dioxin-like compounds in exposure media (soil, air, water, biota) resulting from soil contamination, effluent discharges, and stack emissions.

Chapter 5, Demonstration of Methodology, develops hypothetical scenarios and generates exposure and risk estimates to demonstrate the methodologies of this document.

Chapter 6, User Considerations, discusses key issues for users of the methodologies. All model parameters are listed and categorized according to the scheme noted above. Sensitivity analysis is conducted on the algorithms estimating exposure media concentrations. An exercise on estimating the releases from a bounded area of soil contamination is presented. The purpose of this exercise is to determine whether a reservoir of soil contamination would be depleted prior to an assumed duration of exposure.

Chapter 7, Model Comparisons and Validations, presents extensive information aimed at gaining confidence and establishing credibility for the use of the fate models of this assessment to predict the fate, movement, and resulting exposure media concentrations near sources of dioxin release. One section of this chapter presents alternate fate models, and where possible, generates results from these models to compare with results from the models selected for this assessment. The second major section presents several model validation exercises, where the models are paramterized to predict exposure media concentrations, and the results are compared with appropriate real world observations.

Chapter 8, Uncertainty, discusses the sources and possible magnitude of uncertainty in the exposure assessment procedures. Uncertainty and variability of fate and transport, and exposure parameters, are discussed. Monte Carlo and similar numerical methods to quantify variability and uncertainty are discussed, and several literature examples of these types of exercises conducted for dioxin-like compounds are summarized.

1.5. EXECUTIVE SUMMARY OF VOLUME III

Volume III describes procedures for conducting site specific exposure and risk assessments to estimate potential dose, cancer, and non-cancer risks from exposure to dioxin-like compounds from a nearby source of release. Sections below summarize the key issues and results from each chapter of this volume.

1.5.1. Exposure Equation

A potential dose is defined as a daily amount of contaminant inhaled, ingested, or otherwise coming in contact with outer surfaces of the body, averaged over an individual's body

weight and lifetime. The general equation used to estimate potential dose normalized over body weight and lifetime is as follows:

$$\text{Lifetime Average Daily Dose (LADD)} = \frac{(\text{exposure media concentration} \times \text{contact rate} \times \text{contact fraction} \times \text{exposure duration})}{(\text{body weight} \times \text{lifetime})} \quad (1\text{-}2)$$

This procedure is used to estimate dose in the form needed to assess cancer risks. For non-cancer risks, an ADD term is instead derived. ADD is calculated as above except that exposure duration and lifetime are taken out of the equation above. Each of the terms in this exposure equation is discussed briefly below:

- **Exposure media concentrations:** These include the average concentrations in the media to which individuals are exposed. Media considered in this assessment include soil, air, water, vegetables/fruits, fish, beef, milk, and poultry.
- **Contact rate:** These include the ingestion rates, inhalation rates, and soil contact rates for the exposure pathways.
- **Contact fraction:** This term describes the distribution of total contact between contaminated and uncontaminated media. This assessment describes exposures which occur at homes, so the contact rate translates to time spent at home for air, soil, and water exposures, and fraction of total food product produced at home (vegetables/fruits, beef, milk, and poultry) or obtained recreationally (fish) from an impacted water body. This assessment assumes time at home fractions of 0.70 and 0.90 for central and high end scenarios, respectively, and home food production factors, or food contact fractions, of about 0.50 and less.
- **Exposure duration:** This is the overall time period of exposure, mostly pertinent to adult exposures. Central and high end durations of 9 and 30 years, respectively, are assumed in this assessment. Another exposure duration considered in this methodology is one associated with a childhood pattern of soil ingestion. The exposure duration in this case is 5 years.
- **Body weight:** For all the pathways, the human adult body weight of 70 kg is assumed. Although the United States population average is closer to 60 kg (EPA, 1997b), the value of 70 kg has been more traditionally used. The body weight for child soil ingestion is 17 kg.
- **Lifetime:** Following convention, and because cancer slope factors are derived based on a 70-year human lifetime, the average adult lifetime assumed throughout this document is 70 years.

1.5.2. Procedures for Evaluating Cancer and Non-Cancer Risk

Although the focus of the site-specific methodology is to estimate exposures to dioxins, procedures are also presented and demonstrated for estimating cancer and non-cancer risk. The usual procedure used to calculate an upper-limit incremental cancer risk is as follows:

$$R = 1 - e^{-q_1^* \, LADD} \approx q_1^* \, LADD \qquad (1\text{-}3)$$

when q_1^* LADD < 10^{-3} and where q_1^* is the 95% upper confidence limit of the linearized cancer slope factor of the dose-response function (expressed in inverse units of the dose quantity, such as kg-day/pg, or equivalently, $(pg/kg\text{-}day)^{-1}$) and LADD is the dose (which needs to be in units appropriate to cancel those of q_1^*, pg/kg-day). This assessment uses the simplified q_1^* LADD since the exposures and risks demonstrated are generally less than 10^{-3}. The slope factor, q_1^*, for 2,3,7,8-TCDD has been previously estimated by EPA as 0.000156 $(pg/kg\text{-}d)^{-1}$ (EPA, 1984; 1981), but has been reevaluated as 0.001 $(pg/kg\text{-}d)^{-1}$ in this Reassessment. Also, it is being applied to a TEQ dose in this Assessment.

This selected cancer slope factor was based primarily on the meta analysis of the human epidemiology studies where exposure was estimated from dioxin concentrations in blood in occupationally exposed cohorts. The dose estimates used to derive the slope factor were obtained by using a PK model to convert the blood concentrations to an administered, or potential, dose. An administered dose is defined as the dose which contacts the body boundary surfaces, such as the skin as in dermal exposure or the dose ingested prior to absorption. This administered dose was derived by first calculating an absorbed dose and then dividing by 0.8 - i.e., an absorbed dose was assumed to be 80% of an administered dose. Because the potency factor was derived based on an administered dose, the new slope factor can be applied to an administered dose without any adjustment for absorption as long as the absorption is approximately 80%. Although the data are limited, this is probably a reasonable assumption for most types of food ingestion and inhalation. For soil pathways, however, an additional adjustment factor has to be added to account for significantly less absorption. Data suggests that the dose of dioxins absorbed from soil ingestion is about 30% and about 3% from soil dermal contact. For soil dermal contact, an absorbed dose is already calculated; thus the dermal contact pathway yields an absorbed dose already. Therefore, for these two pathways, Equation (1-3) needs an additional adjustment factor equal to 0.3/0.8, or 0.375, for soil ingestion and 1.00/0.8, or 1.25, for soil dermal contact. A full discussion on absorption of administered dioxin through

the various pathways can be found in Chapter 1. Disposition and Pharmacokinetics, of the Health Reassessment Document (EPA, 2000b).

To evaluate incremental non-cancer effects in a risk assessment, EPA uses established Reference Doses (RfDs) for most contaminants. An RfD is defined as an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure of the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. The incremental dose from a particular source is compared with the RfD. However, an RfD has not been established for dioxin-like compounds. It was concluded in the Risk Characterization that setting an RfD using traditional Agency approaches would result in an RfD that would likely be 2-3 orders of magnitude below current background intakes and body burdens. For this reason, EPA concluded that establishing an RfD for assessing the potential for non-cancer effects would not be helpful to risk managers. Instead, it was suggested in the Risk Characterization that risk managers compare the increment of exposure to a specific source with background exposures for assessing the potential for non-cancer effects. For this reason, a "ROIE", or Ratio of Incremental Exposure, was developed. The ROIE was defined as a ratio between the increment of daily exposure from the source in question, the term defined by ADD as noted above, to background daily exposure. A ROIE equaling 1.0 suggests that the increment of exposure from the source in question is equal to background exposure.

Background exposure could be considered to be a national average background exposure, or it could a quantity specifically developed for the site in question. The latter would be appropriate if certain behaviors, such as subsistence fishing or farming, or certain environmental conditions, such as a high local background of dioxin in soil or air due to industrial practices, were present in the vicinity of the specific source being evaluated.

1.5.3. Procedure for Estimating Exposure

Before making exposure estimates, the assessor needs to gain a more complete understanding of the exposure setting and the contamination source. The approach used for this assessment is termed the exposure scenario approach. There are 7 steps in this approach:

Step 1. Identify Source: Three principal sources are addressed in this document: contaminated soils, stack emissions, and effluent discharges.

Step 2. Estimate Release Rates: Estimating the release of contaminants from the initial source is the first step towards estimating the concentration in the exposure media. Releases from soil contamination include volatilization, and wind and soil erosion. Stack emissions and effluent discharges are point source releases into the environment.

Step 3. Estimate Exposure Point Concentrations: Contaminants released from soils, emitted from stacks, or discharged into surface waters move through the environment to points where human exposure may occur, and/or to impact environmental media to which humans are exposed. Various fate, transport, and transfer models are used to predict exposure media concentrations given source releases.

Step 4. Characterize Exposed Individuals and Exposure Patterns: Exposed individuals in the scenarios of this assessment are individuals who are exposed in their home environments. They are residents who breathe air at their residence, fish recreationally, have a home garden, farm, and are children ages 2-6 for the soil ingestion pathway. Exposures which occur at the workplace or other locations are not discussed in this assessment, although the procedures could be adapted for other exposure sites. Each pathway has a set of exposure parameters including contact rates, contact fractions, body weights, exposure durations, and a lifetime. An individual's total exposure is the sum of the exposures from individual pathways.

Step 5. Put It Together in Terms of Exposure Scenarios: A common framework for assessing exposure is with the use of "settings" and "scenarios." Settings are the physical aspects of an exposure area and the scenario characterizes the behavior of the population in the setting and determines the severity of the exposure. A wide range of exposures are possible depending on behavior pattern assumptions. An exposure scenario framework offers the opportunity to vary any number of assumptions and parameters to demonstrate the impact of changes to exposure and risk estimates.

Step 6. Estimate Exposure: The end result of having followed the above 5 steps are estimates of individual exposures to a characterized source of contamination.

Step 7. Assess Uncertainty: Uncertainties should be considered when applying procedures in this document to a particular site. Pertinent issues explored in this assessment include: 1) model predictions of exposure media concentrations compared to field measurements in a series of model validation exercises, 2) similarities and differences for alternate models for estimating exposure media concentrations, 3) sensitivity of model results to a range of values for methodology parameters, 4) mass balance checks, and 5) qualitative and quantitative discussions on the uncertainties with the model parameters and exposure estimates generated for the demonstration scenarios.

1.5.4. Estimating Exposure Media Concentrations

Literally hundreds of fate and transport models have been published which differ widely in their technical sophistication, level of spatial or temporal resolution, need for site specific

parameterization, and so on. This makes selection of the most appropriate one for any particular situation very difficult. For this assessment, relatively simple, screening level models are used to model fate, transport, and transfer of dioxin-like compounds from the source to the exposure media. Simple assumptions are often made in order to arrive at the desired result, which is long-term average exposure media concentrations. Perhaps the most critical of the assumptions made is that the source strength remains constant throughout the period of exposure.

It is important to understand that EPA is not endorsing the algorithms of this assessment as the best ones for use in all dioxin assessments. They are suggested as reasonable starting points for site-specific or general assessments. All assumptions for the models and selection of parameter values are carefully described. If these assumptions do not apply to a particular situation, or where assessors require more spatial or temporal resolution, more complex models should be selected. Finally, it cannot be overemphasized that measured concentrations are generally more reliable than modeled ones. Assessors should use measured concentrations if available and if such measurements can be considered spatially and temporally representative for the exposed populations.

Chapter 4 provides algorithms used to evaluate the fate, transport, and transfer of dioxin-like compounds from contaminated soil, stack emissions, and effluent discharge. These three sources of dioxin release are referred to as "source categories" in this document. Algorithms are presented which link each of these sources to estimated concentrations in a number of media which may be contaminated as a result, and are therefore potential "exposure media": 1) surface soils, 2) surface-water associated media: suspended and bottom sediment and dissolved phase concentrations, 3) air including the vapor phase and in particulate form, and 4) biota including beef, milk, poultry, fruit and vegetables, and fish. The remainder of this section describes how each potential exposure medium can be affected by each source, and the algorithms used to make this link.

- **Surface soils:** Exposure to contaminated soil may be a result of direct contact with soil on the site of the contamination, or indirectly after the contaminated soil has been transported off the site of contamination and onto a nearby site of exposure. These cases are termed "on-site": the site of contamination and the site of exposure are the same, and "off-site": the site of exposure is distant from the site of contamination. In either case, soil concentrations are specified for the contaminated source. For the off-site case, dioxins reach the site of exposure via erosion. Mixing of contaminated and uncontaminated exposure site soil is into either a "tilled" 20-cm depth or a "non-tilled" 2-cm depth. The tilled concentrations are used to estimate concentrations in underground vegetables, and for outdoor dermal contact. The non-tilled concentrations are used for indoor dermal contact events, for childhood soil ingestion in

residential and farm settings, and for cattle soil ingestion (used in estimation of beef and milk concentrations).

Exposure site soils can also be impacted from stack emissions due to air transport of particle-bound dioxins from the stack to the exposure site. Deposition modeling for dioxin-laden particles allows for estimation of tilled and non-tilled soil concentrations. When stack emissions are the source, the nontilled depth of mixing is again assumed to be 2 cm.

A key assumption for evaluating the exposure site as a result of both off-site erosion and stack emissions is that contaminants impact a thin layer of soil and do, in fact, dissipate; no dissipation is assumed if the site of contamination is also the site of exposure. A soil dissipation half-life of 25 years is assumed for all dioxin-like congeners for the shallow 2 cm depth and 100 years is assumed for the residues tilled to 20 cm.

- **Surface Water:** The principal assumption driving the solutions for the soil and stack emission source categories is that the suspended and bottom sediments of water bodies originate as watershed soils, which are subsequently eroded. For the stack emission source category, a portion of the sediments also originates from directly-depositing dioxins. The process of erosion transports soils within the watershed to the water body. Unit rates of erosion along with watershed size determine the total potential amount of soil which could be delivered to the water body. Sediment delivery ratios reduce that potential amount. A mass balance assures that soil eroding on an annual basis becomes either suspended or bottom sediment within an annualized volume of surface water. "Enrichment" of eroded soil is assumed, which means that eroded soil from a contaminated source is assumed to be higher in concentration of dioxin-like compounds than *in situ*, off-site soils. Once in the water body, a standard partitioning model based on the organic carbon partition coefficient, Koc, determines the concentration of contaminant in the water in truly dissolved form and the concentration on suspended sediments. The organic carbon normalized concentrations of suspended and bottom sediment are assumed to be equal. Watershed soil concentrations are model input parameters for determining the effect on surface water from contaminated soils. For stack emissions, a total (dry + wet) deposition rate of contaminant which represents average depositions onto the watershed is specified as an input parameter, as well as a mixing depth representing the watershed. In this way, average watershed soil concentrations are calculated for the stack emission source category.

For effluent discharges as sources, watershed soils are not considered. An amount of contaminant is discharged into an annual flow volume to obtain a simple dilution concentration. This total concentration is partitioned into a truly dissolved phase and a phase sorbed to suspended sediments using the organic carbon partition coefficient, the Koc. Bottom sediments are not considered for effluent discharges.

- **Soil to Air:** From contaminated soils, residues become airborne via the processes of volatilization and wind erosion. For on-site soil contamination, these vapor and particle phase fluxes are translated to ambient air concentrations using a near-field dispersion model. For the off-site scenario, the same approach is used to estimate ambient air exposure site concentrations, except that a far-field dispersion model is used. These airborne reservoirs are the basis for inhalation exposures, and are also used to estimate plant concentrations for vegetable ingestion and in grass and feed for estimating beef and milk concentrations.

- **Stack emissions and atmospheric transport modeling :** Air dispersion/deposition models consider the basic physical processes of advection, turbulent diffusion, and removal via wet and dry deposition to estimate the atmospheric transport, resulting ambient air concentration, and settling of particles. The ISCST3 model is used for air dispersion and deposition modeling. Besides discussions in Chapter 3 on theoretical underpinnings and parameter assignment, further discussions on the ISCST3 model can be found in EPA (1995b).

Application of the ISCST3 model follows these steps:

Step 1. Emission factors: The first step in the use of the ISCST3 model is to determine "emission factors" for dioxin-like congeners. These factors are defined as the μg (or other mass unit) congener emitted per kg (or other mass unit) feed material combusted. Once assuming a rate of feed material combusted in appropriate units, kg/day, these emission factors can be translated to the units appropriate for atmospheric transport modeling, μg/sec. This assessment promotes the generation of specific congener emission factors, rather than emission factors for TEQ or homologue groups. Emission factors for the demonstration of stack emission sources in Chapter 5 were generated from actual test data from an incinerator burning organic wastes (source otherwise unspecified). Emission estimates for this example incinerator are similar to emissions that are known to be emitted from combustors employing sophisticated air pollution control devices (e.g., scrubbers combined with fabric filters).

Step 2. Vapor/particle (V/P) partitioning: The second step in atmospheric transport modeling is to determine the percent of totally emitted dioxin-like congener which is in a vapor phase, and the percent which is in the particle phase. The partitioning of stack emissions into these two phases was examined by reviewing stack testing data, ambient air sampling data, and a theoretical approach developed in Bidleman (1988). From this review, it was generally concluded that the most appropriate representation of partitioning of dioxins for purposes of fate modeling and exposure assessing was provided by the modeling approach, and the V/P partitioning scheme for dioxins and furans shown in Table 1-4 is the one adopted for this Assessment.

Step 3. Two runs of the ISCST3 model: In order to provide estimates of vapor and particle phase concentrations of dioxin-like compounds, as well as estimates of wet/dry particle deposition flux, it is necessary that to run the ISCST3 model twice. Both model runs should assume a "unit emissions release rate", e.g., 1 g/s. Results from these unit runs can easily be transformed to final outputs given the total emission rate of the congener and vapor/particle partitioning. A vapor phase run involves turning wet/dry deposition switches to the "off" position. This inactivates a plume depletion equation that subtracts out losses in ambient air concentration due to particle deposition. What is left are the Gaussian dispersion algorithms. The vapor phase concentrations are used for inhalation exposures and also for vapor transfers onto vegetation for food chain modeling. A second run of ISCST3 with wet/dry deposition switches turned to the "on" position is considered a simulation of particle-bound contaminant. Outputs from this run include wet and dry deposition rates, and air concentrations of contaminants in the particulate phase. The depositions are used in soil and food chain modeling, and the concentrations are added to the vapor phase concentrations from the first ISCST3 run to arrive at the total air-borne reservoir for inhalation exposures.

- **Biota:** Simple bioconcentration/biotransfer approaches are used to estimate biota concentrations in this assessment. Specifics for each biota considered are:

1. Fish - The soil contamination and stack emission source categories estimate the concentration of contaminant on bottom sediments of water bodies. A fish lipid concentration is estimated based the organic carbon normalized bottom sediment concentration and a BSAF, or Biota Sediment Accumulation Factor. Whole fish concentrations for exposure estimation then equal this lipid concentrations times a whole fish lipid content (or a fillet lipid content). For the effluent discharge source category, fish lipid concentrations are estimated as a function of organic carbon normalized concentrations and the closely related BSSAF, or Biota Suspended Solids Accumulation Factor. This recently introduced bioaccumulation factor (EPA, 1993) is analogous to the BSAF, and it is suggested in EPA (1993) that, as a first estimate, it take on the same chemical-specific numerical value as the BSAF.

2. Vegetation - Concentrations in three types of vegetation are considered in this assessment: below ground vegetables (carrots, potatoes, e.g.), above ground vegetables/fruits (tomatoes, apples), and above ground grass and cattle feed which are required for estimation of beef and milk concentrations. Assumptions critical to all three include: above ground vegetation is impacted by vapor phase transfers and particle deposition - there is no root to shoot translocation, outer portions of the vegetation are only impacted with minimal within plant translocation, particle bound contaminants deposit onto and mix in a vegetative reservoir and are subject to a fourteen-day dissipation half-life which represents particle washoff, and

vegetables/fruits which have an outer protective layer (peas, citrus e.g.) are unimpacted by dioxin-like compounds. Below ground vegetable concentrations are estimated from soil water concentrations and a Root Concentration Factor, or RCF. Above ground concentrations in plants due to atmospheric vapor concentrations are modeled using a "biotransfer" approach, where the vapor concentrations are simply multiplied by an air-to-leaf transfer factor, B_{vpa}, and a surface area to volume reduction factor, VG, which is equal to 1.00 for grasses and other leafy vegetation and less than 1.00 for bulky vegetation. This B_{vpa} was found to be one of the most critical parameters for not only vegetation concentration modeling (i.e., above ground vegetations were found to be dominated by vapor transfers over particle phase depositions), but for subsequent terrestrial animal food chain models. The B_{vpa} was developed for the dioxins in a field calibration exercise.

3. Beef and Milk - Weighted average concentrations of dioxin-like compounds in the diets of cattle raised for beef or lactating cattle are multiplied by a congener-specific bioconcentration factor, BCF, which yields the concentrations in the fat of beef or milk. The same congener-specific BCF is used for beef and milk. This presumes that dioxin-like compounds bioaccumulate equally in body fat and milk fat of beef and dairy cattle. The difference between the two food products is mostly a function of the diets presumed for beef cattle and lactating cows. A set of BCFs for all dioxin-like congeners for this assessment were based on a set of data on a lactating cow (i.e., dietary intakes of dioxin congeners, concentrations in milk, and other pertinent quantities; McLachlan, et al., 1990). A later feeding experiment by Fries, et al. (1999) found BCFs very similar to the McLachlan, et al. (1990) single cow BCFs adopted for this assessment. Beef and dairy cattle diets are described in terms of proportions in pasture grass, cattle feed (silage, grains), and soil. Models described above estimate concentrations in these cattle intakes.

4. Chicken and Eggs - The algorithm to estimate the concentration of contaminant in chicken and/or eggs is essentially the same algorithm as in beef/milk above: the concentration in the lipid of chicken/eggs is a function of the weighted average concentration in the chicken diet (comprised of vegetation and soil) and chicken/egg bioconcentration factors. The experiments used to develop the chicken and egg bioconcentration factors were conducted by the Hazardous Materials Laboratory at the California EPA (Stephens, et al. 1995). Three key differences in the application of the chicken/egg bioconcentration model and beef/milk model were: 1) data was available and robust enough to assign different bioconcentration factors for chicken and eggs, 2) chickens, both layers and non-layers, were assumed to "free range" in the demonstrations of this pathway in Chapter 5, which translated to a higher exposure to soil in their diet - 10% for free range chickens vs. 4% for beef cattle and 2% for dairy cattle, and 3) based on information in

Stephens, et al. (1995), chicken feed was assumed to originate from protected vegetation and was therefore assumed to be dioxin-free.

1.5.5. Demonstration of Methodology

EPA (1992b) states, "In exposure scenario evaluation, the assessor attempts to determine the concentrations of chemicals in a medium or location and link this information with the time that individuals or populations contact the chemical. The set of assumptions about how this contact takes place is an exposure scenario." These assumptions can be made many different ways producing a wide variety of scenarios and associated exposure levels. The number of people exposed at different levels form a distribution of exposures. Ideally assessors would develop this entire distribution to fully describe the exposed population. Since the necessary information for developing a population distribution is rarely available, EPA (1992b) recommends developing a central and high end scenario to provide some idea of the possible range of exposure levels.

1.5.5.1. Description of the Demonstration Scenarios

The basic setting for which the methodologies are demonstrated is a rural setting which contains both farms and non-farm residences. The three principal sources of contamination, soil, stack emissions, and effluent discharges, are assumed to exist in such a setting. "Central" scenarios are based on typical behavior at a residence and "high end" scenarios are comprised of a farm family that raises a portion of its own food. Key distinguishing features between the high end and central scenarios include: 1) individuals in high end scenarios are assumed to be at their home a greater proportion of the day than the central scenarios (which impacts assignment of contact fraction), 2) individuals in high end scenarios are exposed to impacted beef from cattle which they raise on their farm while these exposures are not considered for the central scenarios, 3) in contrast, individuals in the central scenario recreationally fish, 4) the exposure duration for individuals in the high end scenario is 30 years compared to 9 years for the central scenario, and 5) certain exposure parameters, such as water ingestion rate which is 1.4 L/day for the central scenarios and 2 L/day for the high end scenario, are different.

The example scenarios were carefully crafted to be plausible and meaningful, considering key factors such as source strength, fate and transport parameterization, exposure parameters, and selection of exposure pathways. However, it should be clearly understood that the purpose of the demonstration scenarios is to provide users of this methodologies with a comprehensive example of their application. The demonstration exposure scenarios were:

Scenarios 1 and 2: Background conditions, Residence and Farm

Surface soils within the watershed are initialized to soil concentrations of the 17 dioxin-like congeners (no dioxin-like PCBs) which have been found in an actual rural setting. Also, air concentrations of the 17 congeners are initialized to air concentrations which have been found in this same rural setting. Scenario 1 is the central residential scenario, and Scenario 2 is the high end farming scenario. The exposure pathways for Scenario 1 are: water ingestion, air inhalation, fish ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion. The exposure pathways for Scenario 2 are: water ingestion, air inhalation, beef ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion. It is noted that for a background condition, it could be argued that all exposure is to background concentrations in exposure media. In other words, all contact fractions would be 1.00. However, if an assessor wished to compare the incremental impacts from a specific source of dioxin release with impacts an individual would receive by contact with the same exposure media which has only background concentrations of dioxins, than the assessor would assume all the same exposure behaviors (rates of contact, contact fractions). This demonstration takes this approach.

Exposure Scenario 3: Soil Contamination, Farm

A 40,000 m^2 rural farm is located 150 m (500 ft roughly) from a 40,000 m^2 area of bare soil contamination; an area that might be typical of contaminated industrial property. The surface soil at this property is contaminated with three example dioxin-like compounds to the same concentration of 1 part per billion (ppb). These compounds are: 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, and 2,3,3',4,4',5,5'-HPCB. The 1 ppb soil concentration is reasonable for industrial sites of contamination of dioxin-like compounds, and generally about three orders of magnitude higher than the concentrations of these congeners in background settings. As in the above and all scenarios, bottom sediment in a nearby river is impacted, which impacts the water and fish. The exposure pathways include: water ingestion, air inhalation, beef ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion.

Exposure Scenarios 4 and 5: Stack Emissions, Residence and Farm

A 4,000 m^2 rural residence (Scenario 4) is located 5000 meters from an incinerator, and a 40,000 m^2 (Scenario 5) rural farm is located 500 meters downwind from an incinerator. Emission data of the suite of 17 dioxin-like dioxin and furan congeners (no dioxin-like PCBs) is available from stack testing of an actual incinerator. This allows for estimation of impacts from each congener individually, and estimation of WHO_{98}-TEQ_{DF} impacts. The exposure pathways for Scenario 4 are: water ingestion, air inhalation, fish ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion. The exposure pathways for Scenario 5 are: water ingestion, air inhalation, beef ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion.

Exposure Scenario 6: Effluent Discharge into a River

Exposure parameters associated with central behaviors for the water and fish ingestion pathways were chosen to demonstrate this source category. The source strength was developed from data on pulp and paper mill discharges of 2,3,7,8-TCDD. The discharges of the other two example compounds are assumed to be the same for purposes of demonstration. Obviously, however, there is less of a tie to real data for the discharge rate for these other two example compounds.

Food pathway analyses outside of the scenario framework: The food consumption pathways of fish, milk, chicken, and eggs are demonstrated using source strength characteristics of the three high end scenarios above: Scenarios 2 (background conditions), 3 (soil contamination), and 5 (stack emission). These food pathways were not modeled in the scenarios themselves. In these analyses, exposure media concentrations are calculated for each source and the pathway exposure estimates are provided. The purpose of these external pathway analyses was to provide further demonstration and to compare impacts from the various food pathways where methodologies have been provided in this assessment.

1.5.5.2. Results from the Demonstration Scenarios

For brevity, only a subset of results from the demonstrations will be summarized. Table 1-5 gives the exposure media concentrations for WHO_{98}-TEQ_{DF} for Example Scenarios #1 and #2, demonstrating a background setting, and Scenarios #4 and #5, the central and high end scenarios for the stack emission source category. Table 1-6 gives the estimated Lifetime Average Daily Doses, LADDs, and the cancer risk for Scenarios #2 and #5, the high end scenarios for the background setting and stack emission source.

Much of the differences between exposure pathways and scenarios is due to differences in exposure media estimation. Following are some of the observations on exposure media concentrations, LADDs, cancer and non-cancer risks for the background and stack emission scenario demonstrations:

1) Concentrations in environmental and exposure media for the stack emission central and high end scenario were about 3 and 2 orders of magnitude lower than the central and high end scenarios demonstrating background conditions, respectively. For example, the background WHO_{98}-TEQ_{DF} air concentration was 0.021 pg/m^3. In contrast, the WHO_{98}-TEQ_{DF} air concentration for the stack emission source was 2 orders of magnitude lower at 500 meters from the stack, at 0.00024 pg/m^3, and was lower still at 5000 meters from the stack, at 0.000085 pg/m^3. This suggests that the example stack emission source, which was a single emission source with a high level of pollution control, would contribute little to overall background exposure levels.

2) For both the background scenarios, 1 and 2, and the stack emission scenarios, 4 and 5, WHO_{98}-TEQ_{DF} soil concentrations were over an order of magnitude higher than 2,3,7,8-TCDD concentrations. The difference in 2,3,7,8-TCDD and WHO_{98}-TEQ_{DF} impacts to all media mirrors the difference in stack emissions of 2,3,7,8-TCDD and stack emissions of WHO_{98}-TEQ_{DF}. This trend in differences between 2,3,7,8-TCDD and TEQ impacts occurs in all exposure media estimations for both the background scenarios and the stack emission scenarios.

3) Within each demonstration scenario, there appears to be a reasonably narrow range of predicted lipid concentrations among beef, milk, chicken, and egg fat. The difference is about a factor of 3 to 4. The lowest concentrations are noted for the stack emission demonstration scenarios, in the 10^{-3} to 10^{-2} pg WHO_{98}-TEQ_{DF}/g (ppt) range, lipid basis. The background concentrations were next highest, about two orders of magnitude higher in the 10^{-1} to 10^{0} ppt range. The average concentration of WHO_{98}-TEQ_{DF} in lipids of terrestrial animal food products measured in US food products, as described in Volume II of the Exposure Reassessment Document, is similar to the background concentration predictions. This is not unexpected since concentrations of dioxins in terrestrial food animals in the background scenarios were modeled based on a profile of dioxins and furans found in air in an actual rural setting.

4) Table 1-6 shows the percent of total scenario exposure which is accounted for by each pathway. The total scenario LADD was calculated simply as the sum of the pathway LADDs in the scenario, without accounting for any differences in body absorption. As discussed above, inhalation and food/water ingestion pathways have an absorption in the range of 80%, soil ingestion has an absorption of 30%, and soil dermal contact has absorption already considered, so LADD estimates are already at 100% absorption. From Table 1-6, it is seen that the beef pathway dominates the scenarios. For the central scenarios (not summarized in this section), which included fish ingestion but not beef or milk ingestion, the fish ingestion dominated. Interestingly, the beef ingestion pathway LADD was over an order of magnitude higher than the fish ingestion pathway LADD. This was more due to differences in the exposure parameters including the ingestion and contact rates, and the differences in the lipid content of the full product, rather than lipid concentrations themselves since the fish lipid concentrations tended to be higher than the beef lipid concentrations for a given source.

5) Differences between analogous "central" and "high end" exposure pathway estimates for the background demonstration scenarios, 1 and 2, were near or less than an order of magnitude (inhalation exposure for the central background scenario and the inhalation exposure for high end on-site scenario are analogous exposures). This is because the exposure parameters used to distinguish typical and high end exposures, the contact rates, contact fractions, and exposure durations, themselves did not differ significantly, and these were the only

distinguishing features for analogous pathways in the background demonstrations. For the total exposure, however, there was a difference of a factor of 20 between high end and central exposure in the background demonstration scenarios. This is because the high end scenario included consumption of beef, which was the highest exposure pathway and exceeded the fish pathway of the central scenario by over an order of magnitude.

6) In the stack emission scenarios, placing exposed individuals either 500 or 5000 meters away from the incinerator did significantly impact the results. The order of magnitude difference in distance added about an order of magnitude difference in exposure media concentrations and hence LADD estimates. Therefore, the full difference in analogous pathways between the central and high end was closer to 2 orders of magnitude for the stack emission demonstration scenarios.

7) The LADD of 0.093 WHO_{98}-TEQ_{DF}/kg-day for the background high scenario is about an order of magnitude lower than the adult background dose of 0.64 pg WHO_{98}-TEQ_{DF}/kg-day generated in Volume II, Chapter 4. The reasons for this difference are: 1) the Volume II background exposure estimate was an average daily dose, ADD, not an LADD calculated in the demonstration scenarios here. The LADD estimated in this chapter assumes 30 years of exposure. The ADD during the exposure period would be just over twice, or 70/30, as high as the LADD; 2) the Volume II background exposure estimate considered additional pathways including fish, dairy ingestion (milk and otherwise), eggs, pork, and poultry. If one adds the additional pathways for the background high scenario - milk, chicken, egg, and fish, the LADD (and ADD) roughly doubles; 3) the exposure factors are different, with the most important difference being that in the exposure scenarios considered in this chapter, contact fractions of less than 1.0 were assumed - less than 0.5 for the terrestrial animal pathways, in fact.

Some of these differences between the Volume II background exposure estimate and the LADD estimates for the background high scenario also are relevant for the procedures demonstrated here to characterize non-cancer risk. As described earlier, a “ratio of incremental exposure”, or ROIE, is the current recommended approach for evaluating non-cancer risk. This is defined as the ratio of the incremental dose due to the source being evaluated and the background dose, multiplied by 100%. The background dose can be a generic US background dose, or a site-specific dose. The generic adult background dose of WHO_{98}-TEQ_{DF}, as noted above, is 0.64 pg TEQ/kg-day. A background dose for the specific site being evaluated here has not yet been developed. All of the exposures and risks displayed in previous tables assumed a less-than-lifetime exposure, a limited set of exposure pathways, and contact fractions less than 1.0 (meaning that a fraction of their total consumption was from home-produced and impacted food). Producing a site-specific background exposure requires an assessor to estimate the total

exposure of an individual (or individuals) to dioxins if the nearby source were not in existence. In that circumstance, the family would be still be consuming home produced foods. But they would also be consuming store bought or restaurant bought foods. The "total" exposure would include all pathways considered in the scenarios of this chapter, but other pathways as well.

For the purposes of the demonstration in Chapter 5, it was assumed that the farming family in the background scenario consume foods at similar rates whether or not they are consuming home produced or store bought food products, and that their exposure is characterized by all the pathways in the formal demonstration scenarios, as well as the additional scenarios that were demonstrated in Chapter 5, including milk, chicken, eggs, and fish. To estimate their average background daily dose over a lifetime, the exposure duration will increase from 30 to 70 years, and the contact fractions will all rise to 1.00. The resulting daily exposure is 1.16 pg WHO_{98}-TEQ_{DF}/kg-day. This 1.16 pg WHO_{98}-TEQ_{DF}/kg-day will be used here as the "site-specific background dose" against which one can develop ROIEs for the incinerator source.

As discussed in Chapter 2, a pertinent issue for generation of ROIEs is the use of LADDs or ADDs. Chapter 2 recommends the use of ADD for ROIEs, but this demonstration will show a ROIE calculation for both LADD and ADD. The total LADD for the stack emission high end scenario, as displayed in Table 1-7, is $1.01 * 10^{-3}$ pg WHO_{98}-TEQ_{DF} /kg-day. The ADD can be simply calculated as this LADD times 70/30, or $2.36 * 10^{-3}$ pg WHO_{98}-TEQ_{DF}/kg-day. The ROIEs are then easily calculated as:

using LADD: $[(1.01*10^{-3})/(1.16)] * 100\% = 0.09\%$
using ADD: $[(2.36*10^{-3})/(1.16)] * 100\% = 0.20\%$

As seen by these two calculations, the ROIE is less than 1%. If the generic US background dose of 0.64 pg WHO_{98}-TEQ_{DF}/kg-day were used instead of the site-specific background dose of 1.16 pg WHO_{98}-TEQ_{DF}/kg-day, the ROIEs would not be significantly different: 0.16% using LADD and 0.37% for ADD.

1.5.6. Sensitivity Analysis

This section discusses three sensitivity analysis issues pertinent to use of the site-specific methodologies promoted in this document: 1) the appropriate use and categorization of model parameters, 2) a sensitivity analysis exercise on the parameters required for algorithms estimating exposure media concentrations, and 3) the issue of mass balance with regard to the source strength terms of the four source categories.

1.5.6.1. Categorization and Use of Model Parameters

Table 6.1 in Chapter 6 lists all the parameters, including names, definitions, and units, that are required for the methodologies of this assessment except the exposure parameters. Exposure parameters are given in Table 2.1 in Chapter 2. Table 6.1 also gives four additional pieces of information for each parameter listed. Three are numerical values which were used in the sensitivity analysis exercises that are described below. One of those parameters is labeled "selected", which were the ones used in the demonstration exposure scenarios. High and low values of parameters selected for sensitivity analysis were carefully developed and might be considered a reasonable range of values for other uses of the methodology (with obvious exceptions such as areas of contamination, distances from contaminated to exposure site, and so on). The fourth piece of information is a qualitative judgement on the part of the authors of this document as to the appropriateness of using the "selected" parameter values for other assessments. This judgement is categorized in three ways:

1) **First Order Defaults:** As defaults, these parameters are independent of site specific characteristics. As first order defaults, it is felt that the values selected for the demonstration scenarios carry a sufficient weight of evidence from current literature such that these values are recommended for other assessments. Several of the chemical specific parameters, such as the Henry's Constant, H, and the organic carbon partition coefficient, Koc, fall into this category. The qualifier above, "current literature", indicates that new information could lead to changes in these values.

2) **Second Order Defaults:** Like the above category, these parameters are judged to be independent of site specific characteristics. However, unlike the above category, the current scientific weight of evidence is judged insufficient to describe values selected for demonstration purposes as first order defaults. Parameters of principal note in this category are the bioconcentration parameters specific to the chemicals, such as the Biota Sediment Accumulation Factor, or BSAF. This parameter translates a bottom sediment concentration to a fish tissue concentration. Users should carefully review the justification for the SOD values selected for the demonstration scenarios before using the same values.

3) **Site Specific:** These parameters should or can be assigned values based on site-specific information. The information provided on their assignment for the demonstration scenarios, and for selection of high and low values for sensitivity analysis testing, is useful for determining alternate values for a specific site. A key class of SS parameters which are the source strength terms - the soil concentrations, effluent discharge rates, and stack emission rates. If users are unable to obtain site-specific information, or their use of the methodologies is for general purposes, they should review the justification for selection of values for methodology

demonstration, as well as information provided giving ranges of likely values for model parameters.

The exposure parameters can be categorized as have the contaminant fate and transport/transfer parameters. Assignment of these values are critical as LADD estimates are linearly related to parameter assignments - doubling exposure duration assumptions double LADDs, and so on. Some of the exposure parameters are appropriately described as first order defaults. These include: lifetime, body weights, water ingestion rates, inhalation rates, and an exposure duration for a childhood pattern of soil ingestion. All of the other exposure parameters are better described as either second order defaults or site-specific. All exposure parameters were developed based on information and recommendations in EPA's *Exposure Factors Handbook* (EPA, 1997b) and *Dermal Exposure Assessment: Principals and Applications* (EPA, 1992c). Attaining site-specific information is recommended for exposure parameters.

1.5.6.2. Sensitivity Analysis

Sensitivity analysis was undertaken in order to evaluate the impact to exposure media concentration estimations with changes in fate and transport/transfer model parameters. Figure I-5 shows an example of sensitivity analysis conducted. This figure describes the impact of key factors for the stack emission source category for determining impacts to beef. The x-axis contains the names of the parameters evaluated. The key below the figure gives the definition of the parameters and the values selected for the demonstration scenarios. The y-axis shows the fractional change to the key model result, in this case, beef fat concentrations, to the changes made in the parameter. These actual changes in model predictions are noted above and below the bars. For example, beef fat concentrations increase by about a factor 2 with a 10-fold increase in the soil concentration. In contrast, there appears to be almost a linear relationship between an increase in vegetation concentration with beef fat concentration, as shown by the sensitivity test displayed next to the soil concentration test. There, a 10-fold increase in grass and other feed concentration resulted in a 10-fold increase in beef fat concentration. This was not the same trend that was tested for the soil contamination source category. There, soil dioxin provides the source term for vegetation and cattle impacts, not the air source of the stack emission category. In the soil contamination source category, the soil-to-cattle pathway dominates the prediction of beef fat concentration, whereas in the stack emission source category, the air-to-plant-to-cattle dominates. The right side of Figure 1 shows how the beef fat predictions are effected by changes in the assumptions regarding how the beef cattle are exposed, as expressed in the exposure parameters BCSDF (beef cattle soil diet fraction), BCFDF (beef cattle feed diet fraction), and the others listed in Figure 1-2. When....

Following are key overall observations from the several sensitivity analysis exercises undertaken in Chapter 6:

1) Source terms are the most critical for exposure media impacts. Source terms include soil concentrations, stack emission rates, and effluent discharge rates. In all cases, the impact to exposure media is linear with changes to source terms. Proximity to the source term can be important as well, as demonstrated with differences in distance from the stack emission source.

2) Chemical-specific parameters, particularly the bioconcentration/biotransfer parameters, are the second most critical model inputs. Some of these have lesser impacts within the range tested, such as the organic carbon partition coefficient, Koc, for surface water impacts. Generally, at least an order of magnitude in range in possible media concentrations is noted with the range of chemical-specific parameter ranges tested. The impact of changes to bioconcentration/biotransfer parameters is mostly linear. This is because these transfer factors estimate media concentrations as a linear transfer from one media to another. For example, fish lipid concentrations are a linear function of the organic carbon normalized concentration of contaminants in sediments. These transfer parameters are also identified as uncertain parameters. Tested ranges sometimes spanned over an order of magnitude for 2,3,7,8-TCDD.

3) All other parameters had less of an impact as compared to source strength and chemical specific parameters; nearly all impacts were within an order of magnitude for the range of tested values. Part of the reason for this trend is that there is a reasonably narrow range for many of the non-chemical specific or source term parameters - soil properties, wind speeds, vegetation yields, and others.

4) The sensitivity analysis exercises unearthed a dichotomy in model performance, and likely therefore behavior in the real world, when soil is the source of dioxins as compared to when stack emissions are the source of dioxins. The on-site soil source category was demonstrated with a 1 ppt soil concentration of 2,3,7,8-TCDD, a concentration similar to measured concentrations of 2,3,7,8-TCDD in rural settings. Air concentrations are estimated to be $4*10^{-5}$ pg/m^3 (vapor+particle phases summed). Atmospheric transport modeling in the demonstration of the stack emission source category resulted in an exposure site air concentration (vapor+particle phases summed also) at 500 meters from the stack to be $1*10^{-5}$ pg/m^3. With similar air concentrations predicted to occur at the exposure site for the demonstration of the soil and stack emission categories, one might hypothesize that all subsequent impacts would be similar. That was not the case. The stack emission source algorithms deposited particulates onto soil to estimate a soil concentration that was in the 10^{-3} ppt range for the 1-cm untilled depth and the 10^{-5} range for the 20-cm tilled depth. This

compares to the 1 ppt concentration for the on-site soil source category demonstration. With similar air concentrations but a 3+ order of magnitude difference in soil concentrations in the demonstration of the soil and the stack emission sources, the following trends were noted: 1) below ground vegetables had much higher concentrations for the soil source demonstration scenario; 2) soil-related exposures (dermal contact and soil ingestion) were much higher for the soil source demonstration scenario; 3) soil was significantly more critical in predicting beef and milk fat concentrations in the soil source category. The following shows the relative impact of soil versus vegetation (grass and cattle feed) for the on-site soil demonstration and the stack emission demonstration:

	Percent impact due to ingestion of:		
Description	Soil	Grass	Feed
Soil contamination, beef	90	7	3
Soil contamination, milk	87	2	11
Stack emission, beef	5	59	32
Stack emission, milk	3	15	82

Subsequently, beef and milk concentrations were almost two orders of magnitude higher for the soil source category as compared to the stack emission source category, 4) because above ground vegetation are driven by air concentrations, above ground vegetables/fruit and grass/cattle feed concentrations were similar for both demonstrations.

1.5.6.3. Mass Balance

A mass balance exercise was undertaken to evaluate whether a principal of mass balance will be violated with the models and parameters used for the demonstration of the soil source category - that principal being that dioxin releases from a site cannot exceed the original amount at the site (assuming no replenishment). A simplifying assumption for the soil source category was that the soil concentration remained constant over the period of exposure - there was not a systematic depletion of the reservoir over time due to modeled dissipation processes.

First, an estimate of the "reservoir" of 2,3,7,8-TCDD that is implied with the demonstration parameters was made. Then, an estimate of the rate at which this reservoir dissipated using the solution algorithms for dissipation: volatilization and wind erosion flux from

soils, soil erosion, the soil ingestion by cattle and children, losses in runoff and leaching, the loss via dermal contact, and the removal via harvest of below ground vegetation. The premise examined was that, if it takes substantially more time than the exposure period to dissipate the reservoir, then the assumption of a constant soil concentration may be suitable for purposes of exposure assessments. On the other hand, complete dissipation within a time period less than or even near to the period of exposure would mean that exposures and risks are being overestimated. This analysis led to a conclusion that the reservoir modeled in the exercise above would take more than 90 years to dissipate.

This was not a definitive exercise, by any means, but it does lend some confidence that a principal of mass balance may not have been violated for the soil source categories, and for the assumption of 30 years exposure duration.

1.5.7. Model Comparisons and Model Validations

Chapter 7 contains a series of tests of the fate models, including comparisons with other available models and model validation exercises. Brief summaries of these exercises providing an overview and qualitative statement about the results are provided below; Chapter 7 provides all the detail and the quantitative results. Overall, model comparison and validation tests in Chapter 7 showed that: 1) the empirical models selected for this methodology compared well with most other models, many of them empirical as well, 2) since many of the key models of this assessment, in particular the bioconcentration models relating a biota concentration (vegetation, terrestrial animal lipid concentration) to an adjacent media concentration (air, animal feeds), were developed from field data, it is not surprising that when tested against other field data, they were shown to reproduce the field data reasonably well. It can be concluded that, with careful parameter assignment, model predictions of environmental/exposure media concentrations of dioxin-like compounds should be reasonably realistic for most uses. Nonetheless, it should be understood that model testing is an ongoing process. The model comparisons and validations summarized here are, by no means, expected to establish model validity beyond any doubt. Users of this methodology are encouraged to subject the models to any number of tests, validation or otherwise, as they use the models described in this document to conduct site-specific assessments for dioxin-like compounds.

1.5.7.1. Model Comparisons

1. Evaluation of alternative air-to-leaf modeling approaches Three empirical air-to-leaf models for estimating grass concentrations from air concentrations are described and tested against two field data sets. Both field data sets contained simultaneous air concentration and grass concentration measurements of dioxin-like congeners. One set was in a rural and the other in an industrial setting in the United Kingdom. Therefore, this test was both a model comparison test as well as a validation of the air-to-plant modeling developed in this methodology. A principal finding of this exercise was that the model selected for this assessment provided the best fit of the data to the model.

2. Estimating water concentrations given a steady input load from overland sources

The WASP4 model, a substantially more complicated aquatic fate model than the one developed in this methodology, was tested in a dynamic and a steady-state mode for Lake Ontario (EPA, 1990a). Conditions in the steady state run were duplicated for the simple dilution model used in the effluent discharge source category of this assessment. Results suggest that the simple dilution model of this assessment produces reasonably similar results as the more complicated WASP4 model.

3. Estimating fish tissue concentrations based on water column concentrations rather than bottom sediment concentrations A water column measure of the potential for a contaminant to accumulate in fish tissue is termed the Bioaccumulation Factor, or BAF. Bioaccumulation refers to the net accumulation of a chemical from exposure via food and sediments as well as water, and is calculated as the ratio of the chemical concentration in the fish to that in the water. A $ssBAF_l^t$ and a $ssBAF_l^d$ (defined respectively as the steady state BAF, lipid- and total water concentration-based, and steady state BAF, lipid- and dissolved water concentration-based) were developed for lake trout, 2,3,7,8-TCDD, and for Lake Ontario 1987 contamination conditions (EPA, 1990a). WASP4 model runs assuming steady loadings to Lake Ontario were duplicated using the watershed modeling approach of this assessment, where water body concentrations were a function of soil erosion loading, followed by simple partitioning and dilution algorithms.

The prediction of whole fish tissue concentrations using $ssBAF_l^t$ and $ssBAF_l^d$ in the WASP4 modeling exercise was similar to fish concentrations predicted using the simple dilution model and the use of the BSAF of this assessment. Differences were further studied using changes in key modeling parameters including sediment organic carbon fraction and others.

4. Other modeling approaches and considerations for air concentrations resulting from soil volatilization For the soil contamination source category, air concentrations result from volatilization of vapor phase dioxins and suspension of particle-bound dioxins. Dioxins released in these two ways disperse over the soils using simple dispersion models. Two alternate modeling approaches for soil volatilization were tested, and one alternate air dispersion model was tested. One of the alternate volatilization approaches was developed by Jury and co-workers (Jury, et al., 1983, 1984a,b). If one assumes that the contaminant moves through the soil column in only the vapor phase, a simplification of the fundamental equations used by Jury offers another option for modeling soil volatilization. This model comparison test showed that the volatilization model chosen for this methodology predicted an average flux over 30 years roughly four times higher than the average flux predicted by the Jury model. The exact reason for this four-fold difference was not ascertained, and could lie in differences in assumed boundary conditions. In any case, it is judged that both models predict comparable volatilization fluxes. On the other hand, the vapor diffusion model predicted volatilization rates that were 100 times less than the Jury models and about 250 times lower than the model of this methodology. The reason for this discrepancy also could not be ascertained.

The alternate approach to estimating on-site dispersion is the "box-model" approach. This is a simple dilution approach similar to the dilution model used to model the dispersion of dioxins emitted from a pipe effluent discharge. Model testing showed that the box model predicted air concentrations above a soil that was 10 times higher than the near-field dispersion model used in this methodology and 100 times higher than the far-field solution.

5. An alternate model for estimating plant concentrations from soil concentrations For plants grown in contaminated soils, plant concentrations are modeled as a two-step process: vapor and particle-phase releases from soil disperse in the air and settle (particle-bound) or

transfer (vapor-phase) to the vegetation in the models of this assessment. An alternate and simpler approach was developed from field data on above ground vegetation concentrations correlated to soil concentrations of contaminants and the octanol water partition coefficient in Travis and Arms (1988). This correlation led to an empirical bioconcentration factor for vegetation, B_v, regressed against the contaminant log Kow, and defined by the authors as the concentration in above ground plant parts divided by the concentration in soil. The B_v calculated for 2,3,7,8-TCDD is 0.0041. This compares with two plant:soil ratios calculated using the soil-to-air-to-plant algorithms of this assessment: they were in the range of 10^{-5} for bulky vegetables and 10^{-3} for leafy vegetation.

6. Alternate modeling approaches for estimating beef and milk concentrations

Webster and Connett (1990) compared five models which estimated the 2,3,7,8-TCDD content of cow's milk from 2,3,7,8-TCDD air contamination. All five models have the same basic framework. Particulate-bound 2,3,7,8-TCDD deposits onto the ground and vegetation, cattle feed and pasture grass, to which the cattle are exposed. Algorithms to estimate soil concentrations in these models are the same ones used in this approach, but the vegetation algorithms importantly do not consider vapor phase dioxins. Model validation exercises done in Chapter 6, and model sensitivity analysis exercises done in Chapter 5 both show that neglecting the vapor phase will result in a significant underprediction in vegetation impacts for the lower chlorinated dioxins.

These models use a “biotransfer factor” approach to estimating dioxin concentrations in cow’s milk. This approach converts a daily dosage of dioxin, in units of mass/day, into a dioxin concentration. The “bioconcentration” approach in this assessment first calculates an average dioxin concentration in the whole diet, considering fractions of the diet in vegetation and soil and the concentrations in these diet components, and then multiplies this average concentration by a bioconcentration factor. The most sophisticated biotransfer factor was developed by Travis and Arms (1988), who developed a beef and a milk biotransfer factor, B_b and B_m, as a function of the log Kow of the contaminant. Given a log Kow of 6.8 for 2,3,7,8-TCDD (assumed in this assessment), B_b is solved for as 0.16 and B_m is solved for as 0.03. The beef/milk bioconcentration factors of this document were developed from a data in a study by McLachlan,

et al. (1990). This same data can be used to calculate biotransfer factors. The 2,3,7,8-TCDD B_m from that data set is calculated at 0.01. While this 0.01 looks similar to the 0.03 calculated using the empirical relationship developed by Travis and Arms (1988), this does not imply that the Travis and Arms relationship is valid for dioxin-like compounds. In fact, the Travis and Arms relationship calculates a larger B_m as log Kow increases, while the McLachlan data suggest that B_m decreases as the degree of chlorination increases. It was concluded that the Travis and Arms relationship is not valid for compounds with high log Kow, and definitely not valid for dioxin-like compounds.

1.5.7.2. Model Validations

1. The impact of dioxin soil contamination to nearby soils The demonstration of the "soil source" category in Chapter 5 suggested that the concentration at a site of exposure 100 meters away would be 40% of the concentration at the contaminated site for the 2 cm depth and 6% for the 20-cm depth. The literature contained several, somewhat anecdotal, information on elevations of dioxin in soils near a contaminated site, and these were reviewed, including derivation of a similar percentage when possible. One of those sites was the Dow Chemical site in Midland, MI, and percentages derived with their data ranged from 3.5% to 15%, depending on what soil concentration was assumed to represent contamination and what represented impacted.

2. Background soil concentration to bottom sediment concentration ratio A "sediment enrichment ratio" of 3.00 in the model increases the concentration of dioxins in eroding soil as compared to the concentration in the basin draining into a water body. The concentrations of dioxins in the water body will be predicted to be higher than watershed soils, but not necessarily three times higher. Other factors, particularly the organic carbon partition coefficient of the dioxin compound and organic carbon fraction of the water body sediments, also influence the prediction of water body sediment concentration. In the demonstration of background conditions in Chapter 5, the ratio of the concentration of 2,3,7,8-TCDD in water soil to the water body sediment was 2.8. A set of data on 2,3,7,8-TCDD in bottom sediment and background soil concentration from several water bodies and nearby soils was used to derive several similar

ratios. Although there was variability among the various water bodies, the average ratio derived using all soil samples (n = 77) and all sediment concentrations (n = 346) was also 2.8.

3. Soil-to-Air and Air-to-Soil Modeling Air and soil measurements of the 17 dioxin congeners at a rural site were available for model testing. Two tests were conducted - one assumed air was the source of dioxins in the soil and soil concentrations were predicted based on deposition of dioxins from the air, and the other assumed that soil was the source of dioxins in the air and modeled the release and dispersion of dioxins. It was found that, when air dioxin was assumed to be source of dioxin in the soil, a good match between predicted and observed soil concentrations were found. When soil was instead assumed to be the source of dioxins in the air, it was found that air concentrations were underpredicted by about three orders of magnitude. This supports findings described earlier in the fate and transport overview of Volume III that long range transport of dioxins by air is the cause for widespread dispersal of dioxins in the environment.

4. Soil to Below Ground Vegetation A laboratory test in which carrots and potatoes were grown in soil at various 2,3,7,8-TCDD levels provided a test for the soil-to-below ground vegetation model. In that model, an RCF (root concentration factor) is multiplied by soil water concentration to predict root concentration. For bulky below ground vegetables, an additional VG_{bg} reduced the concentration predicted only with RCF since this RCF was developed from experiments on barley roots grown in solution. It was found that the measured concentrations in the carrots and potatoes exceeded the predictions made using the RCF and a VG_{bg} initially set at 0.01. It was found that the measured peel concentrations were similar to model predictions without the VG_{bg}. This suggested that the dioxins translocated more than expected into the carrots and potatoes, and on the basis of these tests, the VG_{bg} was increased from 0.01 to 0.25 for application of this model to below ground vegetables.

5. Paper and Pulp Mill Discharges and the Subsequent Impact to Fish Emissions of 2,3,7,8-TCDD measured in the 101 mill study (EPA, 1990b) were combined with average streamflow data from the rivers and streams into which the paper mills discharged. Predictions

of 2,3,7,8-TCDD in fish were compared with measurements of TCDD in fish from EPA's National Bioaccumulation Study (EPA, 1992c). These fish were known to be downstream of the pulp and paper mills. First, it was found that the model significantly underpredicted fish concentrations when the mill discharged into the largest water bodies where paired data was available - those with streamflows averaging $2.8 * 10^{10}$ L/hr, with a narrow range of 1 to $4 * 10^{10}$ L/hr. The predicted concentrations were about two orders of magnitude lower than measured. It was speculated that there were many more sources of dioxin input to the rivers in these larger systems; this modeling exercise assumed that the pulp mill was the only source of dioxins to impact the fish. The predictions of TCDD in fish were much better in other paired data sets when the streamflows averaged $5.4 * 10^{8}$ L/hr, with a range of 10^{7} to 10^{9} L/hr. These lower streamflows characterized 38 of 47 mills used in this model validation exercise. The average of 38 mills and 74 fish for modeled and observed fish concentrations is 7 ppt and 15 ppt, respectively. Also of note and perhaps not ironically, the highest observed fish concentration of 143.3 ppt is matched by the highest predicted fish concentration of 89.2 ppt, for these lower streamflow conditions. The average of 9 mills and 21 fish associated with large receiving water bodies for modeled and observed fish concentrations is 0.7 and 5.3 ppt, respectively.

6. ISCST3 Modeling of the Release of Large Amounts of Dioxin from a Municipal Solid Waste Incinerator and the Subsequent Impacts to Air and Soil Measurements of dioxin TEQ emissions at nearly 1 kg/yr from a municipal solid waste incinerator in Columbus, OH, in 1994 caused EPA's Region 5 to issue an Emergency Order requiring operators of this incinerator to install MACT, Maximum Achievable Control Technology, pollution devices on an accelerated basis. The incinerator had been in operation 11 years at this time, and a soil study clearly showed elevations of dioxins in soils to about 3 km from the incinerator. Air measurements taken at the same time additional stack measurements were taken were also available, and the stack, air, soil, and obtained meteorological data allowed for a comprehensive test of the ISCST3 model to predict short-term air concentrations, and with predicted depositions, long-term soil concentrations. It was found that the prediction of highest 48-hour air concentrations were generally in the same direction and magnitude as was found in the air monitoring program. With specific congener differences, the model also showed the highest soil

concentrations near the incinerator, with reduced concentrations in both measured and modeled concentrations as the distance increased. An important observation was that the modeled soil concentrations retained a similar relative profile as the stack-emitted dioxins. Differences between the soil and stack profiles were only due to vapor/particle partitioning - there was no modeling of air degradation (there was plume depletion due to deposition), and all congeners were modeled to dissipate in soil at a similar half-life of 25 years. On the other hand, the measured soil concentrations, while unambiguously and significantly elevated near the incinerator, had a relative profile very similar to dioxin profiles found in a typical background urban or rural soil profile, where concentrations are much lower. This shows that, while high emissions clearly resulted in high soil concentrations near the Ohio incinerator, differential dissipation mechanisms for the congeners in the soil and/or in the air resulted in a very typical profile that was not modeled by ISCST3 and the soil concentration model. Future modeling exercises for dioxins in air and depositing to soil using the ISCST3 or similar models should focus on this disparity.

1.5.8. Uncertainty

Some discussion of the issues commonly lumped into the term "uncertainty" is needed at the outset. The following questions capture the range of issues typically involved in uncertainty evaluations:

(1) How certain are site specific exposure predictions that can be made with the methods?

(2) How variable are the levels of exposure among different members of an exposed local population?

(3) How variable are exposures associated with different sources of contamination?

The emphasis in Volume III is in providing the technical tools needed to perform site-specific exposure assessments. For the assessor focusing on a particular site, question (1) will be of preeminent importance. Therefore, the emphasis of the uncertainty evaluation is to elucidate those uncertainties inherent to the exposure assessment tools presented. This chapter examines the capabilities and uncertainties associated with estimating exposure media concentrations of the dioxin-like compounds using the fate, transport, and transfer algorithms, and also identifies

and discusses uncertain parameters associated with human exposure patterns (contact rates and fractions, exposure durations, etc.).

A site specific assessment will also need to address the variability of risks among different members of the exposed population, the second key question above. The level of detail with which this can be done depends on the assessors knowledge about the actual or likely activities of the exposed population. In this document, one approach to evaluating this variability is demonstrated. Separate "central" and "high end" scenario calculations are presented to reflect different patterns of human activities within a hypothetical rural population.

A key issue with regard to intra-population variability is that it is best (if not only) addressed within the context of a specifically identified population. If such information is available, a powerful tool that can be used to evaluate the variability within a population is Monte Carlo Analysis. Three recent Monte Carlo studies which have been done for exposure to 2,3,7,8-TCDD were reviewed. Assumptions on distributions of exposure patterns and fate and transport parameter distributions are described, as are the results of their analyses.

With regard to question (3), this document does not present a detailed evaluation of how exposure levels will vary between different sources of release of dioxin-like compounds into the environment. While Volume III does demonstrate the methodologies developed for sources of release of dioxin-like compounds into the environment with source strengths and environments crafted to be plausible and meaningful, there is still a great deal of variability on both the source strengths and on the environments into which the releases occur. For example, the frequency with which farms and rural residences are near stack emissions of dioxin-like compounds is not addressed. Such analysis is beyond the scope of this document.

Chapter 7 identifies some of the key uncertainties, as well as the key supporting evidence, for the procedures and parameters associated with all the pathways. A summary of discussions from the uncertainty evaluation is now presented. First is a summary of three exposure parameters common to all pathways:

1. Lifetime, Body Weights, and Exposure Durations: Of these three parameters, the exposure duration is the most uncertain. The estimates of 9 and 30 years were made in this assessment for non-farming residents in rural settings, and farming residents in rural settings.

An adult body weight of 70 kilograms and a lifetime of 70 years are standard assumptions for exposure and risk and, although variability is recognized for these parameters, these variations are not expected to add significant uncertainty in exposure estimates. The same is true for the 17 kg child body weight in the childhood exposure pattern of soil ingestion.

2. Soil Ingestion and Soil Dermal Contact: Soil ingestion for older children and adults were not considered, which may have underestimated lifetime soil ingestion exposures. Pica soil ingestion patterns were not evaluated in this assessment. The ingestion rates (100 mg/day for central scenarios and 600 mg/day for high end scenarios, during ages 2-6) considering this appear reasonable. For the soil dermal contact pathway, key uncertain parameters include the contact rate, (0.005 and 0.1 mg/cm^2-event for indoor and outdoor events for the high end farming scenario) and the absorption fraction (0.03 for dioxin-like compounds).

A major area of uncertainty for both pathways is the estimation of soil concentrations where the source of contamination is located distant from the site of exposure. For this assessment, this includes the off-site soil source category and the stack emission source category. Validation exercises described above seem to suggest that prediction of soil concentrations from airborne depositions or from soil erosion appear reasonable. Key uncertain parameters identified include the dissipation rate (0.0693 yr^{-1}), the mixing depth (2 cm), and the use of an enrichment ratio (equal to 3.0) which increases the concentration of dioxin-like compound on eroded soil relative to in-situ soil.

3. Ingestion of Water: A comparison of alternate modeling approaches for estimating water concentrations showed similar results to the models adopted for this assessment. There also does not appear to be a wide range of possible values for water ingestion rate (1.4 L/day for central scenarios and 2.0 L/day for high end scenarios) and contact fraction (0.75 for central scenarios and 0.90 for high end scenarios), and these are not expected to introduce significant uncertainty into water ingestion exposure estimates.

4. Inhalation: The inhalation rate assumed for both central and high end scenarios was 20 m^3/day. The distinction in the scenarios was in the contact fractions: central scenarios assumed a contact fraction of 0.75 and high end scenarios had a 0.90 contact fraction. These

fractions correspond to time at the home environment. These fractions and the inhalation rate are not expected to add significant uncertainty in inhalation exposure estimates.

Sensitivity analysis showed air concentrations resulting from soil emissions to be sensitive to Koc and H, and also to key source strength and delivery terms such as areas of contamination and wind speed. Assuming these non-chemical specific parameters can be known with reasonable certainty for site-specific applications, the most uncertainty lies with chemical specific data.

Alternate approaches for volatilization and air dispersion tested included the volatilization approach developed by Jury, et al. (1983, 1984a,b) and the box model for dispersion calculations. The Jury model predicted about 1/3 as much volatilization flux (given the selection of parameters, made equal to or most analogous to the models of this assessment) as the Hwang, et al. (1986) model of this assessment. The box model predicted about 6 times higher air concentrations than the near-field dispersion approach of this assessment. This reasonable comparison lends some credibility to the models selected.

Approaches to estimate particulate phase concentrations are empirical and based on field data. They are based on highly erodible soils but are specific to inhalable size particles, those less than 10 μm. As such, they may overestimate inhalation exposures, but may underestimate the total reservoir of particulates, which becomes critical for the particle deposition to vegetation algorithms. Another area of uncertainty is the assumption that volatilized contaminants do not become sorbed to airborne particles - this is also critical because vapor phase transfers dominate plant concentration estimation. A final key area of uncertainty is that transported contaminants from a contaminated to an exposure site via erosion are assumed not to volatilize or resuspend at the exposure site or from soils between the contaminated and the exposure site - air borne exposure site concentrations may be underestimated as a result.

5. Fruit and Vegetable Ingestion: All ingestion parameters assumed are evaluated as reasonable for general exposure to broad categories of fruits and vegetables. However, great variability is expected if using these procedures on a specific site where home gardening practices can be more precisely ascertained. Concepts of below and above ground vegetations were developed to accommodate soil to root algorithms and soil to air to vegetation algorithms.

Protected vegetation - those with outer inedible protections such as citrus or corn - were assumed not to be impacted by dioxin-like compounds.

A key assumption in the vegetation algorithm, that dioxin-like compounds do not translocate from root to shoot, was verified by two experiments. Vapor-phase contributions to vegetation dominated the contaminated soil and stack emission source categories, with one exception. Particle depositions were more important for above ground fruit/vegetable concentrations for the stack emission source.

Critical empirical parameters were the above and below ground correction factors, VG_{ag} and VG_{bg}, which were set at 0.01 and 0.25, respectively, for fruits and vegetables. The VG_{ag} was justified based on the fact that the above-ground transfer algorithm was based on experiments for the azalea leaf, and this leafy vegetation would differ for fruits such as apples where translocation into the fruit would be minimal; the VG_{ag} for grass was 1.00 for this same reason. Support for this VG_{ag} for bulky above ground vegetation came from independent experiments by McCrady (1994). The VG_{bg} was given a value of 0.25 based on the testing of the root transfer algorithm on experiments on carrots and potatoes.

Important experimentally derived empirical factors describing the transfer of dioxin-like compounds from one media to plants include the RCF, the soil to below ground vegetables transfer factor, and B_{vpa}, the vapor-phase to above ground plant transfer factor. Validation exercises described above on both of these factors lent a degree a credibility to the independent use of these transfer factors.

6. Ingestion of Fish: The key exposure parameter for this pathway was the fish ingestion rate. The rates assumed in the demonstration scenarios were low in comparison to estimates given for subsistence fisherman or others who live near large water bodies where fish are commercially caught. The justification for the lower ingestion rate for demonstration purposes was that the setting demonstrated was described as rural, containing farms and non-farm residences, where the emphasis is on agriculture. A relatively small watershed with a small impacted water body was assumed. Daily ingestion rates of 8 (central) and 25 (high end) g/day were assumed, based on data from recreational fisherman surveys summarized in EPA (1997b) and on subsequent recommendations for these values in EPA (1997b).

Other models for estimating fish concentration based on water column concentrations, rather than suspended sediment concentrations, were described in EPA (1993) and demonstrated in this assessment. Results indicated that the water column approaches would predict similar whole fish concentrations compared with the sediment concentration approaches of this assessment. A key uncertain parameter for estimating fish tissue concentrations is the Biota Sediment Accumulation Factor, or BSAF, and the Biota Suspended Sediment Accumulation Factor, or BSSAF. A range of 0.03 to 0.30 for 2,3,7,8-TCDD is hypothesized for column feeding fish, while the Connecticut data (CDEP, 1992) and some other data on bottom feeding fish indicate higher BSAFs ranging up to 0.86 for 2,3,7,8-TCDD. A value of 0.09 for 2,3,7,8-TCDD for BSAF and BSSAF is used in this assessments. A "Bioequivalency Factor", or BEF, approach is used to assign values to other dioxin-like congeners. In this approach, a relative rating scheme provides factors to multiply the 2,3,7,8-TCDD bioconcentration parameter to get this same factor for the other dioxin congeners. Another key parameter is the fish lipid content, which can vary from below 0.05 to above 0.20. The model estimates a fish lipid concentration. Multiplying fish lipid concentration by fish lipid content arrives at a whole fish concentration or an edible fish concentration, depending on the user's assignment and characterization of the fish lipid content variable. For this assignment, the fish lipid content was assigned a value of 0.07 for the demonstration scenarios, based on lipid content of fish in EPA's Lake Ontario study (EPA, 1990a).

7. Beef and Milk Ingestion: The rates of beef and milk fat ingestion are 2.45 and 14.0 g/day, respectively. Beef fat and milk fat contents are assumed to be 22% and 3.5%, respectively. An additional factor of 0.55 accounts for cooking and post cooking loss of beef. The assumptions for contact fractions for beef and milk (fractions of their total consumption that comes from home supplies) was 0.48 and 0.21, respectively. Since exposure estimates from these pathways are linearly related to ingestion rate and contact fraction, these are critical exposure parameters for site specific applications.

Comparison with earlier modeling approaches showed that the current approach to estimating beef and milk concentrations is the same as earlier approaches, although mathematically formulated differently. Early efforts in the literature did not consider vapor transfers to vegetation; one later assessment did include vapor transfers, and a key result in that

assessment, as well as this one, is that vapor transfers are critical for beef impacts. Finally, earlier assessments considered the practice of fattening beef cattle prior to slaughter by feeding them residue-free grains. These efforts estimated over a 50% reduction in beef concentration due to residue degradation or elimination and/or dilution with increases in body fat. The demonstration scenarios in this assessment did not consider this practice. However, this practice was considered in the air-to-beef food chain validation exercise. There, a 50% reduction in beef concentrations due to feedlot fattening was assumed.

Key uncertain and variable parameters for beef/milk concentrations include: 1) the beef and milk fat bioconcentration factor, BCF, 2) the beef cattle and dairy cow exposure assumptions (fractions of their feed in which feed categories), 3) the assumptions concerning vapor/particle partitioning for the stack emission source category, and 4) the air-to-leaf transfer parameter, B_{vpa}, for vapor phase contaminants.

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Table 1-1. The TEF scheme for I-TEQ_{DF}

Dioxin (D) Congener	TEF	Furan (F) Congener	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		OCDF	0.001

Table 1-2. The TEF scheme for dioxin-like coplanar PCBs, as determined by the World Health Organization in 1994

Chemical Structure	IUPAC Number	TEF
3,3',4,4'-TeCB	PCB-77	0.0005
2,3,3',4,4'-PeCB	PCB-105	0.0001
2,3,4,4',5-PeCB	PCB-114	0.0005
2,3',4,4',5-PeCB	PCB-118	0.0001
2',3,4,4',5-PeCB	PCB-123	0.0001
3,3',4,4',5-PeCB	PCB-126	0.1
2,3,3',4,4',5-HxCB	PCB-156	0.0005
2,3,3',4,4',5'-HxCB	PCB-157	0.0005
2,3',4,4',5,5'-HxCB	PCB-167	0.00001
3,3',4,4',5,5'-HxCB	PCB-169	0.01
2,2',3,3',4,4',5-HpCB	PCB-170	0.0001
2,2',3,4,4',5,5'-HpCB	PCB-180	0.00001
2,3,3',4,4',5,5'-HpCB	PCB-189	0.0001

Table 1-3. The TEF scheme for TEQ_{DFP}-WHO_{98}

Dioxin Congeners	TEF	Furan Congeners	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	1.0	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
OCDD	0.0001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		OCDF	0.0001

Chemical Structure	IUPAC Number	TEF
3,3',4,4'-TeCB	PCB-77	0.0001
3,4,4',5-TCB	PCB-81	0.0001
2,3,3',4,4'-PeCB	PCB-105	0.0001
2,3,4,4',5-PeCB	PCB-114	0.0005
2,3',4,4',5-PeCB	PCB-118	0.0001
2',3,4,4',5-PeCB	PCB-123	0.0001
3,3',4,4',5-PeCB	PCB-126	0.1
2,3,3',4,4',5-HxCB	PCB-156	0.0005
2,3,3',4,4',5'-HxCB	PCB-157	0.0005
2,3',4,4',5,5'-HxCB	PCB-167	0.00001
3,3',4,4',5,5'-HxCB	PCB-169	0.01
2,3,3',4,4',5,5'-HpCB	PCB-189	0.0001

Table 1-4. Particle fractions, ϕ, in four airsheds at 20°C for the dioxin-like congeners.

Congener	Clean Continental	Average Background	Background Plus Local Sources	Urban
2378-TCDD	0.10	0.29	0.49	0.75
12378-PCDD	0.44	0.74	0.87	0.95
123478-HxCDD	0.78	0.93	0.97	0.99
123678-HxCDD	0.78	0.93	0.97	0.99
123789-HxCDD	0.78	0.93	0.97	0.99
1234678-HpCDD	0.93	0.98	0.99	0.997
OCDD	0.98	0.995	0.998	0.999
2378-TCDF	0.09	0.27	0.47	0.73
12378-PCDF	0.27	0.57	0.75	0.91
23478-PCDF	0.38	0.69	0.84	0.94
123478-HxCDF	0.63	0.86	0.93	0.98
123678-HxCDF	0.63	0.86	0.93	0.98
123789-HxCDF	0.74	0.91	0.96	0.99
234678-HxCDF	0.74	0.91	0.96	0.99
1234678-HpCDF	0.86	0.96	0.98	0.99
1234789-HpCDF	0.92	0.98	0.99	0.997
OCDF	0.98	0.995	0.998	0.999

Table 1-5. WHO_{98}-TEQ_{DF} environmental and exposure media concentrations for the background conditions scenarios, #1 and #2, and the stack emissions demonstration scenarios, #4 and #5.

Description	Background, Scenarios 1 and 2	Emission, Central Scenario 4	Emission, High End Scenario 5
Air, vapor phase, pg/m^3	$2.59*10^{-3}$	$2.45*10^{-5}$	$6.94*10^{-5}$
Air, particle phase, pg/m^3	$1.87*10^{-2}$	$6.04*10^{-5}$	$1.74*10^{-4}$
Soil, untilled, pg/g	1.29	$4.46*10^{-3}$	$3.51*10^{-2}$
Soil, tilled, pg/g	0.65	$4.46*10^{-4}$	$3.51*10^{-3}$
Soil, watershed, pg/g	1.29	$8.91*10^{-4}$	$8.91*10^{-4}$
Surface water, pg/L	$2.63*10^{-3}$	$3.80*10^{-5}$	$3.80*10^{-5}$
Sediment, pg/g	3.37	$2.39*10^{-3}$	$2.39*10^{-3}$
fish lipid, pg/g*	6.33	$5.64*10^{-3}$	$5.64*10^{-3}$
leafy vegetation, pg/g dry	0.45	$1.86*10^{-3}$	$6.39*10^{-3}$
above ground fruit/veg, pg/g fresh	$5.74*10^{-3}$	$1.20*10^{-5}$	$6.37*10^{-5}$
below ground vegetables, pg/g fresh	$1.94*10^{-2}$	$1.63*10^{-5}$	$1.29*10^{-4}$
beef fat, pg/g	1.58	$4.35*10^{-3}$	$1.65*10^{-2}$
milk fat, pg/g	1.10	$3.05*10^{-3}$	$1.11*10^{-3}$
chicken fat, pg/g	0.61	$2.02*10^{-3}$	$1.38*10^{-2}$
egg fat, pg/g	0.71	$2.25*10^{-3}$	$1.55*10^{-2}$

Table 1-6. Lifetime average daily doses, LADD, and cancer risk estimates, of WHO_{98}-TEQ_{DF} for the high end background scenario, #2, and for the high end stack emission scenarios, #5.

Scenario/Pathway	LADD, ng/kg-day	Percent of total scenario exposure	Cancer Risk
Scenario 2 - Background High			
Soil Ingestion	$3.25*10^{-6}$	3	$1.22*10^{-6}$
Soil Dermal Contact	$1.40*10^{-6}$	2	$5.27*10^{-8}$
Inhalation	$2.34*10^{-6}$	3	$2.34*10^{-6}$
Water Ingestion	$2.90*10^{-8}$	<1	$2.90*10^{-7}$
Beef Ingestion	$8.30*10^{-5}$	89	$8.30*10^{-5}$
Vegetable Ingestion	$2.32*10^{-6}$	2	$2.36*10^{-6}$
Fruit Ingestion	$3.65*10^{-7}$	<1	$3.65*10^{-7}$
Total	$9.30*10^{-5}$	100	$8.96*10^{-5}$
Scenario 5 - Stack Emission High			
Soil Ingestion	$8.86*10^{-8}$	9	$3.32*10^{-8}$
Soil dermal contact	$8.51*10^{-9}$	1	$3.19*10^{-10}$
Inhalation	$2.68*10^{-8}$	2	$2.68*10^{-8}$
Water ingestion	$4.19*10^{-10}$	<1	$4.19*10^{-10}$
Beef ingestion	$8.65*10^{-7}$	86	$8.65*10^{-7}$
Vegetable ingestion	$1.83*10^{-8}$	2	$1.83*10^{-8}$
Fruit ingestion	$4.05*10^{-9}$	<1	$4.05*10^{-9}$
Total	$1.01*10^{-6}$	100	$9.48*10^{-7}$

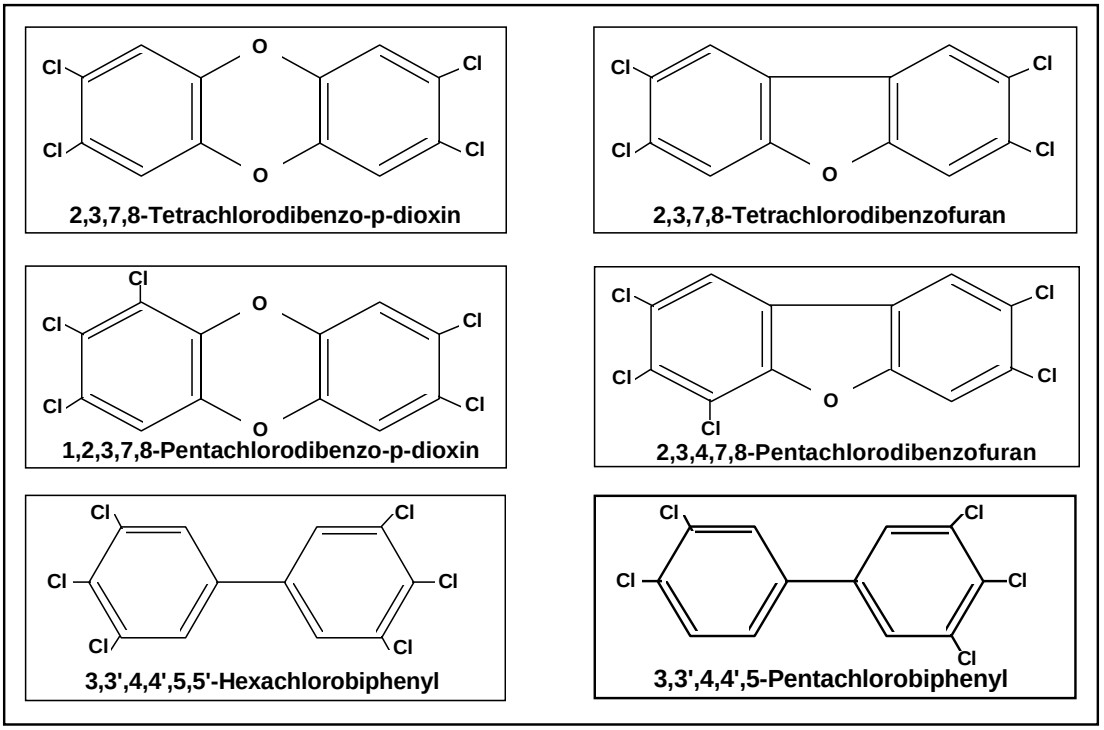

Figure 1-1. Chemical structure of 2,3,7,8-TCDD and related compounds

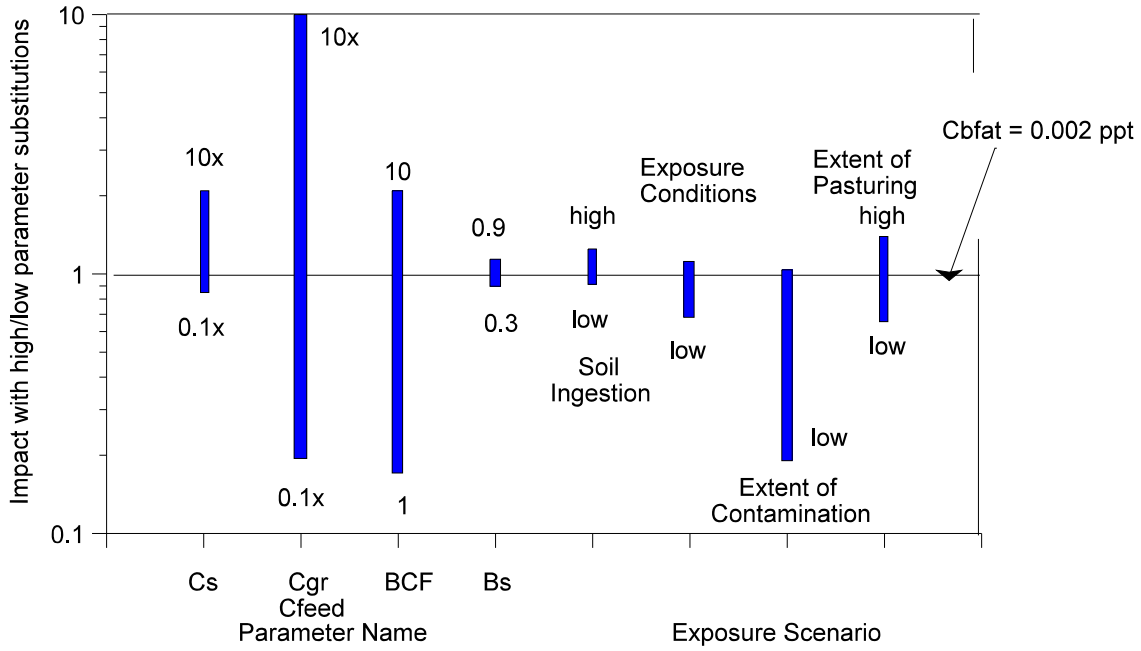

Figure 1-2. Results of sensitivity analysis of algorithms estimating beef fat concentrations in the stack emission source category.

Parameter Name	Definition	Selected
Cs	2,3,7,8-TCDD soil concentration, pg/g	0.001
Cgr	2,3,7,8-TCDD grass concentration, pg/g dry wt.	0.0004
Cfeed	2,3,7,8-TCDD feed concentration, pg/g dry wt.	0.0002
Cbfat	2,3,7,8-TCDD beef fat concentration, pg/g	0.002
BCF	beef/milk bioconcentration factor, unitless	5.76
Bs	bioavailability of contaminant on soil relative to vegetation	0.65
<u>Exposure Scenario Parameters:</u>		
BCSDF	beef cattle soil diet fraction	0.04
BCFDF	beef cattle feed diet fraction	0.48
BCGDF	beef cattle grass diet fraction	0.48
BCGRA	beef cattle fraction of contaminated grazing land	1.00
BCFOD	beef cattle fraction of contaminated feed	1.00

2. ESTIMATING EXPOSURES AND RISKS

2.1. INTRODUCTION

In this chapter, the framework for assessing exposure and risk to 2,3,7,8-TCDD and related dioxin-like compounds will be described. Section 2.2 introduces the exposure equation and its key terms. Section 2.3 describes how cancer risk and non-cancer risk estimates are generated, given exposure estimates. Section 2.4 summarizes procedures for calculating exposure and risk for dioxin toxic equivalents. Section 2.5 provides the overview of the procedures used in this document. Section 2.6 describes the development of exposure scenarios for this assessment. Finally, Section 2.7 discusses the exposure pathways and exposure parameters chosen for this assessment.

The development of exposure assessment methods, scenarios and associated parameter values raises many issues which are generic to all chemicals. In order to keep the scope of this document reasonable, the decision was made to focus on issues specific to dioxin-like compounds and to avoid evaluating generic issues. Thus, priority is given to addressing issues such as fish bioconcentration, dermal absorption, degradation, and other chemical/physical properties of these compounds. The approach used to address generic issues such as soil ingestion rates, inhalation rates and other behavior parameters is based on published Agency documents, primarily the Exposure Factors Handbook, published first in 1989 (EPA, 1989). The current version of the Exposure Factors Handbook was published in 1997 (EPA, 1997a). Exposure factors used in this chapter are based on this version.

Another generic issue which has been raised in connection with this document is the use of Monte Carlo procedures to define exposure scenarios. These procedures require distributions for the input parameters used in the assessment. Such distributions are now being addressed in the Exposure Factors Handbook. However, this document has not demonstrated Monte Carlo and related procedures on the scenarios developed in this chapter. Individuals outside of the Agency have published assessments which applied Monte Carlo procedures to problems involving dioxin-like compounds. In recognition of the high interest in this area, a general description of this technique and summaries of assessments which applied it to dioxin-like compounds are included in Chapter 8 of this Volume.

2.2. EXPOSURE EQUATION

This document describes procedures for conducting exposure assessments to estimate either potential or internal dose. A potential dose is defined as a daily amount of contaminant

inhaled, ingested, or otherwise coming in contact with outer surfaces of the body, averaged over an individual's body weight. An internal dose is defined as the amount of the potential dose which is absorbed into the body. Section 2.3 below discusses the relevancy of this distinction for dioxin-like compounds.

The general equation used to estimate potential dose normalized over body weight and lifetime is as follows:

$$\text{Lifetime Average Daily Dose (LADD)} = \frac{(\text{exposure media concentration} \times \text{contact rate} \times \text{contact fraction} \times \text{exposure duration})}{(\text{body weight} \times \text{lifetime})} \quad (2\text{-}1)$$

The LADD is used to assess cancer risks. Non-cancer risks from exposure to dioxin-like compounds can be assessed using the Average Daily Dose, or ADD. This is calculated as in Equation (2-1), but without the exposure duration in the numerator and the lifetime in the denominator. Each of the terms in this exposure equation is discussed briefly below:

- **Exposure media concentrations:** These include the concentrations in soil for the dermal contact and soil ingestion exposure pathways, in the vapor and particulate phases in air for the inhalation exposure pathway, in water for the water ingestion pathway, and in food products such as fish, fruits and vegetables, and beef and milk, for the food ingestion pathways. The concentrations used should represent an average over the exposure period. Chapter 4 provides models for estimating exposure media concentrations.
- **Contact rate:** These include the ingestion rates, inhalation rates, and soil contact rates for the exposure pathways. These quantities are generally the total amount of food ingested, air inhaled, etc. Only a portion of this material may be contaminated. The next term, the contact fraction, which is 1.0 or less, reduces the total contact rate to the rate specific to the contaminated media.
- **Contact fraction:** As noted, this term describes the distribution of total contact between contaminated and uncontaminated media. For example, a contact fraction of 0.8 for inhalation means that 80% of the air inhaled over the exposure period contains dioxin-like compounds in vapor form or sorbed to air-borne particulates. The contact fractions for the exposure pathways of air inhalation and water ingestion are related to the time individuals spend at home. Other pathways such as fish ingestion or ingestion of home grown foods are not related to time at home. Similarly, contact fractions for individuals exposed at work places relate

largely to time spent at the work place. EPA (1997a) discusses several time use studies which can be used to make assumptions about time spent at home (and outdoors at the home environment) versus time spent away from home. Generally, these time use studies asked participants to keep 24 hour diaries of all activities. Studies summarized were national in scope, involved large numbers of individuals, cross-sections of populations in terms of age and other factors, and up to 87 categories of activities. Results from different studies reviewed in EPA (1997a) consistently indicate that the average adult spends between 68 to 73% of time at the home environment.

- **Exposure duration:** This is the overall time period of exposure. Values of 9 years and 30 years are used in the example scenarios described in Chapter 5. EPA (1997a) describes several population mobility studies. A recent study by the U.S. Bureau of the Census (1993) covered a national sample of 55,000 interviews. The 50th and 90th percentile values of values for years living in current residence were determined to be 9.1 and 32.7 years, which are rounded here simply to 9 and 30 years. The 9 years will be used in a residential scenario and the 30 years for the farming scenario. The fact that farmers tend to live longer in their residents than average individuals was supported by a second study (Isreali and Nelson,1992) described in EPA (1997a) which categorized respondents in a number of different ways. The average time living in current residence for individuals in farms was 17.3 years, while it was 7.8 years for individuals in rural settings and 4.6 years for all households (Isreali and Nelson,1992). Another exposure duration demonstrated in Chapter 5 is one associated with a childhood pattern of soil ingestion. The exposure duration in this case is 5 years.
- **Body weight:** The human adult body weight of 70 kg is assumed. While the average adult (males and females) body weight is closer to 60 kg (EPA, 1997a), 70 kg has been traditionally used by the Agency and will be used in this assessment where appropriate. This document has chosen to use consumption rate data that are in terms of g food consumed/kg body weight/day, rather than g food consumed/day. Therefore, body weight drops out as an exposure factor for these pathways; it is still required in this assessment for the inhalation, soil ingestion, soil dermal contact, and the water ingestion pathways. The fish consumption pathway still uses the g/day convention since most fish consumption survey data, and the data used in this assessment, are in that form. As such, this pathway also

uses the 70 kg body weight assumption. The average of male and female average body weights at ages 1 through 6 was 16.6 (EPA, 1997a). This was used to assume an average body weight of 17 kg for the childhood pattern of soil ingestion. The 70 kg adult body weight will be used in some, but not all of the pathways.

- **Lifetime:** Following traditional assumptions, the average adult lifetime assumed throughout this document is 70 years. Even though actuarial data indicate that the United States average lifetime now exceeds 70 years, this convention is used to be consistent with other Agency assessments of exposure and risk.

2.3. CANCER AND NON-CANCER RISK ASSESSMENT

The primary source of information on the health risks of the dioxin-related compounds is the Health Document of this Reassessment, Part II of the Reassessment Documents (Part I are the Exposure Documents and Part III is the Risk Characterization). While that remains the principal source of information on potential health effects resulting from dioxin exposures, some general procedures for using exposure estimates in support of cancer and non-cancer risk assessments are summarized here.

The Risk Characterization emphasizes that risk assessments for dioxin-like compounds must consider background exposures when evaluating the impact of increments that are due to specific sources:

> *When evaluating incremental exposures associated with specific sources, knowing the increment relative to background may help to understand the impact of the incremental exposure. For instance, it would be misleading to focus on incremental exposure in evaluating the potential impact on human health when a relatively large background body burden of dioxin already exists in the exposed population. In these circumstances, the incremental exposure needs to be evaluated in the context of these background levels. This has led us to suggest that perhaps the best information for a decision-maker to have is: (1) a characterization of effects noted in the low dose range; (2) a characterization of the range and average of "background" exposures, including a discussion of MOE; (3) a characterization of the incremental percent increase over background of individuals or subpopulations of interest; and (4) guidance on when contributions from incremental exposures adding to average "background" become significant for the decision.*

The Risk Characterization as well as the Health Document provide detailed discussions of the effects of dioxin exposure in the low dose, or background, range, and those discussions are not repeated here. These documents also discuss in great deal the Margin Of Exposure, MOE, concept and the MOE associated with current background exposures. The MOE is calculated by dividing a "point of departure" dose or exposure at the low end of the range of observation in human or animal studies by the comparable surrogate of human exposure at a "level of interest". These points of departure could include the human-equivalent lowest observed adverse effect level (LOAEL), the no observed adverse effect level (NOAEL), the benchmark dose (BMD), or the effective dose (ED) at some percentage; ED_{01} is the effective dose for 1% of the population. Points of departure could also be body burden levels associated with health effects. The comparable "level of interest" for dioxin-like compounds are defined here as terms relating to background exposures, or perhaps, background exposures plus incremental exposures due to a specific source being evaluated. The Risk Characterization provides this general guidance regarding interpretation of MOEs:

> *Generally speaking, when considering either background exposures or incremental exposures plus background, MOEs of 100 or more are considered adequate to rule out the likelihood of significant effects occurring in humans based on sensitive animal responses or results from epidemiologic studies and traditional factors used in safety assessment. Conversely, as MOEs approach the range of observation of effects, reaching any conclusion regarding the certainty of no harm is much more difficult.*

The Risk Characterization concludes that the MOE for background exposures are well below 100 and even below 10:

> *One of the difficulties in assessing the potential health risk of exposure to dioxins is that background exposures are often a significant component of total exposure when based on TEQ. The average levels of background intake and associated body burdens of dioxin-like compounds in terms of TEQs in the general population (1 pg TEQ/kgBW/day and 5 ng TEQ/KgBW, respectively) are well within a factor of 10 of human-equivalent levels associated with NOELS, LOAELs, BMDs, or ED_{01} values derived from studies in laboratory animals exposed to TCDD or TCDD equivalents. Therefore, in many cases, the MOE compared to background using these endpoints is a factor of 10 or less....*

The Risk Characterization provides tabular summaries of these health endpoints that show that the MOEs for certain endpoints are even below 5. With MOEs below 10 for background exposures alone, a calculation of an MOE based on background plus incremental exposure may not be of benefit in a site-specific risk assessment. For example, if an MOE for a particular toxicological endpoint of interest is calculated to be 5 for background exposures (5/1), and it were determined that a source resulted in an incremental exposure that is 10% of background, than a resulting MOE considering background plus incremental exposure would be about 4.5 (5/1.1). While this kind information does not appear to be of benefit to decisionmakers, it may be useful to know that a particular source adds 10% more exposure than an individual would get by background exposures alone. This is identified in the third recommendation provided in the first quote above from the Risk Characterization: *"...(3) a characterization of the incremental percent increase over background of individuals or subpopulations of interest"*.

The first section below discusses the quantification of "background exposures" to dioxin-like compounds, from both a dose and body burden standpoint. The second section introduces the "increment above background", or IOB, ratio, which is a ratio that describes the percent increase over background a specific source contributes. The IOB concept is suggested as a way of evaluating non-cancer risk. The final section will discuss the traditional approach to estimating cancer risk, based on an incremental exposure and a slope factor. These approaches will be demonstrated in Chapter 5.

2.3.1. Background Exposure Doses and Body Burdens

The second volume of the Exposure Document, Volume II: Properties, Environmental Levels, and Background Exposures, describes United States background exposures to dioxin-like compounds, both from the perspective of exposure doses and body burden. Combining average adult contact rates (inhalation rate, food consumption rates, etc.) with average concentrations of these compounds in the contact media (air, food, etc.), the current adult background dose to dioxin-like compounds is quantified as 1.0 pg WHO_{98}-TEQ_{DFP}/kg-day. This Volume further provides similar background estimates for children of various ages, and these estimates are: 1-5 yrs: 3.3 pg WHO_{98}-TEQ_{DFP}/kg-day, 6-11 yrs: 1.9 pg WHO_{98}-TEQ_{DFP}/kg-day, and 12-19 yrs: 1.1 pg WHO_{98}-TEQ_{DFP}/kg-day. In addition, background exposures of infants to dioxins in breast milk is also addressed in the Volume II of the Exposure Document.

The average adult body burden of dioxin-like compounds, expressed on a lipid basis, was estimated as 25 pg WHO_{98}-TEQ_{DFP}/g (ppt). This was based on measurements of dioxins in blood of specifically selected "background" populations in six site-specific studies conducted by, or

with the assistance of, the Agency for Toxic Substances and Disease Registry between 1995 and 1997, with the blood analyzed by the Centers for Disease Control (CDC, 2000). A total of 316 adults ranging in age from 20 to 70 years were measured in these studies. The individuals sampled were all U.S. residents with no known exposures to dioxin other than normal background. While the samples in this data set were not collected in a manner that can be considered statistically representative of the national population and lack wide geographic coverage, they are judged to provide the best available indication of current tissue levels in an average adult population in the United States. The Risk Characterization has estimated a national background body burden of 5 pg WHO_{98}-TEQ_{DFP}/g, on a whole weight basis.

An important issue associated with the use of this national body burden estimate is that it represents the average for the wide range of adult ages from 20 through 70. As discussed in Volume II, there is an age trend associated current body burden data - older individuals have higher body burdens. An in-depth analysis of this trend in Lorber (2002) concludes that this trend is due to two factors: 1) that exposures were higher in past, such that older individuals have been exposed to much more dioxin during their lives compared to younger individuals, and 2) that dioxins are long-lived in the human body, such that an individual's body burden will rise as they age if they receive a steady input dose during their life. Lorber (2002) concluded that higher past exposures was much more responsible for this trend than build-up over time in an individual's body. They explored this trend using simple pharmacokinetic modeling. Figure 2-1 shows one result of their analysis. These are modeled populations distributions of body burdens of dioxin and furan TEQ lipid-based concentrations (Lorber's examination didn't include dioxin-like PCBs) corresponding to the hypothetical sampling years 1965, 1985, 1995, and 2030.

There are a few important observations to make regarding the information in this figure. It shows that the average population body burdens are declining, and that by 2030, the average body burdens of WHO_{98}-TEQ_{DF} will be 9 pg/g lipid, or about 2.3 pg/g whole weight basis (assuming 25% body lipids). This trend for 2030 is essentially identical to the trend of how an individual's body burden would very slowly rise through adulthood if they are exposed to a constant dose. This result was derived by assuming that today's dose of dioxin and furan TEQs stayed constant throughout the early decades of the 21st century. It also simplistically modeled dioxin TEQs as though they were a single compound with a single half-life. If one were to redo this to include dioxin-like PCBs, again modeling TEQs as though they were a single compound, it would show that the average adult body burden at the steady intake of 1.0 pg WHO_{98}-TEQ_{DFP}/kg-day would be about 13 pg WHO_{98}-TEQ_{DFP}/g-lipid, or about 3.3 pg WHO_{98}-TEQ_{DFP}/g whole weight. This figures also shows that today's background body burdens (as estimated by

the population distribution for 1995) of younger individuals is lower than the population average: the population average is 28 ppt lipid while the concentrations for the under 30 age group is below 20 ppt lipid. This means that if one were to conduct an analysis of the incremental impact to specific individuals who might comprise the younger portion of an adult population, such as women of child-bearing age, it might be more appropriate to assume a lower average background body burden than the 25 pg WHO_{98}-TEQ_{DFP}/g lipid that characterizes the full range of today's population.

In site-specific assessments, the assessor has the option of using information on current national average daily intakes or body burdens as the "background" against which to compare incremental exposures. In this case, the assessor needs to make it clear that he is comparing incremental exposures and/or body burdens to national background estimates. In certain circumstances, it may be preferable to have an understanding of the "local", or "regional", background rather than the national background. A local background dose or body burden for a site-specific assessment, where a specific source of dioxin release is being evaluated, can be thought of as the overall dose or body burden that an individual potentially impacted by that source of release would experience, or would have, if the source in question were not in existence. Local background exposures for one setting may be higher than in another because, for example, one setting may have more sources of industrial dioxin release (other than the one being evaluated) within it. Another site-specific consideration would be the behaviors of exposed individuals. There may be a water body for fishing in one site, while agriculture may dominate another site. If there is reason to consider a subsistence behavior for a particular setting that could lead to elevated exposures, it may be appropriate to derive a local background exposure to dioxin based on that subsistence behavior, rather than on general behaviors.

While it may be important for risk assessors or risk managers to consider local backgrounds rather than national backgrounds, it should be emphasized that this document will not provide guidance, such as a hierarchy of recommendations, on how to assign background quantities for any quantitative evaluation of the incremental exposures using the increment above background, or IOB, approach described below. Obviously, this choice can be important. If a particular area is likely to have a higher background as compared to a national background, this would influence the numerical value of a ratio such as an IOB ratio. For example, if local background is twice as high as a national background, than an incremental exposure that is equal to 10% of national background would be equal to 5% of a local background. Similarly, if an area is thought to be have lower exposures as compared to background exposures, say half as much for example, than an incremental exposure equal to 10% of national background would be equal

to 20% of a local background. Risk managers could evaluate incremental exposures differently if they are told that the incremental is 5% of background as compared to 20% of background. Perhaps the best general advice that can be offered in this procedures document is to recommend that a risk assessor supply the risk manager with this type of information: 1) the incremental exposure from a specific source, 2) how that compares to the national background exposure, and 3) information on how local exposures may relate to national exposures, if this information is available.

A local background body burden can be ascertained through monitoring. A comprehensive discussion of monitoring approaches of human matrices (blood, adipose tissue, mother's milk) is beyond the scope of this document. However, some key generalizations can be noted here that are relevant to site-specific assessments for dioxin-like compounds:

1) Whether the source is in operation or not: Some site-specific assessments are conducted to evaluate the potential impact of an industrial facility not yet operating. In that case, sampling of the representative population that could be impacted by emissions from the facility would be appropriate. If the facility has been operating, it becomes necessary to sample a population that is not impacted by the facility, but one that is comparable with regard to demographics. Dioxin body burdens are a function of many factors including age, nursing practices, dietary preferences and possibly occupational history. Ideally, the population of concern around a site should be characterized in terms of these factors. If the source is ongoing, and it becomes necessary to locate and sample a different population to characterize background, then a comparison population with similar characteristics should be chosen.

2) How to interpret differences in the study and a comparison population: Since dioxin body burdens reflect contributions from all sources, the portion due to releases from the site of concern cannot be definitively established. Sometimes measurements from a comparison population can be difficult to interpret; the better the demographic match between the study and comparison populations, the more likely it is that any differences between the groups can be attributed to the site or source of concern.

3) Body matrix to sample: As noted above, the background body burden of 25 ppt WHO_{98}-TEQ_{DFP} lipid-basis was determined from sampling of blood in background populations from several site-specific evaluations. Blood is the recommended matrix for sampling in that the entire population can be sampled in a relatively easy, non-invasive manner. In can be costly, however, and obtaining volunteers for a background blood sampling program can be an issue. Mother's milk can be considered and it does have certain advantages over blood: 1) it may be easier to obtain volunteers for a mother's milk sampling program in contrast to a blood sampling

program, 2) mother's milk has a higher lipid content (3-4 %) than blood (<1%), and therefore less milk would be required for analysis than blood, with a greater possibility of being able to quantify concentrations of the lipophilic dioxin-like compounds, and 3) useful information would be gained on potential infant impacts in addition to population exposures. However, mother's milk concentrations should be interpreted carefully, given these considerations: 1) needless to say, these programs monitor only half the population, and 2) proper interpretation of data for the female population can also be an issue. Evidence has shown that breast-feeding provides an avenue of depuration of dioxin-like compounds in the lactating female: breast milk concentrations decline while the mother is breast-feeding and female body burdens are lower for the second and subsequent children as compared to first children. As a matrix for screening studies, mother's milk can be more expedient than blood monitoring. Certainly, important implications exist when unusually high concentrations of dioxin-like compounds are found in breast milk, and general differences between populations can easily be identified in a breast milk monitoring program.

Other issues exist when deriving a background dose rather than a background body burden. A background dose estimate requires two quantities: contact rates and exposure media concentrations. Two options for contact rate assignment could be contact rates derived for a specific site (i.e., subsistence fishing consumption rates), or national average contact rates. National average contact rates were used to develop the 1 pg WHO_{98}-TEQ_{DFP}/kg-day. Four options are available for estimating exposure media concentrations:

1) National average exposure media concentrations: Combining site-specific contact rates with national average exposure media concentrations could provide the assessor with useful information at minimal cost, and would be quite acceptable in most cases where the assessor has no reason to believe that local concentrations are substantially different than national average concentrations. In other circumstances, it might be most appropriate to conclude that local concentrations are different than national average concentrations, necessitating a different approach for estimating concentrations.

2) Measurement of Local Exposure Media Concentrations: Measurement of concentrations of dioxin-like compounds in all relevant exposure media associated with a site would be the most accurate way to characterize a site-specific exposure media, but it would prove costly and, in fact, it may not be useful if the source in question has been in existence for several years. For example, a measurement of dioxins in air and soil in the vicinity of an operating incinerator source would reflect the impacts of the incinerator. Measurements in environmental/exposure media in the vicinity of an incinerator, even if it was shut down, could

still be influenced by past emissions from the incinerator. This would be the case if measuring soil around a closed incinerator. It would not be the case, however, for measuring air concentrations in a vicinity around a closed incinerator. In this case, the measured air concentrations would be appropriate reflections of background air concentrations for that site (although small contributions to that measured air concentration could come from releases of dioxins from soils; evidence suggests that these contributions would be small). The measurement of exposure media concentrations is mostly feasible (but still costly) if the assessment is prospective in nature - i.e., that it evaluates a new source not yet emitting dioxins. Another possibility is to use existing measurements or take new measurements in a nearby area which is matched as closely as possible to the study area, but doesn't have a similar dioxin source present. EPA's National Dioxin Air Monitoring Network, NDAMN, has been collecting air concentrations in background areas of the United States on a quarterly basis (4 samples/yr) since 1998 (Cleverly, et al., 2001). These concentrations could be used as background air concentrations for a site-specific assessment. However, the purpose of this network is to measure background air concentrations in settings where no apparent sources are present, such as in national parks. For this reason, NDAMN measurements might be lower than would exist in urban or suburban settings where a source of release is being evaluated with the methodologies of this document. Lorber, et al. (1998) showed how concentrations of dioxins in soil in Columbus, OH, approached a local urban background about 12 kilometers away from an incinerator. Soil or air measurements on the order of 10 kilometers or more from an air source being evaluated, but still within a very similar urban or rural setting, might be reasonable surrogates for background concentrations for specific sites.

3. Modeling of Exposure Media Concentrations: There are at least two ways in which background exposure media concentrations could be estimated with the use of models alone. One is to model the impacts from all major sources in the area being evaluated except for the source in question and then adding impacts at points of interest. This assumes that the impacts from all modeled sources are independent. The model ISCST3 used in this site-specific methodology document does, in fact, have the capability of combining inputs from multiple sources. In a complex setting, this option may be more costly and difficult than can be justified given the uncertainty in the exercise and the output. Specifically, the assessor must consider issues such as, have all sources been identified?, how accurate are source emission estimates?, and so on. Another possibility, for some time in the future, is to use results from studies now underway to develop multiple source, large-scale air dispersion/deposition models specific to dioxin. As an example, EPA is developing an application of the RELMAP model, which is the

model originally developed for acid rain assessments by EPA's Office of Air Quality and Planning Standards, and was also used to predict national fate of mercury emissions in EPA (1997b). This model takes, as input, emissions into the air from specifically defined sources in the United States, and predicts, for any location (on a 40 km grid) in the United States, deposition rates and air concentrations for modeled contaminants. Air concentrations and depositions could then serve as the input for modeling impacts to the terrestrial and aquatic environment using the steady state models discussed in this assessment. The uncertainties involved in using RELMAP and similar models to predict impacts of dioxin sources are not well quantified at the present time. EPA initiated a study in 2001 to compare modeled to measured air concentrations, and to compare RELMAP outputs to outputs generated with other similar regional models. These comparisons will help to reduce the uncertainty and to refine/calibrate these models for future possible site-specific applications involving dioxin-like compounds. Exposure media concentrations modeled by RELMAP or other aggregate source models would represent the "background" concentrations. The source in question is modeled separately and any predicted concentration would be in addition to the "background" concentration predicted by the aggregate modeling.

4. A combination of modeling and limited monitoring: This may be a reasonable way to estimate background exposure media concentrations for a specific site, if useful site-specific monitoring is available. For example, if an incinerator were no longer operating, then air concentrations measured in the vicinity of the shut down incinerator could give an estimate of the background air concentrations for that site. These air concentrations could then be routed through the terrestrial and aquatic fate models to predict soil and food concentrations for background exposure estimation. Careful monitoring of soil and air concentrations in the vicinity of the source while it is still operating is another possibility. Specifically, if several air monitors in all directions from an incinerator source were sampled on several days, during which time wind rose data were also taken, then one could probably identify air concentrations most and least likely to be impacted by the source in question by a careful examination of the wind rose data. Soil concentration data several miles away from an incinerator source, or a soil contamination source, may be an appropriate measure of dioxin impacts to soils not including the source in question. An example of careful monitoring around an incinerator emitting large amounts of dioxin allowed Lorber, et al (1998) to distinguish background air and soil concentrations from impacted air and soil. Again, these intermediate exposure media concentrations could be used with the steady-state models described in this assessment to estimate the full range of terrestrial and aquatic impacts.

A demonstration of a site-specific background scenario is presented in Chapter 5. Specifically, this scenario uses site-specific exposure factors and option 4 above to derive exposure media concentrations. Actual air and soil measurements in a background setting are used for the inhalation and soil related pathways. These measured concentrations are routed through the terrestrial and aquatic food chain models to predict concentrations in food products. Background dose estimates are calculated using these site-specific exposure factors and these hybrid exposure media concentrations. As such, the "background doses" in this example scenario in Chapter 5 can be thought of as specific to the region in which the source in question exists.

2.3.2. The Increment Over Background Concept for Non-Cancer Risk Assessment

EPA's Office of Solid Waste (OSW) has evaluated the potential for non-cancer impacts from individual sources of dioxin release based on an "increment above background", or IOB, approach. They have recommended that assessments conducted for hazardous waste incinerators use, on a provisional and site-specific basis, an IOB calculated as the ratio of the incremental exposure dose divided by the background exposure dose for dioxins, and then multiplying by 100%, so that the IOB is expressed in terms of a percentage. Some of the experience using this approach in OSW has been compiled and reported upon in Canter, et al. (1998). OSW has termed this ratio the margin of incremental exposure, or MOIE. That terminology and acronym will not be used here as it is similar to the MOE, or margin of exposure, which is used here and has a specific meaning in Agency risk assessing.

The other important difference is that the IOB approach developed here will be used to characterize the incremental increase to body burden and not to dose. The Risk Characterization concludes that non-cancer health effects due to dioxin exposure are best correlated to body burden and not to dose. If a dose has been occurring for a long period of time such that the body burden approaches a steady state, than of course dose and body burden are related. A percent increase in dose over background dose will be similar to a percent increase in body burden over background body burden in this circumstance. If an incremental dose has been occurring for a short amount of time, than the body burden will not rise to the level it would reach at steady state from that incremental dose. Therefore, a percent increase over background in terms of dose could be significantly higher than a percent increase over background in terms of body burden for short duration exposures. For that reason, the IOB approach developed here will be focused on body burden.

The IOB equation for body burden is given as:

$$IOB_{bb} = \frac{IBB}{BB_{bk}} * 100\% \quad (2\text{-}2)$$

where:

IOB_{bb}	=	increment over background ratios for body burden (bb), %
IBB	=	increment of body burden increase due to the incremental exposure, pg/g whole weight
BB_{bk}	=	background body burden, pg/g whole weight basis

To use this equation, a background body burden needs to be assigned, and an approach needs to be developed to estimate the increment of body burden that is due to the source being evaluated. Discussions in the previous section address the assignment of the background body burden. As discussed above, issues to consider include: whether to use a national or a local background body burden, whether to consider the background body burden for younger adults rather than the full range of adult ages (younger adults would have a lower background body burden), whether to consider specific populations such as women of child-bearing age (which again might imply a lower concentration as compared to a full population average), and so on.

The focus on the procedures in this volume are on predicting exposure media concentrations and estimating site-specific intake doses. A simple procedure is recommended here to estimate body burdens given intake doses to dioxin-like compounds. Specifically, the simple one-compartment, first-order pharmacokinetic model is recommended. The non steady-state form of this model to predict body burden from a constant intake dose is given by:

$$L \frac{dC_L}{dt} = D - kLC_L \quad (2\text{-}3)$$

where:

C_L	=	concentration in lipid, pg/g;
L	=	lipid mass, g
	=	BW * F_{lipid} (= body weight * fraction lipid)
D	=	steady-state absorbed dose, pg/day (* 365 d/yr = pg/yr)
k	=	first-order dissipation rate constant, 1/day (or 1/yr, if D is in 1/yr units)

= $0.693/t_{1/2}$

$t_{1/2}$ = half-life, days (or years)

t = time period of interest, most often the full duration of exposure

The closed form solution for Equation (2-4) is given as:

$$C_L(t) = C_L(0)\, e^{-kt} + \frac{D}{kL}\,(1 - e^{-kt}) \qquad (2\text{-}4)$$

The first term on the right hand side of Equation (2-4) describes the decline in an initial body burden. If using Equation (2-4) to solve for the full body burden after a period of exposure denoted by "t", than one has to also assign a value of "D" equal to the incremental dose plus the ongoing background dose times an absorption fraction. However, if using this solution to estimate the incremental body burden due to the incremental dose only, than the first term drops out and the equation for solving IBB is:

$$IBB = \frac{ADD\ AF}{kL}\,(1 - e^{-kt}) \qquad (2\text{-}5)$$

where the term "D" has been replaced by ADD * AF, where ADD is the average daily incremental dose, and AF is the absorption fraction. The Risk Characterization has assumed a value of 0.8 for the absorption fraction, 70 kg for the body weight (BW) and 7.1 years for the half-life ($t_{1/2}$), when using this model for WHO_{98}-TEQ_{DFP} in a backwards mode to estimate a steady-state dose that is associated with a body burden. For site-specific assessments, the assessor can assign values to these parameters based on whether they intend to model individual dioxin-like compounds (which could influence the assignment of $t_{1/2}$ or A) and/or whether they intend to consider different sexes and/or stages of life (which could influence the assignment of BW).

2.3.3. Traditional Agency Cancer Risk Assessment Procedures

The usual procedure used to calculate an upper-limit incremental cancer risk is based on an assessment of lifetime average daily dose, LADD, and a slope factor, as follows:

$$R = 1 - e^{SF*LADD} \approx SF * LADD \quad (2\text{-}6)$$

where SF is the slope factor, or more precisely, the 95% upper confidence limit of the linearized cancer slope factor of the dose-response function (expressed in units of the probability divided by dose, or probability/[mg/kg-day], which is most often simply shortened to $[mg/kg\text{-}day]^{-1}$) and LADD is the dose (which needs to be in units appropriate to cancel those of SF, mg/kg-day). The estimated R in Equation (2-6) can be understood as the 95% upper confidence probability of incurring cancer during a lifetime as a result of the exposure defined by LADD; the true probability may be less than the quantity R, and may even be zero. The simplified form of the risk equation shown above is reasonably accurate for risks less than 10^{-2}. This assessment uses the simplified SF * LADD form of this equation since the exposures and risks demonstrated are generally less than 10^{-3}. The slope factor, SF, for 2,3,7,8-TCDD has been previously estimated by EPA as $1.56*10^{5}$ $[mg/kg\text{-}day]^{-1}$ (EPA, 1984; 1981), but has been reevaluated as $1.0*10^{6}$ $[mg/kg\text{-}day]^{-1}$ in this Reassessment. Also, it has been recommended in the Risk Characterization that it be applied to a TEQ dose, in addition to a 2,3,7,8-TCDD dose. As detailed in the Risk Characterization, a current estimate of lifetime cancer risk from background exposures to dioxin-like compounds is about 10^{-3}. This is calculated simply as the background exposure dose of 1 pg WHO_{98}- TEQ_{DFP}/kg-day times the slope factor of $1*10^{-3}$ (converted to [pg WHO_{98}-TEQ_{DFP}/kg-day]$^{-1}$ to be consistent with the dose units).

Similar to the estimation of lifetime cancer risk demonstrated above showing a risk of 10^{-3} due to background exposure to dioxin-like compounds, assessors can also estimate the incremental cancer risk in these probability terms. The LADD of Equation (2-6) would simply be $LADD_{ss}$. These LADDs can be for individual exposure pathways assessed, or all exposure pathways combined.

When using Equation (2-6) for estimating incremental cancer risk, the assessor needs to be aware that adjustments may be required for particular pathways. Adjustments are necessary for the soil-related pathways, soil ingestion and soil dermal contact. The selected cancer slope factor was based primarily on the analysis of the human epidemiology studies where exposure was estimated from dioxin concentrations in blood in occupationally exposed cohorts. The dose estimates used to derive the slope factor were obtained by using a pharmacokinetic model to convert the blood concentrations to an administered, or potential, dose. An administered dose is defined as the dose which contacts the body boundary surfaces, such as the skin as in dermal exposure or the dose ingested prior to absorption. This administered dose was derived by first calculating an absorbed dose and then dividing by 0.8 - i.e., an absorbed dose was assumed to be 80% of an administered dose. Because the slope factor was derived based on an administered

dose, the new slope factor can be applied to an administered dose without any adjustment for absorption as long as the absorption is approximately 80%. Although the data are limited, this is probably a reasonable assumption for most types of food ingestion and inhalation.

The absorption from ingested soil or dermal exposure from soil, however, is likely to be less than 80%. Studies have shown that the bioavailability of dioxin from ingested soil is variable depending on properties such as organic carbon content and is best determined on a site specific basis. A full discussion on absorption of administered dioxin through the various pathways can be found in *Chapter 1. Disposition and Pharmacokinetics*, of the Health Document (Part II of these Dioxin Reassessment Documents). Assuming that 30% of dioxin in ingested soil is absorbed, then the slope factor should be multiplied by 30/80 or 0.375 before combining it with the ingested dose to compute risk. For the soil dermal pathway, the absorption of dioxin through the skin has been estimated to range from 0.5 to 3.0% (EPA, 1992a), with assessments typically (conservatively) assuming 3.0%. This assessment adopts the 3% value to calculate the dose of dioxins absorbed through soil dermal contact. As will be described below, this absorption fraction is already considered in the calculation of dioxin dose through soil dermal contact, and the calculated dose is already an absorbed dose. As such, the correction factor is a little different for soil dermal contact - its purpose is to convert a 100% absorbed dose into a dose comparable to other administered doses to which the SF is applied. Specifically, it needs to be adjusted downward to be equivalent to, for example, an inhaled administered dose which is 100% as calculated by the procedures here, but it only 80% (or thereabouts) when absorbed. Therefore, the dermal dose, needs to be adjusted upward by a factor of 1.00/0.8, or 1.25, to be used with the SF. The adjustments for the soil pathways to estimate cancer risk are given as:

$$R_s = SF\ LADD_s\ AF_s \qquad (2\text{-}7)$$

where:

	R_s	=	lifetime excess cancer risk from soil pathways, ingestion and dermal contact
	SF	=	cancer slope factor, $(mg/kg\text{-}day)^{-1}$
	$LADD_s$	=	administered dose from soil ingestion and soil dermal contact, mg/kg-day
	AF_s	=	absorption correction factor for the soil pathways, 0.375 for soil ingestion and 1.25 for soil dermal contact

An assessor can easily apply the IOB concept for cancer risk: simply divide the incremental cancer risk by an appropriate background cancer risk, and then multiply by 100% As noted above and discussed in the Risk Characterization, the current average background cancer risk is 10^{-3}. One can use this national average cancer risk estimate or derive a site-specific background cancer risk by determining a site-specific LADD and multiplying it by the slope factor. For example, if the incremental cancer risk is 10^{-5}, and the national background cancer risk of 10^{-3} is used, then the IOB for cancer risk is estimated as 1%.

2.3.4. Interpretation of Cancer and Non-Cancer Risk Assessment Results for Dioxins

Chapter 5 will demonstrate the procedures for estimating incremental cancer risk and for characterizing non-cancer risk for dioxin-like compounds using the IOB approach. This demonstration will include generation of site-specific background estimates of dose and body burden that are distinct from the national averages above, and the generation of the IOB and incremental cancer risk estimates. However, no interpretations for these results will be provided. Interpretations of risk assessment results is where risk management takes over, and it is beyond the scope of this document to provide risk management guidance for assessing incremental impacts of the dioxin-like compounds from specific sources of release.

Still, some general comments can be provided here as background. For cancer risk for compounds other than the dioxin-like compounds, EPA has based regulatory actions on a wide spectrum of levels, generally in the range of 10^{-6} to 10^{-4} lifetime cancer risk. Estimated lifetime individual risks below 10^{-6} have rarely been found to be sufficient basis for action, while in most cases levels above 10^{-4} result in some form of action, although not necessarily regulation. As described above, the current background cancer risk from exposure to dioxin-like compounds is at 10^{-3}. In performing a site-specific assessment for a specific source of dioxin release, an assessor should assume that an individual's exposure and resulting lifetime cancer risk to dioxin-like compounds are already at 10^{-3} (or a different site-specific lifetime cancer risk) and that the source adds to this impact. For example, if assessing impacts to farmers who live near an incinerator and consume a portion of their agricultural produce, it must be assumed that their produce has dioxin concentrations already at background levels and that the incinerator emissions add to this concentration. The challenge for risk managers in such a circumstance is to determine what level of incremental lifetime cancer risk posed by the specific source warrants concern, when the background lifetime cancer risk is already at a level near where, for other

contaminants and other circumstances, EPA has historically judged that some form of action may be warranted.

Similar issues arise when trying to put the site-specific IOB in perspective. As discussed above, the MOE for background exposures for non-cancer effects is already in a range (<10) that is of concern. An incremental exposure will decrease this margin.

In both cancer and non-cancer risk assessment, therefore, traditional rules-of-thumb may not be of immediate use to the risk assessor, because background levels translate to concern as defined by traditional Agency methods. The Risk Characterization recognizes the difficulty posed by this circumstance, and suggests that the Agency take a broad, long-term view of dioxin risk management:

> *In this case, a strategy might be to bring average "background" exposures down and to also focus on larger incremental exposures or highly susceptible populations. This would be a strategy that would parallel the Agency's approach to control lead exposures. Other parallel science and management issues between dioxin-like compounds and lead are under discussion within the Agency. Providing guidance on the how to judge the significance of incremental increases to background using the MOE approach is beyond the science scope of the reassessment and will have to be addressed elsewhere by EPA.*

2.4. THE TOXIC EQUIVALENCY PROCEDURE

Assessments very rarely focus on 2,3,7,8-TCDD alone, but rather on the suite of 17 dioxin and furan dioxin-like congeners, and also the 12 dioxin-like coplanar PCBs. Chapter 1 describes the "toxicity equivalency factor", or TEF, approach to handling mixtures of dioxin-like compounds. The TEF for a congener of interest is a measure of the potency of that congener divided by the potency of 2,3,7,8-TCDD. As shown in Table 1-1 in Chapter 1, the TEFs for 2,3,7,8-TCDD and 1,2,3,7,8-PCDD are 1 and all other dioxin-like compounds have TEFs less than 1. The combined risk resulting from exposure to a mixture of dioxin-like compounds can be computed using the TEFs and assuming that the risks are additive. This assessment recommends that assessors model the fate of all the congeners individually until the estimate of the exposure media concentration is made. At that point, the Toxic Equivalent exposure media concentration, C_{TEQ}, can be calculated as:

$$C_{TEQ} = \Sigma\ TEF_i\ C_i \qquad (2\text{-}8)$$

where C_i is the concentration of the individual congener. LADDs and ADDs can then be estimated for a TEQ concentration. Cancer risk on a TEQ basis can be assessed using the q_1^* for 2,3,7,8-TCDD in combination with the TEQ-based LADD. Non-cancer risk procedures are similarly driven by TEQ body burdens or increments above background.

2.5. PROCEDURE FOR ESTIMATING EXPOSURE

Section 2.2 described the exposure equation as it applies to dioxin and dioxin-like compounds. Before making exposure estimates, the assessor needs to gain a more complete understanding of the exposure setting and be prepared to estimate exposure media concentrations. The purpose of this section is to provide guidance for the procedures followed in this assessment to define such settings and estimate exposure media concentrations. The approach used here is termed the exposure scenario approach. Brief descriptions of the steps and associated document chapters are presented below.

Step 1. Identify Source

Three principal sources are addressed in this document. The first, identified as "soil contamination", is called a source in that the starting point of the assessment is a bounded area of soil contamination. Of course, the ultimate source for soil contamination is some unidentified cause for the soil to become contaminated. For exposure and risk assessment purposes, the cause for contamination is not relevant except to assume that the cause is not ongoing and that the impact of the "initial" levels is what is being evaluated. For contaminated soils, exposures could occur on the site of contamination or distant from the site of contamination. Examples of on-site exposures include exposures to workers on Superfund or similar sites, or special circumstances such as Times Beach where residential properties become contaminated. A common example of an off-site impact would be impacts to residents who live near a Superfund (or similar) site whose property becomes contaminated due to erosion and whose air contains elevated levels of the contaminant due to dust erosion or volatilization followed by atmospheric transport. The second principal source is called "stack emissions." Unlike the soil source, the contamination is assumed to be on-going. Stack emissions in particulate form are assumed to deposit onto the soil and vegetation at the site of exposure, and emissions in vapor form result in air-borne concentrations which transfer into vegetation at sites of exposure. It is noted that individuals working at the site where stack emissions occur are also exposed. The procedures in this document only apply to residents who are not associated with the site where stack emissions occur. The third principal source is called "effluent discharges". Such discharges represent point

source inputs to surface water bodies. Like the stack emission source, impacts to surface water bodies are assumed to be ongoing during the period of exposure. Unlike either of the above two sources, only the impacts to water and fish are considered for this source category.

Step 2. Estimate Release Rates

Estimating the release of contaminants from the initial source is the first step towards estimating the concentration in the exposure media. Releases from soil contamination include volatilization, and wind and soil erosion. Chapter 4 on estimating exposure media concentrations describes fate and transport modeling procedures for estimating soil releases. Stack emissions and effluent discharges are point source releases into the environment. Background on stack emissions including details on modeling from the stack to a site of exposure are provided in Chapter 3.

Step 3. Estimate Exposure Point Concentrations

Contaminants released from soils, emitted from stacks, or discharged into surface waters move through the environment to points where human exposure may occur. Contaminated soil that is near but not at the site of exposure is assumed to slowly erode and contaminate the exposure site soil, but to a level lower than the level at the contaminated site. The only time when the source concentrations equal the exposure concentrations is for the soil pathways, soil ingestion and dermal contact, when the soil contamination is at the site of exposure. Chapter 3 describes the use of the ISCST3 Model to estimate dispersion of stack plumes to predict air-borne concentrations at the site of exposure as well as deposition rates of dioxins sorbed to stack emitted particulates. Chapter 4 describes how soil and vegetation concentrations are estimated given contaminant concentrations and deposition rates, and also how release rates from soil initially contaminated translate to exposure point concentrations. Chapter 4 also describes a simple dilution model which translates effluent discharges into surface water and fish tissue concentrations.

Step 4. Characterize Exposed Individuals and Exposure Patterns

The patterns of exposure are described in Sections 2.6 and 2.7 of this Chapter. Exposed individuals in the scenarios of this assessment are individuals who are exposed in their home environments. They are adult residents who also recreationally fish, have a home garden, farm, and are children ages 2-6 for the soil ingestion pathway. Each of these pathways is evaluated separately. Although it is unlikely that individuals would experience all of these pathways

simultaneously, quite often exposure assessments do add exposures across pathways. In this document, the doses across pathways are added. Exposure pathways evaluated, which have generally been alluded to in discussions above, include inhalation, ingestion, and soil dermal contact. Each pathway has the set of parameters including contact rates, contact fractions, body weights, and lifetime. These parameters were defined earlier in Section 2.2.

Step 5. Put It Together in Terms of Exposure Scenarios

A common framework for assessing exposure is with the use of "settings" and "scenarios." Settings are the physical aspects of an exposure area and the scenario characterizes the behavior of the population in the setting and determines the severity of the exposure. A wide range of exposures are possible depending on behavior pattern assumptions. An exposure scenario framework offers the opportunity to vary any number of assumptions and parameters to demonstrate the impact of changes to exposure and risk estimates. Exposure estimates for six example scenarios are demonstrated in Chapter 5.

Step 6. Estimate Exposure and Risk

Section 2.2 described the basic equation that estimates exposure for every assumed pathway in an exposure scenario. Chapter 5 demonstrates the methodology on six example scenarios, which includes the generation of exposure estimates for ten different exposure pathways and the suite of 17 dioxins and furans, and one dioxin-like PCB.

Step 7. Assess Uncertainty

Chapter 7 provides a discussion on model validation and provides several exercises where the models of this assessment were validated with real world data. Chapter 8 addresses the issue of uncertainty more generally, identifying possible sources of uncertainty associated with this methodology. These uncertainties should be considered when applying this procedures to a particular site. Chapter 6 on User Considerations includes discussions on other pertinent topics such as sensitivity of model results to parameter selection, and judgements on use of the parameters selected for the demonstration scenarios for other applications.

2.6. STRATEGY FOR DEVISING EXPOSURE SCENARIOS

EPA (1992b) states, "In exposure scenario evaluation, the assessor attempts to determine the concentrations of chemicals in a medium or location and link this information with the time that individuals or populations contact the chemical. The set of assumptions about how this

contact takes place is an exposure scenario." These assumptions can be made many different ways producing a wide variety of scenarios and associated exposure levels. The number of people exposed at different levels form a distribution of exposures. Ideally, assessors would develop this entire distribution to fully describe the exposed population. Such distributions could be defined using Monte Carlo techniques if sufficient input data are available. However, as discussed in Section 2.1 above, generic issues surrounding use of Monte Carlo are not evaluated here. Discussions of how other assessors have applied Monte Carlo to problems involving dioxin-like compounds are presented in Chapter 8. Since the necessary information for developing a population distribution is rarely available, EPA (1992b) recommends developing a central and high end scenario to provide some idea of the possible range of exposure levels. Since that set of guidelines, an additional set of guidelines had been developed (Browner, 1995) which reaffirms this recommendation for central and high end risk descriptors, and adds other recommendation to identify “highly susceptible” or “highly exposed” subpopulations. There have also been instances where an EPA program office has provided guidelines which specify, almost in cookbook fashion, the make-up of exposure scenarios for evaluating a source. EPA’s Office of Solid Waste and Emergency Response provided such guidance for evaluation of hazardous waste incinerators (EPA, 1994b). US EPA’s Region 6 has more recently published similar guidance for hazardous waste incinerators (EPA, 1998).

This section will illustrate the concept of central and high end scenario development as it could be applied to specific sources of release of the dioxin-like compounds. In addition, this section identifies the exposure pathways which are relevant to these compounds, and provides background and justification for the exposure parameters which were selected for the demonstrations in Chapter 5.

For any physical setting, a wide variety of exposure scenarios are possible. The range of exposure levels results from a number of different factors including individual behavior patterns, proximity of individuals to the source of contamination, the fate characteristics of the contaminant, and others. In order to illustrate the possible range, the assessor should try to characterize a central and high end scenario. The general strategy recommended here for defining these scenarios is to first identify and quantify the source of contamination. Next, the assessor should determine the geographic area that is impacted by this source. The contaminant levels are likely to vary widely over this area. Select locations of interest within this area such as the location of the nearest exposed individual or most heavily populated area. For each of these locations, identify behavior patterns which characterize central and high end exposure patterns. Central scenarios correspond to average or median levels and high end scenarios are defined as

levels above the 90th percentile but within the actual range of exposure levels (EPA, 1992b; Browner, 1995).

Statistical data are rarely available to precisely define such scenarios. Instead, judgement is usually required to identify behavior patterns meeting these criteria. For example, most rural areas probably include both farming and nonfarming residents. Farmers who grow or raise a portion of their own food could be selected to represent the high end scenario and those living in typical residential areas could represent the central scenario. Alternatively, if more detail is desired, central and high end scenarios could be defined for both segments of the population, i.e., farmers and residents. For each scenario, determine relevant exposure pathways and assign values for exposure parameters such as contact rate, exposure duration, and so on, which represent a central and/or high end pattern for the type of receptor. Finally, compute the associated exposure level. The resulting range of exposure levels for each location can be used to illustrate the possible range of exposures.

Reference has been made in this chapter to the example scenarios found in Chapter 5, Demonstration of Methodology. Three "source categories", categories of contamination sources described in Chapter 4, are demonstrated in Chapter 5. The stack emission source is assumed to expose a relatively large population in a rural area containing residences and farms. For this source, both central and high end scenarios are defined in the manner outlined above. Specifically, a central scenario is based on typical behavior at a residence and the high end is based on a farm family that raises a portion of its own food. For the soil contamination and effluent discharge sources, only one scenario each will be defined and demonstrated. The soil contamination category will be demonstrated with a high end scenario - a farm is located near the site of contamination. Soil on the farm becomes impacted through the process of soil erosion. Other individuals within a community can also be impacted by a site of high soil contamination. Such individuals would include those visiting or trespassing on the site, volatilized residues can reach their residences, they may obtain water and fish from a nearby impacted water body, and so on. As such, alternate scenarios demonstrating the impact of a site of soil contamination could be developed. For the sake of brevity, and also considering that those residing nearest the contaminated are most impacted, only a high end scenario is developed for the soil contamination source category. The effluent discharge source category is unique in that only the pathways of water ingestion and fish ingestion are considered. For this category, fish and water ingestion patterns will be those adopted for the central scenarios. Again, other patterns of fish and water ingestion could be evaluated for this source category. As a matter of brevity again, only central patterns of behavior with regard to fish and water ingestion are demonstrated.

Two other scenarios, a central and a high end scenario, will be developed for "background" conditions. In this special circumstance demonstrated in Chapter 5, a unique point source such as a tall stack or an effluent pipe, or diffuse source in the case of a large area of soil contamination, is not considered. Rather, all the soil in a hypothetical setting contains dioxins at background levels. Similarly, the air concentration in the hypothetical setting will be initialized to background levels of dioxins. This demonstration will use fate and transport algorithms that have been developed for both the soil contamination source category as well as the stack emission source category. Further details of this structure are described in Chapter 5.

Finally, Chapter 5 will demonstrate some of the pathways outside the scenario structure. These include the chicken and the egg ingestion pathways. These were not included in the central or high scenario because it seems somewhat unlikely to assume that individuals living on farms in rural settings would generate quantities of several food items simultaneously on the farm or homestead. In a real setting, it may be plausible that there are farmers who raise cattle and use a portion of their stock to supply the family with beef and/or milk, farms or residences where chickens are raised that provide the family with eggs and/or chickens, and so on, but it is unlikely that a single farm would raise two or more distinct food animals. Also, if a farm is producing foods that are consumed locally, than a high end scenario could be comprised of individuals who don't live on farms but who do consume local foods. In this document, the high end scenario is defined as a farm raising only one type of terrestrial animal which is used to supply the family with terrestrial animal food products; specifically, the farm family raises cattle and consumes beef and milk from their own stock.

The methodologies used to estimate exposure media concentrations are described in Chapter 4 as screening level in their technical sophistication, but site specific in their application. Defining populations that are typical of central and/or high end exposures is clearly a site specific exercise. Assessors need to make the kinds of assumptions discussed here for their own source and populations of concern. Many acceptable ways could be used to define central and high end scenarios. The approach used here was done for demonstration purposes only. On the other hand, the example scenarios in Chapter 5 were carefully crafted to be plausible and meaningful, considering key factors such as source strength, fate and transport parameterization, exposure parameters, and selection of exposure pathways.

Key source strength terms were carefully developed and defined. These include soil concentrations, effluent discharge rates, and stack emission rates. For the demonstration of the soil contamination category, for example, the concentration of 2,3,7,8-TCDD and two other example compounds were set at 1 ppb, which was a typical concentration of 2,3,7,8-TCDD

found in Superfund-like sites studied in the National Dioxin Study (EPA, 1987). Concentrations in soil in the demonstration of background conditions were characterized as typical of background levels and were based on concentrations found in rural settings. Researchers investigating concentrations of 2,3,7,8-TCDD in "background" or "rural" settings have typically found it in the ppt range or not detected it (with a detection limit generally less than 1 ppt), which contrasts the 1 ppb assumed for 2,3,7,8-TCDD in the demonstration of the soil contamination source category. Introductory sections of Chapter 5 provide a more complete description of the example scenarios.

2.7. EXPOSURE PATHWAYS AND PARAMETERS

The dioxin-like compounds have been found primarily in air, soil, sediment and biota and to a lesser extent in water. Thus, the most likely exposure pathways are:

- Ingestion of soil, water, terrestrial animal food products (beef, pork, chicken, eggs, dairy products), fish, fruit, and vegetables
- Dermal contact with soil
- Inhalation of particulates and vapors.

The following sections describe the selection of central and high end exposure parameters for these pathways. Table 2-1 summarizes all the exposure parameters selected to represent the central and high end demonstration scenarios of Chapter 5.

2.7.1. Soil Related Exposures

The two soil related exposures which will be demonstrated in this assessment include a childhood pattern of soil ingestion and an adult pattern of soil dermal contact. The soil ingestion pathway will involve the assignment of central and high ingestion quantities in units of mg/day and it will assume a child body weight of 17 kg. This contrasts the food pathways described below in Section 2.7.4, where the contact rate is defined in units of g/kg/day. Parameters for the soil dermal contact pathway were developed using the Exposure Factors Handbook (EPA, 1997a). Further details on this pathway can be found in EPA's Dermal Exposure Assessment: Principals and Applications (EPA, 1992a).

2.7.1.1. *Soil Ingestion*

Soil ingestion occurs commonly among children during activities such as mouthing of toys and other objects, nonsanitary eating habits, and inadvertent hand-to-mouth transfers. In addition to normal soil ingestion activities, some individuals exhibit behavior known as pica

which involves intentional soil ingestion. Soil ingestion rates associated with pica are probably much higher. Very limited values for pica patterns have been reported in the literature. Based on some limited data, EPA (1997a) reports that a 5 to 10 g/day for deliberate soil ingestion rates for children may not be unreasonable. This dioxin assessment considers only normal soil ingestion among children.

To a lesser extent, soil ingestion also occurs among adults from activities such as hand-to-mouth transfer when eating sandwiches or smoking. However, the data to estimate the adult rate of soil ingestion is scarce. EPA (1997a) notes that the data available on adult soil ingestion is consistent with a 50 mg/day assumption often used by EPA program offices to model this pathway. Adult soil ingestion is not demonstrated in this assessment. Paustenbach (1987) and Sheenan et al. (1991) have suggested calculating exposures for this pathway (as well as dermal contact and inhalation) separately over three to four age periods to reflect major changes in body weight, surface area and inhalation rates. In general, exposure assessments can be refined by estimating exposures separately over each year of age that is of interest and summing to get the total. Age specific data for body weight, surface area and inhalation rate are presented in EPA (1989, 1992b, and 1997a). These procedures are not presented here, but readers interested in refining exposure estimates are encouraged to check the above references for further guidance.

Based on the review of literature, EPA (1997a) suggests that a child soil ingestion rate of 100 mg/day appears to represent a central estimate of the mean for children under 6 years old. This value will be adopted for the central scenarios. Of the studies which were considered appropriate in EPA (1997a), upper percentile values ranged from 106 mg/day to 1,432 mg/day with an average of 383 mg/day for soil ingestion and 587 mg/day for soil and dust ingestion. On this basis, a value of 600 mg/day will be used for the high end exposure.

In cooler climates where the children may have little exposure to outdoor soils for a significant portion of time, it may be appropriate to develop a time-weighted average daily soil ingestion rate based on indoor and outdoor behaviors. Hawley (1985), for example, assumed that young children ingest 100 mg of housedust per day while spending all their time indoors during the winter months, that they ingest 250 mg/day while playing outdoors during the summer months, and that they ingest 50 mg/day while playing indoors during the summer. His time-weighted annual average, considering this different summer and winter patterns, was calculated at 150 mg/day.

For the soil ingestion pathway, contact fraction refers to the portion of ingestion soil which is contaminated. For the residential setting, the assumption is made here that all soil ingestion by children occurs in and around the home, and that all the soil at the home is

contaminated. Thus, a value of 1 has been adopted in the example scenarios presented in Chapter 5. In situations where the contaminated area is located remote from where children live, and children have some access to these areas (if the areas are parks or playgrounds, e.g.), lower fractions would be appropriate.

Another issue for the soil ingestion, and the soil dermal contact pathway discussed below, is the concentration of dioxin-like compounds to which individuals are exposed. As described later in Chapter 4, two "source categories" discussed in this document include stack emission sources and off-site soil contamination (i.e., a site of soil contamination distant from the site of exposure). Dioxins arrive at the site of exposure either from the air, as in the stack emission source, or via overland erosion, as in the off-site soil contamination scenario. Residues of dioxin mix into either a shallow (2 cm) depth of soil which is "untilled", or a 20-cm depth which is "tilled" (by gardening or farming). Obviously, tilled concentrations are lower than untilled concentrations. Given that ingestion is only modeled for children who are likely not too heavily involved in gardening or farming, it is assumed that their contact is with untilled soils, and the higher concentration associated with these soils is used.

2.7.1.2. *Soil Dermal Contact*

The total annual dermal contact to soil alone, expressed in mg/yr, is the product of three terms: the contact rate per soil contact event, the surface area of contact, and the number of dermal contact events per year. The soil contact rate is also known as the soil adherence rate to reflect that it is not only the amount of soil contacted, but the amount of contact that adheres. Current guidance in the Exposure Factors Handbook (EPA, 1997a) suggest that soil dermal exposure can be divided into components for indoor and outdoor exposures; for indoor exposures, the medium might be better described as "indoor dust", and for outdoor exposures, the medium would be soil. The adherence rate is also a function of the body part - with hands usually having the highest adherence, with other exposed parts such as arms and legs usually having lower adherences. The Exposure Factors Handbook provides details on these factors. A summary pertinent to the applications demonstrated here is:

- Contact rate: <0.002 to >20 mg/cm^2-event. The very high adherence rates were found for the scenario described as, "kids-in-mud", and was from data on children playing by a lakeshore. The lower range was found for an indoor Tae Kwon Do setting. Adherences for a day-care setting ranged from 0.03 for arms and legs to

0.1 for hands. Outdoor adherences for gardeners ranged from 0.005 for legs to 0.02 for arms to 0.2 for hands.

- Body surface area: Average adult and child body surface areas are in the neighborhood of 20,000 and 6500 cm^2 (for a child ages 2-5). The selection of the surface area considered for a dermal contact event depends on the nature of the event and the assumptions about which part(s) of the body are involved in that event. For a child ages 2-5, hands comprise about 5.5% of total body surface area, arms about 13%, and legs about 25%. For adults, hands are similarly about 5%, arms are about 13%, and legs about 32%.
- Event frequency: This is a factor more based on exposure assessment judgement, rather than data, as in the above two factors. Obviously, climate, activity, age, and similar factors play into assignment of this parameter. This factor can be expressed in terms of events per time period, usually events/yr. For consistency in use in the exposure equation, it is usually transformed to an event/day basis.

All other pathways assessed here estimate an "administered" or "potential" dose, which is defined as the dose which comes in contact with the body. For this pathway, however, an "absorbed" dose will be estimated. This is because for all other pathways, a significant amount of the dose that comes in contact with the body is absorbed - about 80% for the inhalation and ingestion pathways (except for soil ingestion, when the fraction absorbed is more like 30%). An absorption fraction, or AF, is added in the calculation of a LADD for the dermal contact pathway. EPA (1992a) reviews the data to conclude that the absorption of dioxin through the skin has been estimated to range from 0.5 to 3.0%. This document will adopt the conservative estimate of 3.0%, or an AF of 0.03, to give the following for LADD for the soil dermal contact pathway:

$$LADD_{dc} = \frac{C_s \; CR \; SA \; EF \; AF \; ED \; 10^{-6}}{AT \; BW} \qquad (2\text{-}9)$$

where:

$LADD_{dc}$	=	lifetime average daily dose due to soil dermal contact, mg/kg-day
C_s	=	concentration in soil, mg/kg
CR	=	contact, or adherence, rate, mg/cm^2-event
SA	=	surface area of contact, cm^2

EF	=	event frequency, events/day
AF	=	absorption fraction, 0.03
ED	=	exposure duration, yr
AT	=	averaging time, 70 yr for LADD
BW	=	body weight, kg
10^{-6}	=	units conversion factor, kg/mg

In this document, soil dermal contact exposures are demonstrated only for an adult for a "gardening" central tendency pathway and a "farming" high end pathway. Indoor activities for both the central and high end scenarios will assume Tae Kwon do-like activities which translate to a contact rate of 0.005 mg/cm^2-event, with dermal contact only with the hands which translates to 1,000 cm^2 (20,000 cm^2 total surface area * 5% surface area for hands) and 1 event per day (or 365 times per year). Outdoor dermal contact will be modeled on a gardening scenario for the central scenarios and a farming scenario for the high end pathways. The gardening scenarios assume 0.03 mg/cm^2 for contact rate, 10,000 cm^2 surface area contact which assumes hands, arms, and legs, and 0.27 events/day (or 100 events/yr). In comparison to outdoor gardening, the farming scenario assumes a greater adherence at 0.1 mg/cm^2, a smaller surface area of 3600 cm^2 which assumes hands and arms only, more frequent events at 0.96 events/day (or 350 events per year).

Another difference between indoor and outdoor activities in this assessment is the concentration to which the individuals are exposed. As described in the previous section on soil ingestion, tilled (lower in concentration) and untilled (higher) soil concentrations are derived for the stack emission and off-site soil contamination sources. In this assessment, outdoor dermal contact events are assumed to occur in association with tilled soils (gardening or farming), while indoor contact events are assumed to occur in association with untilled soils.

2.7.2. Vapor and Dust Inhalation

EPA (1997a) describes the derivation of ventilation rates, which include assumptions regarding number of hours in sleep, hours inactive, and hours in various levels of activity. Several inhalation studies are reviewed. The final recommendation for continuous exposure assessments in which specific activity patterns are not known is 13.3 m^3/day based on Layton (1993). A rate of 13.0 m^3/day (rounded for simplicity) will be adopted in this assessment. EPA (1997a) suggests that a value of 20 m^3/day represents an upper percentile estimate among adults, and this will be adopted in this assessment as a high end.

The contact fraction for this pathway is equal to the fraction of total inhaled air which is contaminated. Thus it relates largely to percent of time spent in the contaminated area. For the demonstration scenarios in Chapter 5, the contaminated area is the home environment. Therefore, information on the time spent at home versus away from home is pertinent. In EPA (1997a), several activity pattern studies are reviewed. Two of the studies reviewed contained information on time spent at home and away from home, and both studies had very similar results for time spent in the home environment. Robinson and Thomas (1991) reviewed and compared data from the 1987-88 California Air Resources Board (CARB) time activity study with a similar 1985 national study titled, "American's Use of Time." In an average day comprising 1440 minutes, Robinson and Thomas (1991) found an average of 954 minutes at home from the national study, or 66% of the time, compared to 892 minutes (62%) for Californians. Sexton and Ryan (1987) reviewed the procedures for assessing inhalation exposures, and in so doing, reviewed two previous studies on time use including information on time at home and away from home. One study showed 69% of the time at home and the second study showed 71%. Based on these, a central estimate for the fraction of time spent at home will be 70%.

EPA (1997a) did not make specific recommendations for a high end contact fraction. Such a fraction should be relevant to the population defined as high end, which in this assessment is a subsistence farm. It seems reasonable to assume that a rural farming family may have more time at home as compared to the general population. Without rigorous justification, a high end contact fraction will be assumed to be 90%.

The two key parameters discussed above, contact rate and contact fraction, when multiplied together, will yield a contact rate for contact with the contaminated media. For the central scenario, the two key quantities are 13.0 m^3/day and 0.70, which yield a contact rate with impacted air of 9.1. For the high end scenario, this calculation is 20.0 m^3/day times 0.90, which is 18 m^3/day. Therefore, the difference between central and high end from behavior assumptions alone is about a factor of two.

An additional assumption needs to be made for the vapor and dust inhalation pathways. This pertains to an assumption concerning the differences in air quality between indoor and outdoor conditions. Algorithms for both particulate and vapor-phase air-borne concentrations of contaminants are specific to outdoor air. Hawley (1985) assumed, based on several other studies in which measurements were made, that the concentration of suspended particulate matter in indoor air is equal to 75% of that outside. Also, his report stated that most household dust is outdoor dust that is transported into the house, and that only a small percentage is developed

from sources within. He then concluded that 80% of the indoor dust is identical in contaminant content to outdoor soil. Refinements to the concentration of contaminants on indoor versus outdoor dust should have a minor effect on exposure estimates. A similar trend is assumed for air-borne vapor phase concentrations. For this reason, differences between indoor and outdoor concentrations are not specifically considered, or equivalently, no distinctions are made for outdoor and indoor air quality.

2.7.3. Water Ingestion

The water ingestion rate of 2 L/day has been traditionally assumed for exposure through drinking water. However, EPA (1997a), after review of several literature sources, concludes that 2 L/day may be more appropriately described as a 84% value, or a value for high end exposure estimates (the 90% value was actually calculated to be 2.34 L/day). For this reason, a water ingestion rate of 2 L/day is assumed only for the high end exposure estimates. Since the high end scenario includes a farm and the farming family, it is also argued that farm labor requirements justify the higher rate of water ingestion. EPA (1997a) recommends a rate of 1.4 L/day as representative of average adult tap water drinking water consumption. This is the rate used for central scenarios in Chapter 5. The difference in central and high end tendencies is also modeled using the contact fraction. Again, this fraction is based on the time spent at home. The value of 0.70 is used to model the central estimate, for the residence setting, and the value of 0.90 is used to model the high end estimate, for the farm setting.

2.7.4. Ingestion of Terrestrial Food Products

This section discusses the consumption rates used in the beef, dairy, chicken, eggs, and vegetables/fruits ingestion pathways. All these pathways are similar in that the food products originate from the land. The high end demonstration scenario in Chapter 5 is a farming family which home produces a portion of its beef consumption. In site-specific assessments, home production of foods is often a scenario of concern, particularly if the home producers are located near the source of contaminant release. An exposure pattern similar to home production/consumption of foods is the consumption of locally produced foods. This would be relevant for individuals who live in a setting where food is produced, a rural setting for example, who do not produce any of their own food but who rely on local foods, such as from farmer's markets.

In order to estimate the contact rates for consumption of home produced foods, analysis of the USDA National Food Consumption Survey (abbreviated NFCS; USDA, 1992) of 1987-88 as

conducted in EPA (1997a) will be used in this dioxin exposure reassessment. Specifically, EPA (1997a) used the household component of this survey. This component collects information over a 7-day period on the socioeconomic and demographic characteristics of households, and the types, values, and sources of foods consumed. Like the use of any survey data, use of this data must be understood by users. EPA (1997a) took from the household survey this information: 1) whether or not the food product was used in the house that week, 2) whether or not the food product used that week was home produced, 3) the quantity (mass, such as pounds or kilograms) of food consumed (home produced or not) in the house that week, 4) the number, age, and body weight of individuals in the household, and 5) the number of weekly meals consumed by each family member. If the household reported consumption that week, than EPA could calculate an individual consumption rate for "consumers only". To do this, EPA (1997a) then assumed that all individuals in the household consumed some of the product, and the amount of individual consumption was based on average serving sizes for each individual (different as a function of the age of the individual) and number of meals consumed by each individual. Then, dividing by 7 (as in days of the week) and the body weights of the individuals, they derived consumer only consumption rates in terms of g/kg/d.

EPA (1997a) also looked at a second major USDA food consumption survey - the Continuing Survey of Food Intakes by Individuals (CSFII). This measured the food consumption patterns of all individuals throughout a 3-day period, whether the food was eaten at home or not, and did not have questions on home production practices. EPA (1997a) used this survey to derive general population per capita consumption rates (see next paragraph for definition of per capita).

In order to understand how the EPA (1997a) analysis of USDA data was used for this dioxin exposure document, it is important first to understand three types of generic food consumption rates: *1) Per Capita Consumption Rate*: This is an average consumption rate and includes all consumers as well as nonconsumers. *2) Consumption Rate for Consumers Only:* This is the consumption rate calculated only for individuals who report consumption of the food product in question. A per capita consumption rate can be calculated as a product of the consumption rate for consumers only and the ratio of those reporting consumption and all respondents including those who reported consumption plus those who didn't report consumption (or equivalently, reported nonconsumption):

$$C_{pc} = C_{co} \frac{N_c}{N_c + N_{nc}} \qquad (2\text{-}10)$$

where C_{pc} is the per capita consumption rate, C_{co} is the consumer only consumption rate, N_c is the number of consumers, and N_{nc} is the number of non-consumers, and *3) Consumption rates, Per Capita or Consumer Only, for Consumers of Home Produced Products:* Home producers/consumers are a critical subpopulation, as noted earlier. EPA (1997a) was able to estimate consumer only consumption rates for home producers/consumers for a variety of food products from the household survey of the NFCS. These consumer only home producer/consumer rates are used in the demonstrations of Chapter 5.

The use of the consumer only consumption rate for home produced foods from the household survey of the USDA NFCS represents a significant departure from earlier versions of the dioxin exposure reassessments (EPA, 1992c; EPA, 1994a). It is the most appropriate type of rate to use when the scenario is a farm where individuals consume the food they produce - that is precisely what the definition of these rates are. Unlike earlier consumption rates, body weights are not used as the consumption rates are derived over the range of individuals including infants and children. It is also important to note that the consumer only consumption rates for the food products appear significantly higher than other consumption rates generated in EPA (1997a). For example, the general population per capita consumption rate for beef using the CSFII was 0.83 g/kg-day. The consumer only consumption rate for home produced beef was 2.45 g/kg/day. The following describes some of the differences in these two beef ingestion rates, 0.83 and 2.45 g/kg/day:

1) The household survey reports on total food product brought into the household, and this data is used directly for the calculation of consumers only consumption rates in EPA (1997a). Their calculation does not include bone and other wastage, trimmable fat, cooking loss, or uneaten foods. By contrast, intake rates developed from data in the 1-day individual consumption survey are defined “as eaten” meaning that these rates do account for cooking loss, wastage, and uneaten food. As will be described below, cooking and post cooking losses will be accounted for the meat product consumption rates developed from household data. The appropriate factor for beef is calculated to be 0.55. While the household data does not account for cooking and post cooking loss (without the correction introduced below), it does not include food eaten away from home, which could lead to underestimation of total consumption rates.

2) The 0.83 g/kg/day rate derived from the CSFII is a per capita consumption, meaning that it is calculated considering non-consumers as well as consumers. The percent consuming beef,

according to the CSFII, is 91%. Therfore, solving for the consumers only rate, using Equation (2-8) above, is 0.91 g/kg/day (0.83 g/kg/day divided by 0.91).

3) It is likely that home producing consumers - ie., only those who reported eating home produced beef which is what the 2.45 g/kg-day rate is - eat a fair amount of their home-produced beef during the weeks in which they reported this behavior. Other weeks they may also eat beef that was not home produced, but it might be smaller amounts so that their overall consumption rate of meat is likely to be lower than is reflected in these home producing consumers only rates. No data was available in EPA (1997a) to evaluate this speculation, but it seems reasonable (isn't it true that when the tomatoes in the home garden are ripe, the family will eat more fresh salad than usual?).

4) Two other differences between the CSFII and the household component of the NFCS which could lead to over or underestimation of actual behaviors include three-day versus week-long information (unclear which direction this would lead to) and individual recall versus head of household recall (again unclear).

To account for cooking and post cooking losses for the meat products which are home produced, information was obtained from USDA (1975). This data is summarized in Table 2-2.

This assessment uses the home producing consumers only consumption rate for home produced beef, milk, chicken, eggs, vegetables, and fruits. The following section describes how the "contact fraction" for these consumption rates is calculated. As has been defined, this describes the fraction of total food category consumption which is home produced. Following a description of this parameter for the dioxin reassessment, sections will describe the derivation of consumers only consumption rates for the various food products.

2.7.4.1. *Derivation of the Contact Fractions for Beef, Milk, Chicken, Eggs, Vegetables, and Fruits*

The home producer consumer-only consumption rate needs to be adjusted downward by consideration of the contact fraction. The average "consumer only" consumption rate for home producers developed from NFCS data will include weeks where only a little of the product in question is eaten and weeks when much of the product is eaten. Most importantly, however, this calculated "average" will only be an average during which consumption of home produced foods actually occurs. It is probably not reasonable to assume that average consumption weeks occur

52 weeks a year; there will be weeks where no consumption of the home produced product occurs. In other words, the contact fraction, or CF, will be less than 1.00.

Means to assign values to CF for site-specific applications will require judgement on the part of assessors. If localized information is available for a site-specific assessment, this could be used. For example, climate or local agronomic practices could assist in the assignment of a CF. One could assume, for example, that home production of dairy does not occur from December through February (13 weeks), and use this information to reduce the consumers only dairy consumption by 25% (13 weeks/52 weeks); i.e., the CF = 0.75. This assumes that a home producer of dairy products is producing at least some dairy during all weeks between February and December. EPA (1997a) did break out the household consumption survey data into seasons and it is clear that there was less consumption of home-produced food products during the winter as compared to the summer. But what is still true regardless of any refinement of this type is that the consumers only analysis of the USDA household survey is still only a reporting of households which did consume during the week.

EPA (1997a) developed data from the NFCS which will be used to assign values of CF for home produced foods. Based on questionnaire responses, EPA (1997a) was able to determine the fractions of total food intake that is home-produced; that is, of all the food product consumed by respondents in the survey, what fraction of that product was home-produced. For example, 3.8% of all beef consumed is home produced. This 3.8% includes, however, both those who raise cattle and then consume it (actual home producers) and those who took part in the survey, but did not raise any animals. Therefore, this 3.8% is not what is needed for current purposes. What is instead needed is the percentage (or fraction) of total beef consumed by people who raise cattle, that comes from their own stock. This could not be ascertained perfectly from the household survey because there was not this direct a question: “Knowing that you raise cattle, what percent of your home consumption is from your own stock?” Still, there were questions that were asked that are close to this. There was the question, “During the past year (1986), did anyone in the household produce any animal products such as milk, eggs, meat, or poultry for home use in your household?” The households which answered yes to this question form the universe of home producers of animal food products. These individuals were also asked questions about whether they consumed home-produced foods the week of the survey. For beef, 48% of households in this universe of home producers said that they did eat home-produced beef that week, while 52% said they did not. Therefore, 0.48 becomes the contact fraction for beef. Other contact fractions that were ascertained using this intersection of questions include: for diary - 0.21, for poultry - 0.15, and for eggs - 0.21. For fruits and vegetables, the universe of

home producers was ascertained by those who answered yes to the question of whether there was gardening in the household. Responses of yes for consumption that week of the category "exposed vegetables" - 0.233, and "root vegetables" - 0.106, was averaged to yield a 0.17 that is used in this assessment as the CF for vegetables. The CF for fruits in this assessment is 0.12, based on a yes response to consumption that week of home produced "exposed fruits".

2.7.4.2. *Beef Ingestion*

The high end farming scenarios include this pathway for purposes of demonstration. Other terrestrial animal consumption pathways are demonstrated separately. EPA (1997a) calculated a consumers only overall (over all ages and regions of the US) average consumption rate for home produced beef of 2.45 g/kg/day. Applying the CF of 0.478 for beef as described above leads to an average consumption rate for home produced beef of 1.17 g/kg/day. This is further adjusted with the use of a preparation term. As shown in Table 2-2, the percent losses during cooking and after cooking is 27 and 24%, respectively. Therefore, the average consumption rate with these considerations is now estimated as, 1.17 g/kg/day * 0.73 * 0.76 = 0.65 g/kg/day.

Consumption rates of terrestrial animal food products are expressed in terms of fat ingested per day for two reasons. One, dioxin-like compounds tend to partition strongly toward lipids and virtually all of such compounds will be found in the fat portion of animal food products. Two, the algorithms to estimate concentrations in these food products estimated fat concentrations and not whole product concentrations. EPA (1997a) reports that USDA's Agricultural Handbook Number 8 (USDA, 1979-1984) lists the fat content of cooked beef, including lean and fat, as 21.54. This will be rounded to 22% in this assessment. Therefore, the ingestion of beef fat for individuals in the high end farming scenarios of Chapter 5 will be 0.143 g/kg/day (0.65 * 0.22).

2.7.4.3. *Dairy Ingestion*

As noted above, this pathway will be demonstrated in Chapter 5, but outside of any defined scenario. EPA (1997a) calculated a consumers only overall average consumption rate for home produced dairy of 14.0 g/kg/day. Applying the CF of 0.207 for dairy as described above leads to a final long term consumption rate of 2.90 g/kg/day. EPA (1997a) reports that USDA's Agricultural Handbook Number 8 (USDA, 1979-1984) lists the fat content of whole milk of 3.16. This will be rounded to 3% in this assessment. Therefore, the ingestion of dairy fat for this pathway demonstrated in Chapter 5 will be 0.087 g/kg/day.

2.7.4.4. *Chicken Ingestion*

Like the diary ingestion pathway, the chicken ingestion pathway will be demonstrated outside of a defined scenario. Furthermore, it will be assumed that the chickens are allowed to free range. A full discussion of predicting the concentration of dioxins in chickens and eggs, including free range chickens, is given in Chapter 4. EPA (1997a) calculates a consumers only consumption rate for home produced chickens of 1.57 g/kg/day. As described above, a CF of 0.151 will be adopted for home-produced chicken consumption leading to a total of 0.24 g/kg/day. As with beef, a preparation factor will be added, and as seen in Table 2-2, this factor will be equal to 0.70 * 0.70, or 0.49. The final consumption rate for chicken is estimated as 0.12 g/kg/day. EPA (1997a) reports that USDA's Agricultural Handbook Number 8 (USDA, 1979-1984) lists the fat content of meat and skin cooked chicken is 13.6. This will be rounded to 14% in this assessment. Therefore, the ingestion of chicken fat for this pathway demonstrated in Chapter 5 will be 0.010 g/kg/day.

2.7.4.5. *Egg Ingestion*

Like the diary and chicken ingestion pathways, the egg ingestion pathway will be demonstrated outside of a defined scenario. EPA (1997a) calculates a consumers only consumption rate for home produced eggs of 0.73 g/kg/day. As described above, a CF of 0.214 will be adopted for home-produced egg consumption leading to a total of 0.156 g/kg/day. EPA (1997a) reports that USDA's Agricultural Handbook Number 8 (USDA, 1979-1984) lists the fat content of eggs as 8.35%. This will be rounded to 8% in this assessment. This is the fat content of the entire egg, as the fat content of the yolk (which has all the egg fat) is about 30%. Therefore, the ingestion of egg fat for this pathway demonstrated in Chapter 5 will be 0.012 g/kg/day.

2.7.4.6. *Vegetable and Fruit Ingestion*

EPA (1997a) analyzed data from the NFCS household survey to estimate the amount of homegrown "exposed above ground vegetables/fruits" and "root vegetables". Protected vegetables/fruits, as opposed to exposed, were defined as vegetables/fruits which have outer protective coverings which are removed prior to consumption such as peas or oranges. No root vegetables were considered to be protected although, of course, it is common to consume some below ground vegetables such as carrots or potatoes after removal of the skin. The overall consumers only average of home grown fruits, above ground vegetables, and root vegetables was

1.49, 1.52, and 1.16 g/kg/d. These data are in fresh weight. These numbers were somewhat influenced by higher consumption rates for younger children of lesser body weight, as the consumption rate for three age ranges less than 5.0 ranged from 1.28 g/kg/day to 5.75 g/kg/day. The fruit and vegetable pathways will be included in both the central and high end scenarios of Chapter 5, and it will be assumed that the behaviors in the central and high end scenarios do not differ. The CF for both above and below ground vegetables will be 0.173 and for fruit (above ground only) will be 0.101, leading to final fresh weight consumption rates of 0.15 g/kg-day for fruit, 0.26 g/kg-day for above ground vegetables, and 0.20 g/kg-day for below ground vegetables.

2.7.5. Fish Ingestion

The procedure to estimate exposure to fish from consumption of fish caught in recreational pursuit will be different than that of the terrestrial food products. This is done because it is most common in exposure assessments to model exposure to fish in terms of a g/day consumption rate rather than a g/kg/day rate, and a wealth of data in the g/day format has been generated from consumption and creel surveys. Therefore, the LADD equation will be used with a separate consumption rate in g/day and an assumed body weight of 70 kg.

EPA (1997a) extensively reviewed the literature on fish consumption. Their analysis of available surveys led them to make recommendations on studies which they considered valid for generation of fish consumption rates. They also categorized available consumption rates from these surveys into: 1) General Population, 2) Recreational Marine Anglers, 3) Recreational Freshwater Anglers, and 4) Native American Freshwater Anglers.

The demonstration scenarios of Chapter 5 assume a rural setting which includes farms and non-farm residents. Also, it is assumed that a major river system cuts through the watershed which is used for recreational fishing and drinking. It is assumed to be a freshwater system, and therefore, the "recreational freshwater angler" consumption rates will be used in this assessment. Three studies were deemed valid for characterizing recreational freshwater angler consumption rates, and these include the mailed questionnaire studies of Ebert et al. (1993) and West, et al. (1989) and the diary study of Connelly, et al. (1996). The arithmetic mean consumption rate from these four studies are 5, 12, 17, and 5, respectively. The 95th percentile consumption rates from these studies were 13 (Ebert et al, 1993) , 39 (West, et al., 1989), and 18 g/day (from Connelly, et al., 1996). From these data, EPA (1997a) recommended a mean and a 95th percentile value for recreational anglers of 8 and 25 g/day. The central scenarios including a fish consumption pathway will assume the 8 g/day rate. The high end scenarios, which were defined as a subsistence beef farm, will not include a fish consumption pathway. This is done for

demonstration purposes - it certainly is plausible for a farming family to partake in recreational fishing. A high end fish consumption pathway will be demonstrated outside of a scenario, however, as with other pathways. The high end pathway demonstration will use the 25 g/day rate as recommended in EPA (1997a).

It should be noted that these consumption rates are for all recreational freshwater fishers, not only those who consumed the fish they caught. Therefore, they could be underestimates for the purposes here - modeling individuals who consume fish they reacreationally catch. It is also noted that these rates are probably best described as, "as eaten" since the respondents were asked to estimate the weight of the fish they consumed, and assistance the respondents were given (choices, photos, etc.) were based on as consumed weights by those conducting the surveys. Because these rates are, "as eaten", there is no preparation factor required. Finally, it is assumed that the fish is 7% lipid. There were no specific recommendations in EPA (1997a) regarding this factor; there were tables showing the percent fat for various fish species. The 7% value selected appears to be a reasonable mid-range from those tables, and it was also the percent assumed in previous versions of this dioxin exposure assessment (EPA, 1994a).

As a point of comparison, the general population recommended mean consumption rate was 20.1 g/day (14.1 marine fish and 6.0 freshwater/estuarine fish). The 95th percentile recommended rate was 63 g/day. These were described as long term average consumption rates. For a Native American subsistence population, EPA (1997a) recommends a value of 70 g/day for mean intake of fish, and 170 g/day for the 95th percentile intake.

The current Exposure Factors Handbook (EPA, 1997a) and its predecessor (EPA, 1989) both emphasize the importance of obtaining site-specific information on the exposure parameters, not the least of which is the fish consumption rate. For smaller water bodies, EPA (1989) recommends that surveys of local fisherman would obtain the most appropriate fish consumption information. Alternately, EPA (1989) recommends using judgement regarding how many fish meals per year an individual could obtain from the contaminated waters and assuming meal sizes of 100 to 200 g. This was the approach adopted in the earlier draft of the Dioxin Exposure Assessment document (EPA, 1994a). With that approach, it was assumed that a "central" pattern of consumption of fish from an impacted water body led to 3 meals/person/year, and that a "high end" pattern led to 10 fish meals/person/year. With a meal size of 150 g (the current Exposure Factors Handbook recommends a mean fish meal size of 129 g, and a 95th percentile fish meal size of 326 g), this led to consumption rates of 1.2 g/day as the central estimate and 4.1 g/day as the high end estimate.

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Table 2-1. Summary of exposure pathway parameters selected for the demonstration scenarios of Chapter 5.

Pathway Description	Contact Rates		Contact Fractions	Comments
Soil Ingestion				Only pathway specific to an age-range; 2 to 6 year-old children assumed. Absorption fraction converts potential to absorbed dose for risk estimation.
Central	100 mg/d		1.0	
High End	600 mg/d		1.0	
Absorption fraction	0.30			
Soil Dermal Contact	Indoor	Outdoor		Unlike other pathways, daily contact is not assumed; approach instead estimates exposure in terms of contact/event * events/yr; central pattern based on behavior of non-farming adults, high end behavior based on farming pattern. Absorption fraction converts potential to absorbed dose for risk estimation.
Central			1.00	
CR, mg/cm^2-ev	0.005	0.03		
SA, cm^2	1,000	10,000		
EF, ev/day	1	0.27	1.00	
High End				
CR, mg/cm^2-ev	0.005	0.1		
SA, cm^2	1,000	3600		
EF, ev/day	1	0.96		
Absorption fraction	0.03	0.03		
Vapor/Dust Inhalation				Indoor/outdoor air quality assumed equal; central contact fraction is based on average at-home time from time use surveys
Central	13 m^3/day		0.70	
High End	20 m^3/day		0.90	
Water Ingestion				The more traditional 2.0 L/day was evaluated in EPA (1995) as an high end rather than a central value; 1.4 L/day recommended instead for central assumptions.
Central	1.4 L/day		0.70	
High End	2.0 L/day		0.90	

Table 2-1. (continued)

Pathway Description	Contact Rates	Contact Fractions	Comments
Terrestrial Food Products	All contact rates for the terrestrial food products, including animal food and vegetable/fruit, will be: 1) expressed in terms of g/kg/day thereby not requiring a 70 kg body assumption in the denominator of the LADD equation, and 2) based on the EPA (1997a) analysis of the household part of the USDA National Food Consumption Survey. Fish consumption will be handled in the more traditional way using a g/day fish consumption rate and an assumption of a 70 kg body weight. Central scenarios include fish pathway and veg/fruit ingestion pathway, but no other terrestrial food production; high end scenarios include beef/dairy and veg/fruit ingestion pathway, but no other food production including fish consumption. Chicken and egg pathways will be demonstrated outside the context of an exposure scenario.		
Beef Fat Ingestion Central High End	 NA 2.45 g whole/kg/d	 NA 0.478	2.45 g whole/kg/d is transformed to g fat/kg/d basis assuming 22% fat; additional factor of 0.55 accounts for cooking and post cooking loss
Milk Fat Ingestion Central High End	 NA 14.0 g whole/kg/d	 NA 0.207	14.0 g whole/kg/d is transformed to g fat/kg/d basis assuming 3% fat
Chicken Fat Ingestion Central High End	 NA 0.97 g whole/kg/d	 NA 0.151	0.97 g whole/kg/d is transformed to g fat/kg/d basis assuming 14% fat; additional factor of 0.49 accounts for cooking and post cooking loss
Egg Fat Ingestion Central High End	 NA 0.73 g whole/kg/d	 NA 0.214	0.73 g whole/kg/d is transformed to g fat/kg/d basis assuming 8% fat
Fruit Ingestion Above ground exp. Central High End	 1.47 g fresh/kg/d 1.47 g fresh/kg/d	 0.101 0.101	Central and high end behaviors assumed for residence and farm scenarios, respectively; difference is modeled with contact fractions only.

Table 2-1. (continued)

Pathway Description	Contact Rates	Contact Fractions	Comments
Vegetable Ingestion			Central and high end behaviors assumed for residence and farm scenarios, respectively; both scenarios assume similar behaviors; differences are in other pathways and parameters.
Above ground exp.			
Central	1.52 g fresh/kg/d	0.173	
High End	1.52 g fresh/kg/d	0.173	
Root vegetables			
Central	1.16 g fresh/kg/d	0.173	
High End	1.16 g fresh/kg/d	0.173	
Fish Ingestion			Based on "freshwater recreational angler surveys". Fat content is assumed to be 7%.
Central	8.0 g/day	1.00	
High End	25.0 g/day	1.00	
Exposure Duration, Body Weight, Lifetime: Based on mobility data (EPA, 1997a), a duration of 9 years was assumed for the central residence scenario, and a high end duration was assumed to be 30 years. The childhood soil ingestion pathway had a duration of 5 years. As noted above, a body weight assumption was not used for terrestrial food product pathways. For all others, a body weight of 70 kg was used except for childhood soil ingestion, which used a 17 kg body weight. In all cases, a 70 year lifetime was assumed.			

Table 2-2. Percent weight losses from preparation of various meats.

Meat Type	Mean Net Cooking Loss (%)[a]	Mean Net Post Cooking Loss (%)[b]
Beef	27	24
Chicken	30	30
Lamb	29	34
Pork	28	36
Turkey	31	28
Veal	30	25

[a] Includes dripping and volatile losses during cooking. Averaged over various cuts and preparation methods.

[b] Includes losses from cutting, shrinkage, excess fat, bones, scraps, and juices. Averaged over various cuts and preparation methods.

Source: USDA (1975).

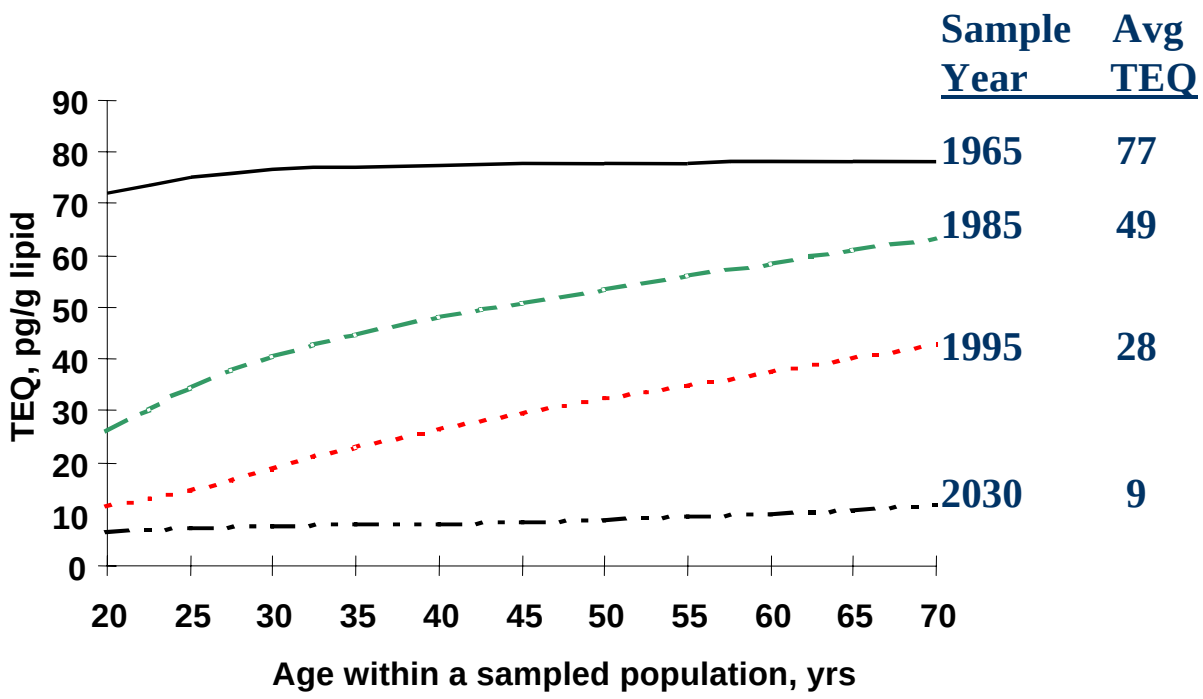

Figure 2-1. Predicted distributions of and average WHO_{98}-TEQ_{DF} concentrations within an adult population for four years: 1965, 1985, 1995, and 2030.

Source: Lorber (2002)

3. EVALUATING ATMOSPHERIC RELEASES OF DIOXIN-LIKE COMPOUNDS FROM COMBUSTION SOURCES

3.1. INTRODUCTION

Since the late 1970's, it has become well established that the combustion of certain fuels containing both organic material and chlorides can form polychlorinated dibenzo-p-dioxins (CDDs) and polychlorinated dibenzofurans (CDFs). This discovery has prompted world-wide research to identify combustion sources, to characterize the conditions favoring the formation of CDD/Fs within the combustion process, and to characterize the emission of dioxin-like compounds to the air from the stack of the process.

The purpose of this chapter is to provide site-specific procedures for evaluating the emission of dioxin-like compounds from stationary combustion sources. The first step is to characterize stack emissions in terms of mass of CDD/F congener released, and then to partition that release into a vapor and a particle phase. Using atmospheric transport modeling, these releases are translated to ambient air vapor and particle phase concentrations, and wet and dry particulate deposition amounts, in the vicinity of the release. This chapter demonstrates these procedures on a hypothetical incinerator using an air dispersion model called the Industrial Source Complex 3, or ISC3. The short-term version of that model, ISCST3, is used in this document. A second purpose of this chapter, therefore, is to provide the background and justification for the model inputs and key parameters for ISCST3. The final results for this model simulation are vapor and particle phase concentrations, and particulate deposition amounts of the specific dioxin-like congeners, which are then used for the demonstration of the stack emission source category in Chapter 5 of this Volume.

This chapter is structured as follows:

- Section 3.2 describes the generation of CDD/F congener-specific emission factors. These factors are defined as the mass of congener emitted per mass of feed material combusted. Subsections within Section 3.2 discuss: 1) a hierarchy of preferred options for generating such emission factors, starting with site-specific stack testing for specific congeners and ending with engineering evaluations when no other data is available, 2) an approach to estimating congener-specific emission factors using congener profiles generated for a source when only total dioxin (sum of homologue group CDD and CDF concentrations) emissions are available; 3) an approach for estimating congener-specific emission rates from CDD and CDF homologue group emissions data if congener profiles are not available; 4) the emission factors for the example incinerator demonstrated in Chapter 5, and assuming a feed rate into the example incinerator, emissions expressed on a mass per time basis (which is required for transport modeling), 5)

partitioning of emissions into a vapor and a particle phase for atmospheric transport modeling, and 6) a procedure to estimate the mass released and concentrations for a related emission of a combustor, that of ash.

- Section 3.3 describes a general air modeling procedure for evaluating the fate and transport of dioxin-like compounds emitted from stacks. The discussion presents a general review of dispersion theory, a general review of dry particle deposition, and a general review of the wet deposition algorithm employed in this analysis. EPA's ISCST3 air dispersion and deposition model is reviewed. Wherever pertinent, Section 3.3 describes the assumptions, equations, and parameter values that were used in the demonstration of methodologies in Chapter 5 of this Volume.
- Sections 3.2 and 3.3 summarized input data and assumptions (emission rates, vapor/particle partitioning assumptions, etc.) that were made for the demonstration of the methodologies for evaluating stack emissions in Chapter 5 of this Volume. Section 3.4 supplies all other key assumptions for the stack emission demonstration, such as stack height and exit temperatures, meteorological data, and others. This Section also provides the final results from the ISCST3 modeling, including vapor phase air concentrations at various distances in the predominant wind direction, and dry and wet deposition fluxes, also at various distances in the predominant wind direction.
- Section 3.5 closes out the chapter by summarizing critical aspects for making site specific evaluations of stack emission sources.

3.2. ESTIMATING THE EMISSIONS OF DIOXIN-LIKE COMPOUNDS FROM ANTHROPOGENIC COMBUSTION SOURCES

Estimating the emission factor is the first step in assessing a specific stack emission source of dioxin-like compound release. For this assessment, an emission factor is defined as the total mass (in vapor and particulate forms) of dioxin-like compound emitted per mass of feed material combusted. An emission factor is a representative value that attempts to relate the quantity of a pollutant released to the atmosphere with an activity associated with the release of that pollutant. Such factors facilitate estimation of emissions from various sources of air pollution. In most cases, these factors are averages of all available data of acceptable quality, and are generally assumed to be representative of long-term averages for all facilities in the same source category.

The general equation for emission estimation is:

$$E_{yr} = A_{yr} * EF \quad (3\text{-}1)$$

where:

E_{yr}	=	emission dioxin/yr; e.g., g/yr
A_{yr}	=	annual activity level of the subject source; e.g. kg/yr
EF	=	emission factor, mass dioxin emitted/ unit of activity level; e.g., ng/kg

Inherent in Equation (3-1) is the assumption that long-term emissions of dioxin-like compounds from a facility is best represented by the mean emission factor. Emission factors are usually developed from measurements of dioxin releases that are associated with normal operating conditions, not upsets nor industrial accidents.

This assessment recommends the generation of emission factors for individual dioxin-like congeners for a site-specific assessment. Volume I, *Sources of Dioxin-Like Compounds in the United States*, contains congener-specific CDD/F emission factors for specific types or classes of combustion processes. The emission factors were developed from stack gas emission measurements at tested facilities, usually as a result of compliance testing under the Clean Air Act, or in conjunction with the issuance of a State operating permit. The actual facility-specific emission rates and the derivation of emission factors representative of classes of combustors are documented in Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States (EPA/600/C-01/012. March, 2001). This database includes congener-specific CDD and CDF emissions data extracted from original engineering test reports. It has been published independently from the Reassessment and is available on Compact Disk-Read only Memory (CD-ROM), without cost, from EPA's National Service Center for Environmental Publications (NSCEP) in Cincinnati, Ohio (telephone: 1-800-490-9198, or 513-489-8190; fax: 513-489-8695). Summary files from the database will be available for downloading from the Web page of the National Center for Environmental Assessment, www.epa.gov/ncea/dioxin.htm. Instructions on how to order and obtain the CD-ROM will also be available on the Web page. This compilation of emission factors is the result of entering raw data of stack emissions from engineering reports of tested facilities data into a series of spreads-sheets. Facilities are classified and sub-classified according to similarity of process, design, types of materials processes or combusted and air pollution control equipment. These emissions factors are current through 1995. However, because most combustion processes are generally configured as they were in 1995, EPA believes the database, in most respects, is current with state-of-the-art technologies. This also applies to air pollution control equipment. EPA will, however, provide a periodic update to the database. Currently, EPA is updating this database to be current with the

year 2000. These updates should reflect changes in the improvements in the combustion-related technology and air pollution control equipment with the passage of time.

When evaluating potential human exposure to dioxin-like compounds using an Air Quality Model, EPA has traditionally converted the stack gas concentrations and emissions of CDD/F mixtures into an equivalent concentration of 2,3,7,8-TCDD, or TEQ (Cleverly, et al., 1989, 1991; EPA, 1987; Mukerjee and Cleverly, 1987), when deriving an emission factor. The fate, transport, and transfer parameters of 2,3,7,8-TCDD were applied to model the environmental fate of this TEQ mixture. For the site-specific procedures in this document, individual dioxin congeners are modeled from source to receptor. Only at the interface to human exposure, e.g., ingestion, inhalation, dermal absorption, etc., are the individual congeners recombined and converted into the toxic equivalence of 2,3,7,8-TCDD to be factored into the quantitative risk assessment.

Section 3.2.1 presents a strategy for development of emission factors for conducting a site-specific assessment. Section 3.2.2 describes an approach to estimating congener-specific emission factors when all that is available are homologue group emission factors. Section 3.2.3 summarizes the emission factors for the hypothetical incinerator demonstrated in Chapter 5. Section 3.2.4 presents an in-depth evaluation of the partitioning of emissions between a vapor and a particle phase for further atmospheric transport modeling. This discussion includes subsections on measurements of partitioning at the stack, measurements of partitioning in ambient air, and the theoretical approach used in this assessment for vapor/particle partitioning. Section 3.3.5 closes this section on emission factors by describing procedures to estimate the mass of ash (fly and bottom) produced and the concentration of dioxin-like compounds on ash.

3.2.1. A Strategy for Generating Emission Factors

The following is a hierarchial listing of data collection options for emission factors:

A. *For facilities that are built and operational*, it is preferred that direct stack measurements be used, using EPA recommended congener-specific stack monitoring and analytical protocols (e.g., EPA Method 23 for stack and EPA Method 1613 revision b for laboratory analysis). Stack monitoring provides concentrations and mass release rates of the pollutant, actual volume of stack gas and temperature. Care should be taken to ensure that the emissions characterization reflects a wide range of operating conditions and also accounts for deterioration in emissions output of the facility over its useful life. Procedures to convert data expressed in concentrations or mass release rates to an emission factor are as follows:

1. Test data of emissions are first placed into common units of measurement. English units are converted into metric, and the concentration term (mass of pollutant per unit volume of combustion gas emitted from the stack) should be corrected to the standard temperature and pressure on a dry gas basis, and standard percent carbon dioxide or oxygen within the combustion gas (e.g.,12% CO_2 or 7% O_2). These adjustments may be necessary if more than one test occurred for stack emissions.

2. The next step involves converting the mass emission concentration of the specific dioxin-like congener in units of nanogram per normal cubic meter (at standard temperature and pressure) of combustion gas corrected to 12% carbon dioxide into an equivalent emission factor in units of grams of pollutant emitted from the stack per kilogram of combustible material or feed (g [CDD/F]/kg feed) that was incinerated at the facility during the duration of stack sampling. This is solved in (Equation 3-2) below. In Equation (3-2), it is important that both the concentration of the dioxin-like compound (C_{fg}) and the volume of combustion gas (V_{fg}) be calibrated to the identical oxygen percent, temperature, and pressure.

$$EF = C_{fg} \times V_{fg} \times A$$

$$EF = \left\{\frac{\text{ng dioxin}}{\text{dscm (STP)}}\right\} \times \left\{\frac{\text{dscm (STP)}}{\text{hr}}\right\} \times \left\{\frac{\text{hr}}{\text{kg combusted}}\right\} \qquad (3\text{-}2)$$

where:

EF	=	congener-specific CDD/F emission factor, ng dioxin/kg
C_{fg}	=	concentration in flue gas, ng dioxin/dscm
V_{fg}	=	volume of combustion gas/unit of time, dscm/hr
A	=	combustion activity level, kg/hr

3. As a final step, the average emission factor of each congener is derived by summing the emission factors and dividing by the number of data points used. The average should represent an approximation of long-term emissions (i.e., annual emissions). Many air dispersion models require that emission factors (ng/kg) be translated into units of amount of the pollutant emitted per second of time (ng/s). Therefore the average emission factor must be adjusted accordingly by adjusting the units in Equation (3-2) to a time-scale of one second.

B. *For facilities that have been constructed, but not yet operational, or are in the planning stages of development, the following procedure is recommended:*

1. Refer to the *Database of Sources of Environmental Releases of Dioxin-like Compounds in the United States* (EPA, 2001). This database contains CDD/F emission factors for a variety of combustion sources through 1995:

   a) municipal solid waste incinerators
   b) medical waste incinerators
   c) cement kilns burning hazardous waste
   d) cement kilns not burning hazardous waste
   e) dedicated hazardous waste incinerators
   f) industrial wood burning
   g) residential wood burning
   h) coal and oil-fired utility boilers
   I) secondary aluminum smelters
   j) iron ore sintering
   k) secondary lead smelting
   l) secondary copper smelting
   m) kraft black liquor boilers
   n) sewage sludge incinerators
   o) boilers/industrial furnaces burning hazardous waste

2. Review the listing of air emission sources and combustor types. From this listing, select the closest analogy to the subject technology in terms of design-type, kinds and types of materials processed or combusted, and air pollution control device. Care should be taken to assure that the subject source type and design, controls, and raw material input are those of the source(s) analyzed to produced the emission factor. This fact should be considered, as well as the age of the information and the user's knowledge of technology advances.

3. After selecting the similar technology, go to the area of the *Dioxin Source Database* where average and congener-specific CDD/F emissions factors have been computed.

D. *If no data exist in the National Database that is relevant to a specific facility, then the Compilation of Air Pollution Emission Factors*, Fifth Edition (EPA, 1997; and subsequent

updates), should be used. This compilation was put together and is periodically updated by EPA's Office of Air Quality Planning and Standards (OAQPS), and is commonly referred to as AP-42. Care should be taken to select emission factors which were developed for technologies that best match the facility under consideration. The basic limitation of these of these data is the fact that emission factors are not usually reflective of specific emission control equipment. The AP-42 emission factors can be found in one of six chapters:

Chapter 1, External Combustion Sources
Chapter 2, Solid Waste Disposal
Chapter 3, Stationary Internal Combustion Sources
Chapter 4, Evaporative Loss Sources
Chapter 5, Petroleum Industry
Chapter 6, Organic Chemical Process Industry

Emission factors presented in AP-42 are designed for estimating emissions from a large number of sources over a wide area. They are averages of values determined at one or more individual facilities. The individual values which are used to develop the average may vary considerably. The use of AP-42 emission factors to estimate emissions from any one facility should be done with great care.

3.2.2. Use of Homologue and Congener-Specific Profiles to Estimate Emission Factors

Situations may occur in which CDD/F emissions data of classes of combustor types are reported as either homologue-groups and/or total CDDs plus CDFs. These data may, however, be most relevant to a combustion source under evaluation. Congener-specific emissions data are needed for the analyses of the ambient air impacts and deposition flux of dioxin-like compounds using air dispersion and deposition models. This is because each specific congener will have different physico-chemical properties, and this will greatly affect the modeling result. This section presents guidance on estimating congener-specific emission rates from homologue-specific and total CDD/F emissions data.

The preferred approach is to convert CDD/F homologue and total CDD/F emissions to congener-specific emissions using congener profiles developed for each source. Congener profiles are the fractional distribution of CDD/F congeners in an environmental release, in an environmental sample, or in a biological sample. Congener-specific profiles have been developed for known anthropogenic source activity in the U.S. as part of this assessment, and these profiles can be reviewed at the end of each Chapter in Volume I, *Sources of Dioxin-Like Compounds in the United States*. The following subsection 3.2.2.1 provides guidance for the use

of congener profiles to estimate congener-specific emission rates when only total CDD/F emissions data are available. In some cases no congener-specific profiles may exist for a source. Subsection 3.2.2.2 provides guidance for assuming a congener-specific emissions if at least homologue data are available.

3.2.2.1 *Using Congener Profiles to Convert Total CDD/F*

The assessor may have stack emissions data displayed as the sum of tetra through octa-CDD and CDF congener-groups, i.e., total CDDs plus CDFs. Congener-specific emissions data are needed for the most accurate assessment of potential air and deposition impacts near a source with the application of an air dispersion and deposition model. Congener-profiles derived from stack emissions data of similar combustion sources may assist this effort.

Congener profiles were determined by dividing the mean congener emission factor for the source class by the total tetra through octa-CDD and CDF emission factor for that class. All nondetects were treated as zero values. The result is an average fractional distribution (unitless) of each toxic CDD/F congener. Figure 3-1 is an example of the congener and homologue profile of typical emissions from sewage sludge incineration. In this example, the most prevalent congener in the emissions from sewage sludge incineration is OCDD. When the congener profile is plotted, OCDD is approximately 27% of the total CDD/F emissions. In this example, 2,3,7,8-TCDD is approximately 1% of total CDD/F emissions. Multiplication of the total CDD/F emission factor by the fractional distribution of each congener gives an estimate of the congener-specific emission factor for the source. For example, if it is assumed that the total CDD/F emission factor is 500 ng/kg of waste feed for a sewage sludge incinerator emissions, then the emission factor for OCDD is estimated from the congener profile to be 135 ng/kg (500 ng total CDD/F * 0.27). By this method, 2,3,7,8-TCDD would have an estimated emission factor of 5 ng/kg.

3.2.2.2 *Estimating Congener-Specific Emissions when no Congener Profiles are Available*

In some cases the congener profile may not available for a specific source of interest. This may be due to the general lack of emissions data for that particular source. However, the assessor may have information on homologue emissions from a combustion source. When only homologue emission factors are available, and no congener-specific profile exists for the source, then rough estimates of congener specific emission factors can still be made. First, an equal probability of occurrence of the specific congener is assumed based on relative proportionality. For example, 2,3,7,8-TCDD is one congener out of 22 possible congeners in the TCDD

homologue. Therefore, the probability of occurrence is assumed to be the ratio of 1/22 or 0.045. Multiplication of a total TCDD emission factor by 0.045 gives an approximation of the emission factor for 2,3,7,8-TCDD. Table 3-1 lists the number of dioxin-like congeners within a homologue group and the total number of congeners within that homologue group.

3.2.3. Estimation of Emissions of Dioxin-Like Compounds from the Hypothetical Incinerator

The emission factors for the dioxin-like compounds from the stack of the hypothetical waste incinerator were derived from actual stack monitoring and emissions testing of an incinerator burning a complex mixture of organic waste. The concentrations of the specific CDD/F congeners in units of nanograms per dry standard cubic meter (at 20° C; 1 atm.; 7% O_2) were available, as was the volume of gas escaping from the stack and feed rates for the material being combusted during the stack tests. Using procedures described in Section 3.2.1, this data was converted to emission factors. Such factors for three test runs are shown in Table 3-2. The fourth column is the average of these emission factors converted to g/sec units, which are the appropriate units for the application of the ISCST3 model. The conversion assumed a constant feed rate of 200 metric tons of feed material per day (further details on the hypothetical incinerator are found in Section 3.5). Human exposures to the coplanar PCBs emitted from a combustion source is not demonstrated in Chapter 5. Therefore, an estimation of congener-specific emission factors of coplanar PCBs for the hypothetical incinerator are not provided.

In order to put the emissions from the hypothetical waste incinerator into perspective, they can be compared with emissions from other incineration sources that are similarly controlled, e.g., equipped with scrubbers and/or fabric filters. Such air pollution control devices can reduce the amount of dioxin that is formed within the system by >99% prior to the release from the stack. In this comparison, emissions typical of waste incineration were taken from Volume 2, Chapter 3. The following types of incineration processes were used: medical waste incineration; hazardous waste incineration; sewage sludge incineration; municipal solid waste incineration, and tire incineration. For comparisons, all emissions factors are expressed in units of nanograms I-TEQ emitted from the stack per kg of waste combusted, and are presented as arithmetic mean emission factors. This should not be confused as typical of the incineration source category, but specific only to sources having scrubbers and/or fabric filters. Volume I, Chapter 3 of this assessment gives an overview of dioxin emissions from incineration technologies equipped with a variety of pollution control systems. The emissions from the

hypothetical incinerator is ranked with the other types of waste incinerators that are well controlled with some combination of a scrubber device and/or a fabric filter, as follows:

1. Medical waste incinerator:	70 ng I-TEQ/kg waste combusted
2 .Municipal solid waste incineration:	16 ng I-TEQ/kg waste combusted.
3. Sewage sludge incineration:	6.9 ng I-TEQ/kg sludge combusted
4. **Hypothetical waste incinerator:**	**4.5 ng I-TEQ/kg waste combusted**
5. Hazardous waste incineration:	3.8 ng I-TEQ/kg waste combusted.
6. Tire incineration:	0.3 ng I-TEQ/kg tires combusted.

From these comparisons it appears that the I-TEQ emission factor derived for the hypothetical incinerator lies well within the range of emission factors developed for well controlled sewage sludge and hazardous waste incinerators, but considerably lower than municipal solid waste and medical waste incinerators. The hypothetical incinerator was arbitrarily assigned a waste combustion rate of 200,000 kg waste/day (i.e., 200 tonnes/day). This charging rate conforms to a large medical waste incinerator, an average hazardous waste facility, and moderate sewage sludge and municipal waste incinerators.

3.2.4. Estimation of the Vapor Phase/Particle Phase Partitioning of Emissions of Dioxin-Like Compounds

The first step in the air modeling is the partitioning of total emissions into a vapor and a particle state. This section will review data on partitioning at the point of stack emission, in ambient air, and a theoretical approach to estimating the partitioning of dioxin- like compounds in ambient air. The true vapor/particle partitioning of dioxin under different conditions has not been directly measured, and therefore, is usually implied from these limited data or by theoretical means.

3.2.4.1. *Vapor Phase/Particulate Phase Inferences from Stack Measurements*

While the available literature is weak in this area, various investigators have made inferences on the vapor phase/particulate phase (V/P) partitioning from in-the-stack sampling of CDD/F emissions from combustion sources. Sampling systems which have been used basically consist of a particulate filter followed by a section designed to condense vapors in impinger glassware surrounded by an ice bath, and a resinous material suitable for absorbing vapor phase compounds. Depending on where the congener is distributed within the component parts of the

sampling apparatus, the investigator reports the fraction associated with particulate, and the fraction found in the vapor absorbing material. In order to collect sufficient mass of particulate for accurate analytical determination of the concentration of the recovered congener at sub-part per trillion levels of detection, it is often necessary to sample in stack for periods of four hours or longer. This introduces the possibility of movement of the collected dioxin sample from one part of the sampling train to another through adsorption, desorption, particulate blow-off, or other such phenomena as the sampling train continues to be exposed to the hot combustion gases. No real-time sampling method currently exists to instantaneously measure the concentration and physical state of the various CDD/F congeners in the fluid turbulence of the hot combustion plasma characteristic of gases from combustion traveling up a cylindrical stack. For these reasons, V/P partitioning based on stack test data is highly uncertain. Additional laboratory research is needed that is specifically directed at identifying the physical state partitioning of individual CDD/F congeners at the exit to the stack under varying temperature profiles and conditions of particulate loading and acid gas concentration. Table 3-3 is a summary of the percent distribution of CDD/Fs between the vapor-phase (V) and the particulate phase (P) as interpreted by various stack sampling techniques employed in the measurement of the compounds during incinerator operations.

Cavallaro, et al. (1982) performed a series of stack tests on six municipal solid waste (MSW) incinerators in Italy. He was one of the first investigators to interpret the V/P ratio from where the CDD/F segregated with the sampling train, e.g., the particulate filter and resinous trap. From these data, the percent distribution of congener groups were estimated. Cavallaro observed that the CDD/F emissions from the stack of the tested incinerators seemed to predominate in vapor phase. He attributed this to the possibility that the relatively high temperatures of the combustion gases during sampling (700 to 900° C) may have promoted desorption of CDD/Fs from particulate, although the sampling probe was kept at a constant 150°C.

Benfenati, et al. (1986) describes the stack testing of a modular MSW incinerator in Italy having a combustion capacity of 1500 kg/hour. The purposes of the study were to analyze the concentration of TCDD and TCDF at various points of the incineration process, to estimate the vapor phase versus the particulate phase partitioning at various sampling points corresponding to changes in temperatures, and to estimate the TCDD/F control efficiency of the pollution control device (an electrostatic precipitator). Comparisons were made between the distribution of TCDD/F after the secondary furnace in a region where combustion gas temperature was about 330°C, and the distribution at the stack where combustion gas temperature was 230° C. Benfenati observed that approximately 85% of the TCDD was in the vapor phase at the exit to

the furnace, and approximately 95% of the TCDD was in the vapor phase at the stack. It was concluded that most of the TCDD predominated in vapor phase at the point of release from the stack at the reported temperature of 230°C. However, Benfenati could not exclude the possibility that the TCDD was adsorbed onto ultra fine, submicron aerosol particles.

Tiernan, et al. (1984) reported on the distribution of CDD/Fs recovered in the stack sampling apparatus (EPA Modified Method 5) following the stack testing of a mass burn MSW incinerator operating in Japan. In the Modified Method 5 procedure, the sampling probe is maintained at a temperature of 120°C while the stack gases are isokinetically sampled. The facility was equipped with a dry scrubber combined with a fabric filter as the primary pollution control device. Tiernan observed congener-specific variability in the V/P partitioning inferred from the sampling method. However, greater than 55% of the CDD/Fs were estimated to be in vapor phase at the point of release to the stack. In an earlier stack test (Tiernan, et al., 1982) of an MSW incinerator equipped with an electrostatic precipitator, Tiernan found that 45% to 89% of the CDD/Fs were associated with particulate.

Clement, et al. (1985) stack tested a mass burn MSW incinerator operational in Canada for the emission of CDD/Fs. Three 24-hour stack samples were taken using the EPA Modified Method 5 train with a stack temperature of 230 - 250°C. The components of the sampling train were analyzed separately. Clement observed that more than 95% of the total CDD/Fs detected in the sampling train samples was found in the impingers used to condense vapor phase organic pollutants. Interpretation of this is difficult. However, it is implied from these data that most of the CDD/Fs prevailed in vapor phase.

Hagenmaier, et. al (1986) conducted field tests of two different stack test methods for the accuracy, precision, and comparability of CDD/F measurements. Both instruments were similarly constructed with a glass fiber filter for the capture of particulate-bound contaminants, a series of water or ice-cooled impingers to promote condensation of vapor phase contaminants, followed by an absorbing material to trap vapor phase pollutants. Eight parallel stack sampling experiments were carried out over a three week period using the sampling trains known as the German simple dilution method and the EPA Modified Method 5. Although the two methods reported quite similar total concentrations of CDD/Fs, the distribution of CDD/Fs between the heated glass filter, and ice-cooled impingers and the sorbent trap were remarkably different. In one train, referred to as Train A by Hagenmaier, the temperature in the filter housing was 140° C, and in the second train, Train B, the temperature was 90° C. The stack gas temperature in both cases was 230° C. Hagenmaier found that the percentage of CDD/Fs in the glass fiber filter was markedly greater in Train B than in Train A. Up to 93% of the PCDDs and 90% of the

PCDFs were detected in the particulate filter in Train B. By comparison, 73% and 58% of PCDDs and PCDFs, respectively, were detected in the particulate filter in Train A. Although Hagenmaier's data is used in Table 3-3, Hagenmaier theorized that this difference in the distribution of CDD/Fs in the two sampling trains was due to the differences in the temperature of the glass fiber filter housing.

EPA (1990a) conducted a field validation study for the EPA stack testing Method 23 (the Modified Method 5) for the collection and retention efficiency of CDD/Fs. A carbon-13 labelled congener was metered into the sampling probe just preceding the glass fiber filter using a dynamic spiking system. The validation procedure involved the isokinetic sampling in the stack of a large mass burn MSW incinerator. Sampling *in situ* in the stack while using a dynamic spiking system demonstrated that most of the isotope was recovered in the filter trap and front half of the sampling train designed to capture particulate, and a lower amount was recovered in the XAD resin designed to capture vapor phase organic compounds. In the particular tests in which the overall percent recovery of the dynamic spike were found to be acceptable, the XAD resin and condensor contained about 49% of the isotope, and 51% was associated with carbonaceous particulate.

3.2.4.2. *Discussion of Vapor/Particle Ratios Derived from Stack Testing Methods*

It is apparent that the stack sampling method gives inconclusive and contradictory evidence of the V/P partitioning of CDD/Fs at the stack of incinerators. Although most of the researchers report finding the greatest quantity of CDD/Fs captured within the resinous material having the physical/chemical properties of absorbing vapor phase organic compounds, a few studies have reported the opposite. What is unusual about the V/P distributions in Table 3-3 is the lack of complete consistency despite the similarity of sampling method. Although the stack gas temperatures may vary, the probe and housing to the sampling instrument is usually kept at a standard temperature while traversing the hot flue gas. A more consistent pattern of V/P should have emerged.

Hagenmaier, et al. (1986) has postulated that, depending on the temperature of the glass fiber particulate filter housing, the CDD/Fs might desorb (volatilize) from particulate matter trapped in the filter during the 4 hours of sampling time required of the stack sampling method. Therefore, Hagenmaier does not believe that the distribution of CDD/Fs between the particulate filter, the condensing impingers, and the vapor absorber gives a true indication of the V/P partitioning of these compounds at the stack.

Tests also have been devised by the EPA (1990a) to study the effect a change in temperature of the glass fiber filter housing might have on the distribution of CDD/Fs in the sampling train. During the sampling period, two sampling trains were used: one inlet to the electrostatic precipitator (ESP), and the other placed near the outlet to the ESP. Temperatures of the filter housing were raised from the standard 120° C to 215° C in both sampling trains. In agreement with the observations of Hagenmaier, et al. (1986), an increase in temperature generally resulted in a change in the distribution of the recovered 13-C labelled CDD/F congeners. However, the temperature effect was most apparent within the sampling train inlet to the ESP. In the inlet sampling train, the higher filter box temperature increased the relative percentage of CDD/Fs trapped in the impingers and XAD-2 resin. An amount estimated to be in the vapor phase, based on the segregation of the compounds within the component parts of inlet sampling train, is as follows (with a range listed from low to high temperature): TCDD = 20 - 55% vapor; HxCDD = 10 - 30% vapor; OCDD = 5 - 18% vapor; HxCDF = 18 - 58% vapor; OCDF = 5 - 18% vapor. In the outlet sampling train (characteristic of stack emissions), this dramatic shifting of the congeners from the filter to the XAD-2 did not occur with an increase in temperature. Interpretation of the vapor phase partitioning in the outlet sampling train from low to high temperatures was as follows: TCDD = 90 - 95% vapor; HxCDD = 85 - 90% vapor; HxCDF = 90 - 95% vapor; OCDD = 75 - 90% vapor; OCDF = 78 - 90% vapor. Both these interpretations were developed using a 500 ng CDD/F spiked congener. Notice that the vapor phase to particle phase ratio is significantly different between the inlet and outlet sampling trains: in the inlet train most of the CDD/F congeners seemed to predominate in the particle phase at the standard temperature of the filter housing, whereas in the outlet train most of the CDD/F congeners seemed to predominate in the vapor phase, as interpreted by the distribution within the apparatus.

The temperature-dependent partitioning has recently been observed by Janssens, et al. (1992) during field validation studies involving the sampling of operating incinerators in Belgium. Janssens observed that the fraction of CDD/Fs collected in the heated portion of the particulate glass filter (temperatures in the range of 250 to 300° C) showed an expected partitioning according to the vapor pressures of the compounds. It was found that a very low proportion of the CDD/Fs were found in the particle phase; nearly all the compounds were detected in the vapor phase. Moreover, Janssens observed that higher temperatures seemed to favor the vaporous state of the lower chlorinated congeners (compounds having one to five chlorines on the aromatic ring), and the particulate phase for higher chlorinated congeners (five to eight chlorines). This agrees well with the decrease in vapor pressures that occurs with an

increase in chlorination, and an increase in vapor pressure that occurs with a decrease in chlorination of CDD/Fs. Adding to the theory of Hagenmaier, et al. (1986), Janssens believed that either the sampling apparatus was giving a true distribution of the V/P ratio of individual congeners, or that a significant portion of the congeners were reversibly sorbed onto particulate surfaces and could be eluded to vapor phase by the passage of the volume of sampled combustion gas over a lengthy time interval, neither of which could be proven by his study.

Benfenati, et al. (1986) has suggested that what may be reported as vapor phase may actually consist of nucleated aerosol particles having diameters less than 0.1 micrometers. The impingers in the sampling method are located a few centimeters behind the heated particulate glass fiber filter, and are bathed in an ice bath. The dramatic reduction in temperature within the impinger glassware may cause sublimation from vapor phase to nucleation of aerosol particles. Downstream of the impingers is the vapor absorbing material, usually XAD-2 resin. Although this has been shown to be an excellent trap for semi-volatile organic compounds, the retention of submicron size particles with CDD/Fs adsorbed onto the surfaces, or absorbed into the interior spaces, cannot be ruled out or excluded as a possible explanation for investigators reporting a preponderance of concentration both in the impingers and the vapor trap.

Complicating any meaningful interpretation of the data is the long duration of sampling time required in the stack measurement method. In order to reach a sub-ppt level of detection of CDD/Fs for reliable quantification of specific congeners, sampling proceeds until approximately a five gram mass of particulate is gathered in the particulate filter. This may require *in situ* placement of the sampling apparatus such that samples are taken isokinetically, and the stack interior diameter is traversed for four or more hours. Thus the sampling instrument is continuously exposed to the hot gas plasma over a long sampling moment. In addition the hot gases also contain precursor compounds, chlorides, oxides of sulfur and HCl which may have an effect on the success of accurately sampling CDD/Fs. Although Janssens, et al. (1992), Hagenmaier, et al. (1986), and EPA (1990a) have all but excluded the possibility that sampling under these conditions creates results by producing CDD/Fs or destroying CDD/Fs somewhere within the sampling train, the possibility that the method creates an illusion of the true V/P ratio cannot be excluded.

The above discussions have indicated the variability in the data and the uncertainty with the stack results of vapor/particle partitioning. For these reasons, these data will not be used to infer the V/P distribution of CDD/Fs at the point of release from the stack.

3.2.4.3. *Vapor/Particle Partitioning of CDD/Fs from Ambient Air Sampling*

The measurement of CDD/Fs in air under ambient conditions has only been achieved since the late 1980's. The ambient air sampler which is most often used to estimate particulate and gaseous fractions consists of a glass or quartz fiber filter followed by a sorbent trap such as polyurethane foam (PUF), XAD resins, or a combination of the two. These are active samplers which utilize electric pumps to draw air through the collector at approximately 0.2 - 0.6 m^3/min. This provides sample volumes of 300 - 600 m^3 in a 24-h period, although longer sampling times are not uncommon. The phase distribution is estimated from the segregation of compounds on the filter and sorbent trap, which are assumed to capture compounds that are particulate and gaseous, respectively. PUF is capable of collecting many semivolatile compounds with high efficiency (Bidleman, 1987; Hart and Pankow, 1994; Pankow, 1989; Tashiro et al., 1989; Wagel, et al., 1989), although its usefulness is limited by the vapor pressure of the compound. Examples of compounds for which PUF can be used are the tetrachloro- and higher CDD/Fs, and three-ring and heavier PAHs and PCBs having three or more chlorines. The more volatile members of these classes as well as chlorobenzenes and chlorophenols are collected with greater efficiency by XAD and similar resins (Bidleman, 1987; Hart and Pankow, 1994; Hornbuckle et al., 1993; Patton et al., 1992; Zaranski et al., 1991). The glass fiber filters used in air samplers are rated to collect particles of diameters $\geq$0.3 micrometer, with 99.9% collection efficiency.

Filtration samplers are subject to artifacts which include loss of organic compounds from the particles on the filter by volatilization ("blow-off") (Eatough et al., 1993; Gundel et al., 1995; Lane et al., 1988; Lewis et al., 1991; Subramanyam et al., 1994) and sorption of gaseous compounds to the particle mass collected on the filter and to the filter itself (Cotham and Bidleman, 1992; Hart and Pankow, 1994; McDow et al., 1990; Turpin et al., 1994). The possibility of blow-off losses are recognized and discussed extensively in the literature, but there is disagreement as to how seriously this artifact will bias estimated particle/gas distributions.

Because sampling of CDD/Fs is not instantaneous (i.e., real time measurement), but requires 24+hour air sampling to assure a level of detection of about 0.03 pg/m^3, the V/P ratios described in this section should be considered as “operationally defined”. Operationally defined are relative and not absolute vapor phase and particle bound phase partitioning behavior within the design contraints of the measurment method. The following is a review of ambient air sampling data on the relative V/P partitioning of CDD/F congeners at ambient temperatures. Table 3-4 provides a summary of the particle percentages (vapor percentage = 100 - particle percentage) inferred from these reports.

Oehme, et al. (1986) first described a method sensitive enough for the congener-specific measurement of CDD/Fs at 0.1 pg/m^3 levels of detection in ambient air. Such low levels of detection introduced the possibility of taking ambient air samples in the vicinity of known combustion sources of CDD/Fs to reliably establish an association with stack emissions. Oehme tested the performance and reliability of an ambient air sampler consisting of a glass fiber filter followed by a polyurethane foam plug. Ambient air was sampled over a predetermined period after first spiking the filter with a known concentration of $^{13}C_{12}$ labelled CDD/F standards. This experiment was designed to determine the percent of the initial spiked labelled standard that could be recovered from the sampler after sampling 1000 m^3 of ambient air. The percent recovery of the standard was a measure of the collection and retention efficiency of the sampler. After collecting a sample, the particulate filter and the PUF plugs were extracted and analyzed separately. This was done in order to establish the particle phase and vapor phase partitioning of the CDD/F congeners. Oehme demonstrated that the sampling method was capable of a high degree of reliability in sampling sub-part per trillion concentrations of CDD/Fs as indicated by highly satisfactory recovery of the isotopically labelled standards in the apparatus, e.g., 88 - 102% recoveries. From the results of separately analyzing the filter and the PUF, Oehme postulated on the typical distribution of CDD/Fs between vapor and particles in ambient air. They suggested that TCDF and PeCDF were mainly present in the vapor phase, and HxCDD, HxCDF as well as the less volatile isomers of HpCDF, HpCDD, OCDF, and OCDD, were mainly present in the particle phase. Oehme took over 60 ambient air samples with this device in rural, suburban, and urban areas of Europe.

Eitzer and Hites (1989) reported on the measurement of CDD/Fs in the ambient atmosphere of Bloomington, Indiana while using a similarly configured ambient air sampling method, the General Metals Works PS-1 sampler. Ambient air is drawn through a glass fiber filter followed by a polyurethane foam plug (PUF). This was a long-term study designed to investigate the daily and seasonal variability of the compounds in the ambient air as measured at a single location, and to examine the vapor-phase, particulate-phase partitioning of the chlorinated congeners under ambient conditions. Samples were taken at four different sites over a 2-3 day sampling period until 1500 to 2400 m^3 of ambient air volume had passed through the apparatus. Sampling was conducted monthly from August, 1985 through July, 1986. The quantitative method produced a limit of detection of the individual chlorinated congeners in the range of ~1 femtogram/m^3. Eitzer and Hites (1989) operationally defined the vapor-phase/particle-bound phase of the chlorinated congeners as any compounds found in the PUF plug and the glass fiber filter, respectively. The V/P ratio was subject to certain restrictions of

the sampling method, which the authors identified as: 1. Particles smaller than 0.1 microns would pass through the filter paper of the glass fiber particulate filter and be absorbed into the polyurethane foam; 2. Diurnal temperature variation could cause particle-bound CDD/Fs collected and retained in the filter to vaporize and be "blown-off" to the PUF plug by the passage of the sampled air stream; 3. At these relatively large sampling volumes of ambient air, it is possible that some breakthrough on the PUF plug occurs, and a portion of the CDD/F sample is lost. The investigators were able to rule-out the latter condition through the addition of a XAD-2 resin trap after the PUF. This was one of the first reports on the congener-specific V/P partitioning in the ambient air under variable average ambient temperatures. Although they could find no seasonal effect on the total concentrations of CDD/Fs, seasonal change in temperature did affect the V/P ratio. It was noted that during the warm summer months the V/P ratio was as great as 2:1, and during the cold winter months the V/P ratio could be <0.5. Thus, at warm temperatures most of the lower chlorinated congeners, e.g., mono through penta-chlorinated CDD/Fs, were mostly found in the vapor phase and the hexa - octachlorinated congeners were mostly particulate-bound. The colder winter temperatures produced the effect of causing the lower chlorinated species to partition more onto airborne particles. The higher chlorinated congeners, e.g., hexa-, hepta-, and octa-CDD/Fs, mostly were found to be particle-bound at both the warm and cold temperatures. These quantitative results of the V/P ratio of individual congeners at three ambient air temperatures (3° C, 16 - 20° C, and >28° C) was again reported by Hites (1991), as shown in Table 3-4. Through these analyses, Eitzer and Hites (1989) and Hites (1991) found two dependant variables controlled the V/P ratio in ambient air: 1. the ambient air temperature; and 2. the vapor pressures of the CDD/F congeners. The authors concluded that because the lower chlorinated compounds have higher vapor pressures, they will be found mostly in the vapor phase, and because the higher chlorinated congeners have lower vapor pressures, they will prevail in the ambient air bound to particulate matter.

Wagel, et al. (1989) reported on the performance of the General Metals Works PS-1 sampler for the collection and retention of CDD/Fs while sampling ambient air. This sampler configuration consists of a quartz glass fiber filter followed by a polyurethane foam (PUF) plug, and the investigators added an XAD-2 resin cartridge after the PUF. The addition of the XAD was a check on whether breakthrough of any CDD/F congeners occurred from the PUF during sampling. The PS-1 is the sampler most often used in the U.S. to quantify CDD/Fs in air under ambient conditions. The protocol of this research was to use two samplers co-located. The particulate filter of one sampler was spiked with $^{13}C_{12}$-labelled CDD/F congeners while the second sampler was used to provide background measurements of native (non-labelled) CDD/Fs.

Both units were operated to sample ambient air for 24-hours. The average ambient temperature during the sampling period was 24° C. Following the sampling the filter and PUF were removed and extracted according to published procedures (Wagel, et al., 1989). Performance of the PS-1 sampler was reported as percent recovery of the labeled standards initially spiked onto the particulate filter. The percent recovery was calculated by subtracting the background contributions from the total detected spike concentration and dividing by the concentration of the labeled standard initially added to the filter. The percent recoveries were reported in a range of from 85% to 124%, with an average recovery of 102%. This indicated a high degree of reliability in collecting and retaining CDD/Fs in the sampler during the 24-hr sampling period.

A second series of experiments were conducted to investigate the distribution of CDD/Fs within the sampling apparatus, e.g., the particulate filter versus the PUF plug, by extracting and analyzing the filter and PUF separately. Subject to the caveats previously discussed, the investigators made observations regarding the V/P ratio of CDD/F congeners. It was observed that CDD/Fs having 7-8 chlorines were mostly detected in the particulate filter, and lower chlorinated species were mostly detected in the PUF. Wagel, et al. (1989) suggested that it was possible that the lower chlorinated congeners volatilized from the particulate filter (somewhat affected by the rate of flow of the sampled air volume), and then were retained by the PUF. Furthermore, Wagel, et al. (1989) warned that if results of separately analyzing the filter and PUF are used to derive a vapor phase and particle phase partitioning of the CDD/Fs under ambient conditions, then this may give erroneously high estimates of the amount present in vapor phase.

Harless and Lewis (1992) have quantitatively evaluated the performance of the General Metals Works PS-1 sampler for the trace-level measurement of CDD/Fs in ambient air, adding to the growing evidence that results are actual measurements and not an artifact of the sampling method. In this study, three samplers were used in the same general vicinity, and were operated for a 24-hour period until an air volume of 350 - 400 m^3 had passed through the system. The quartz glass fiber particulate filters of two of the samplers were then spiked with $^{13}C_{12}$ labeled CDD/F congener with a known concentration after the 24-hour sampling period. The three samplers were then operated another 24-hours. The samplers were then shut down, and the filters and PUF plugs were removed and extracted and analyzed for CDD/Fs separately according to prescribed procedures. A separate series of experiments involved precleaning the glass fiber particulate filters, and adding the isotopically labeled CDD/F spike to the filter prior to sampling for seven days until about 2660 m^3 of ambient air had been sampled. Results of this study confirmed the accuracy and reliability of the PS-1 sampler for collecting and retaining

CDD/Fs at sub-ppt concentrations in ambient air. Performance was defined as the percent of the initial concentration of the labelled isotope recovered in the sampling apparatus following the operation over the predetermined sampling period. The average efficiency of recovery of the 0.8 ng $^{13}C_{12}$-1,2,3,4,-TCDD isotope that was spiked onto the filter prior to sampling was 91%, and similar efficiencies were observed for the recovery of the other labeled CDD/Fs. Additionally, Harless and Lewis (1992) used the spiking system to observe the distribution of CDD/Fs in the filter and the PUF after sampling 400 m^3 of ambient air. It was observed that most of the hepta-, and octa-CDD/Fs were retained by the glass fiber filter, indicating that these compounds were retained and not blown off the filter, and most of the tetra-, penta-, and hexa-CDD/Fs volatilized and were collected by the PUF plug. When partitioning was observed on a congener-specific basis, significant differences were observed in the V/P ratio, as shown in Table 3-4.

Hunt and Maisel (1990) reported on the ambient air measurement of CDD/Fs in a northeastern U.S. urban coastal environment during the fall and winter seasons. Isomer-specific sampling was conducted with the General Metal Works PS-1 sampler in and around Bridgeport, Connecticut from November, 1987 through January, 1988. Nine sampling sessions consisting of a total of 43 ambient air samples were taken in this study. Each sampling session was conducted either over a 24-hour or 72-hour period until about 350 m^3 and 600 m^3 of air volume had passed through the sampler. Hunt and Maisel (1990) reported on the typical vapor phase/particle bound partitioning of individual congeners during cold ambient air temperatures. The V/P ratio was based on the results of separately analyzing the PUF plugs and the glass fiber particulate filters for the presence of CDD/Fs. From these data, the investigators concluded that greater than 92% of all the congeners of CDD/Fs were particulate bound (operationally defined as detected in the particulate filter). The 2,3,7,8-TCDD isomer was not detected in any of the 43 collected samples (reported limit of detection was 5-20 fg/m^3). The particulate bound distribution (reported as a percent of the detected concentration) for some of the other congeners were as follows: 2,3,7,8-TCDF = 93%; 1,2,3,7,8-PeCDF = 94%; 2,3,4,7,8-PeCDF = 99%; 1,2,3,4,7,8-HxCDF = 97%; 1,2,3,4,6,7,8-HpCDF = 100%; 1,2,3,6,7,8-HxCDD = 96%; and the 1,2,3,4,6,7,8-HpCDD = 92%. The vapor phase/ particle bound distribution observed in this study is probably controlled by the cold January temperatures from which these observations were derived (average temperature = -5° C).

At a later date, Hunt and Maisel (1992) conducted ambient air monitoring of CDD/Fs in multiple locations in the warm climate of southern California for the State of California Air Resources Board (CARB). Ambient air samplers, e.g., the General Metal Works PS-1 sampler, were primarily placed in areas of high population density that contained known combustion

sources of CDD/Fs, but sites were also sampled that were considered removed from the influences of any local sources. The purpose of the study was to evaluate the congener-specific spacial distribution of CDD/Fs in ambient air near environmental sources of the compounds, and in remote locations, in order to provide a baseline to evaluate population exposures within the region. Monitoring sites were established at eight locations in the South Coast Air Basin in and around the city of Los Angeles. Nine discrete sample sets were collected from December, 1987 through March, 1989. The authors defined a sample set as consisting of five to seven stations at which one or two co-located samplers were operated. Microscale meteorological data was collected during sampling to include wind speed, wind direction, barometric pressure, and temperature. One sampling site was chosen to investigate the distribution of CDD/Fs in ambient air where average ambient temperatures ranged from 16-20°C. This was done by the usual procedure of separately analyzing the filter and the PUF and making the assumption that what is detected in the glass fiber filter is particulate bound, and what is trapped in the PUF is in vapor phase. The authors noted that under these conditions, the V/P partitioning is operationally defined by the ambient air sampling system, and therefore may not be a true indication of the partitioning in the atmosphere. The majority of the hexa through octa CDD/F congeners were detected in the filter, and the authors observed that they were mainly associated with particulate matter. The authors found these observations were consistent with the V/P ratio observed by Eitzer and Hites (1989) in warm climate conditions. In addition, the authors noted that these observations give further evidence that vapor pressures of the specific CDD/F compounds and ambient air temperatures strongly influence the V/P partitioning. Therefore the tetra- and penta-CDD/Fs are expected to predominate in vapor phase during warm seasons. However, during the cold temperatures of the winter season these congeners are expected to be primarily associated with particulate matter in the ambient air.

Bobet, et. al. (1990) reported the results of an ambient air monitoring network operated by Environment Canada to temporally measure CDD/Fs in the ambient air in southwestern Ontario, Canada. The intent of the study was to monitor possible environmental impacts of a large refuse-derived fuel municipal waste combustor operational in the City of Detroit, Michigan. The ambient air monitoring network consisted on two stations, one in Windsor, Ontario, and the other located in the Walpol Island Indian Reservation 18 km to the northeast of Windsor. The former site was considered in an urban area near the expected point of maximum impact from the stack emissions from the MWC, and the other site was considered rural, and away from the influence of any stationary combustion source. CDD/F samples were collected once every 24 days using an high-volume ambient air sampler consisting of a Teflon-coated

glass fiber particulate filter and a PUF adsorbent trap. Ambient air was sampled over a 24-hour period from July, 1987 to August, 1988 with a total sample volume of 800 - 1000 m^3 of air. From August on, the samplers were operated over a 48-hour period, and 1600 - 2000 m^3 of air passed through the sampler. Mean total concentrations of CDD/Fs were compared between the urban and rural sites, and Bobet observed that concentrations measured at the urban site were 4 - 20 times greater than at the rural site. Additionally, the V/P partitioning of CDD/Fs (as operationally defined by detection in the PUF verses detection in the filter) was investigated at both sampling stations. Bobet stated that the V/P may be influenced by "blow-off" of particulate from the filter to the PUF, and/or the passage of particulate matter <0.1 microns from the filter to the PUF, and if this is the case, then the vapor phase partitioning may be too great as interpreted by the method. Under these circumstances the authors suggested that the V/P partitioning should be considered as roughly representative of the vapor/particulate phases in the ambient air. On a total concentration basis, and on a total of 12 separate ambient air samples, the investigators found the following average percent vapor phase versus percent particle phase partitioning of the CDD/F homologues at the Windsor, Ontario station: TCDD = not detected; PeCDD = 100% V/ 0% P; HxCDD = 35% V/ 65% P; HpCDD = 18% V/ 82% P; OCDD = 0% V/100% P; TCDF = 80% V/20% P; PeCDF = 29% V/ 71% P; HxCDF = 0% V/100% P; HpCDF = 0% V/ 100% P; OCDF = 0% V/ 100% P. At the rural Walpole Island station, no TCDD, PeCDD or TCDF - OCDF were detected in any of the 5 separate ambient air samples. All of the detected HxCDD, HpCDD and OCDD was found in the particulate filter indicating a V/P distribution of 0% V/ 100% P for these compounds. The authors did not report the average ambient air temperature at the two stations.

Welsch-Paulsch et al. (1995) presented results of an experiment in Bayreuth, Germany in which grass was grown in a greenhouse and outdoors on soils having different concentrations of CDD/Fs. The purpose of the experiment was to determine the pathways by which these compounds accumulate in the grass. The principal finding of this study was that dry gaseous deposition, rather than particle deposition or soil-to-plant transfer, explained the concentrations of CDD/Fs in the grass. A subset of these data included measurements of CDD/Fs in the particle and gas phases using a glass fiber filter - XAD resin sampler. Samples were collected over two-week integration times during July - August 1991 when the average air temperature was 18ºC. The particulate percentages determined in the study showed a predominance of tetra- and penta-CDD/Fs in the gas phase, approximately equal percentages of the hexa-CDD/Fs in the gas phase and associated with particles, and most of the hepta- and octa-CDD/Fs in the particle phase.

3.2.4.4. *Discussion of the Vapor/Particle Partitioning in Ambient Air Sampling Studies*

The studies that have been reviewed here indicate the following:

• The high-volume ambient air sampler consisting of a glass fiber particulate filter and polyurethane foam absorbent trap is a reliable method for the collection and retention of CDD/Fs in ambient air.

• Current analytical methods assure detection limits, on a congener specific basis, of about 1 - 10 fg/m^3.

• Experiments involving the recovery of isotopically labeled CDD/Fs within the sampler after 24-hours operation indicate that the sampler does not create artifacts representative of either sample losses or the synthesis of dioxin.

• Because the sampler is not artificially heated or cooled, but is allowed to operate at existing ambient air temperatures during sampling sessions, the method can be used to imply the vapor phase and particle bound partitioning of CDD/Fs in ambient air. This is accomplished by separately extracting and analyzing the glass fiber filter and the polyurethane foam for the presence of CDD/F congeners.

• However, the V/P ratio interpreted from these results is operationally defined. This will only give an approximate indication of the V/P ratio since mass transfer between the particulate matter on the filter and the vapor trap cannot be ruled out. The glass fiber filter will collect particles $\geq$ 0.1 microns in diameter, and therefore it is possible that aerosol particles with smaller diameters will pass through the filter and be trapped in the polyurethane foam plug. If this is the case, the percent observed in vapor phase will be overestimated. The method involves ambient air sampling at a relatively high sample volume, around 300-400 m^3 of air, over a 24-hour period. It is possible that a portion of the CDD/Fs that are sorbed to particulate matter captured by the filter may be volatilized by changes in ambient temperature, and carried with the air flow to the PUF sorbent trap (blow-off effect). If this were to occur, the observed vapor-phase fraction of the CDD/Fs would be an over-estimate (or equivalently, the observed particulate fraction would be underestimated). Unfortunately there are no empirical data that have demonstrated that any of these effects may actually occur.

3.2.4.5. *Junge-Pankow Model of Particle/Gas Distribution in Ambient Air*

A relationship first proposed by Junge (1977) and later reviewed and critically evaluated by Pankow (1987) is the most widely used model for estimating the adsorption of semivolatile compounds to aerosols:

$$\phi = \frac{c\,\Theta}{p^{\circ}_{L} + c\,\Theta} \qquad (3\text{-}3)$$

where:

ϕ	=	fraction of the compound adsorbed to aerosol particles
p°_{L}	=	saturation liquid phase vapor pressure of the pure compound at ambient temperature, Pa
Θ	=	the particle surface area per unit volume of air, cm^2 aerosol/cm^3 air
c	=	a constant which is related to the difference between the heat of desorption from the particle surface, Q_d, and the heat of vaporization of the compound, Q_v. The value of c is often estimated at 17.2 Pa-cm

Pankow (1987) argued that different values of Q_d - Q_v (and therefore c) may be appropriate for different classes of compounds.

Although Junge (1977) did not specify the physical state of the sorbing compound in Equation (3-3), field and laboratory studies of the particle/gas distribution of PAHs and organochlorine compounds indicate that the process is better described by using the vapor pressure of the subcooled liquid rather than the solid-phase vapor pressure (p^{o}_{S}) (Bidleman et al., 1986; Cotham and Bidleman, 1992; Foreman and Bidleman, 1987). The two vapor pressures are related by:

$$\ln \frac{p^{\circ}_{L}}{p^{\circ}_{S}} = \frac{\Delta S_f (T_m - T)}{RT} \qquad (3\text{-}4)$$

where:

p°_{L}	=	liquid sub-cooled vapor pressure of the pure compund, Pa
p°_{S}	=	crystalline solid phase vapor pressure of the pure compound, Pa
ΔS_f	=	the entropy of fusion, J/mol-K
T_m	=	the melting point of the compound, K
T	=	is the ambient temperature, K
R	=	ideal gas constant, 8.314 J/mol-K.

Values of ΔS_f have been summarized for CDD/Fs (Rordorf, 1989) and other semivolatile compounds (Hinckley et al., 1990). In the absence of an experimental value, an average $\Delta S_f/R$ = 6.79 is often used (Hinckley et al., 1990), and it is used in this assessment. Liquid-phase vapor pressures have also been estimated for PCBs, PAHs, CDD/Fs and organochlorine pesticides by capillary gas chromatography (Falconer and Bidleman, 1994; Eitzer and Hites, 1988; Eitzer and Hites, 1989; Hinckley et al., 1990; Yamasaki et al., 1984). The hypothesis that p^o_L controls sorption to aerosols is especially significant for CDD/Fs, as many of these compounds have high melting points and thus large differences between p^o_L and p^o_S.

Estimates of θ are given by Bidleman (1988), based on a study by Whitby (1978) of the size distribution of accumulation mode aerosols. Whitby also estimated the average total volume of particles per unit volume of air (V_T = cm^3 aerosol/cm^3 air). Values of θ and V_T are given in Table 3-5. From V_T and an assumed particle density of 1.4 g/cm^3, the average TSP concentrations in urban and average background air are 98 and 42 μg/m^3. These can be compared to average monitored TSP concentrations of 79 and 30 μg/m^3 in 46 U.S. cities and 20 rural locations in 1975 (Shah et al., 1986). Similar calculations using values of θ yield estimates of the aerosol specific surface area (A_{tsp}) of 11 m^2/g in urban air and 3.6 m^2/g in average background air (Bidleman, 1988). Measurements of A_{tsp} from particles collected on glass fiber filters were 1.9 - 3.1 m^2/g in Pittsburgh, Pennsylvania (Corn et al., 1971) and 2.3 - 8.7 m^2/g in Portland, Oregon (Sheffield and Pankow, 1994). The latter authors noted that particles tended to agglomerate to a greater extent on teflon membrane filters than on glass fiber filters, and that experimentally determined specific surface areas were higher on the glass fiber filters. This suggests that values of A_{tsp} measured on filtered particles may be biased on the low side, although more data are needed in this regard.

The particulate fraction can also be expressed by:

$$\phi = \frac{C_p\ (\ TSP\ )}{C_g + C_p\ (\ TSP\ )} \qquad (3\text{-}5)$$

where:

ϕ = fraction of the compound adsorbed to aerosol particles

C_p = the concentration of semivolatile compounds associated with aerosols, ng/μg particles

C_g = the gas-phase concentration, ng/m^3

TSP = the total suspended particle concentration, $\mu g/m^3$

Equation (3-5) is a general relationship that applies to any experimental or model estimate of C_g and C_p. Combining Equations (3-3) and (3-5) yields:

$$Log \frac{C_p}{C_g} = Log\ K_p = Log \frac{c\ \theta}{TSP} - Log\ p^\circ_L \quad (3\text{-}6)$$

Here and in other work (Falconer et al., 1995; Kamens et al., 1995; Hart and Pankow, 1994; Pankow and Bidleman, 1992) C_p/C_g is referred to as the particle/gas partition coefficient, K_p ($m^3/\mu g$). Its inverse, $C_g/C_p = 1/K_p$, has also been used for these correlations (Cotham and Bidleman, 1992). According to Equation (3-6), the expected slope of log K_p vs. log p^o_L is -1 and the intercept is related to the specific surface area of the aerosol A_{tsp} (m^2/g) = $10^8\theta$/TSP. Plots of log K_p vs. log p^o_L for partitioning data obtained with filtration air samplers are usually well correlated and follow the general relationship:

$$Log\ K_p = m\ Log\ p^\circ_L + b \quad (3\text{-}7)$$

It is often the case that m $\neq$ -1 because of kinetic limitations and/or sampling artifacts. In these situations the intercept b is partially dependent on the slope and cannot be used to estimate θ (Pankow and Bidleman, 1992).

3.2.4.6. *Modeling the Vapor/Particle (V/P) Distribution of CDD/Fs*

A portion of the semivolatile compounds found in ambient air appears to be freely exchangeable between the particulate and gaseous phases. A second portion, the "non-exchangeable" fraction, may be irreversibly sorbed or occluded by the aerosols and not in equilibrium with the corresponding gas phase (Bidleman, 1988; Pankow, 1988; Pankow and Bidleman, 1991, 1992). In this procedure methodology document, it is assumed that all compounds emitted from combustion sources are freely exchangeable unless information exists otherwise.

The first step in the modeling of the V/P distribution is to determine the sub-cooled liquid vapor pressure for the CDD/Fs. Eitzer and Hites (1988,1989) used a capillary GC method to

determine liquid-phase vapor pressures for 63 CDD/F congeners. These measured values will be used to develop the V/P partitioning for the dioxin-like compounds in this assessment. The $p°_L$ given in these references are measurements at 25°C. This section will outline a procedure for calculating the $p°_L$ at different temperatures. The V/P calculations of this assessment assume an ambient temperature of 20 °C, necessitating a conversion of $p°_L$ from 25 to 20°C. Finally, this section will also show the calculation of the $p°_L$ based on the crystalline solid phase vapor pressures, $p°_S$. These calculated $p°_L$ will be compared against the measured $p°_L$.

Table 3-6 lists the crystalline solid vapor pressure, p^o_S, at 25°C for the seventeen CDD/F congeners having dioxin-like toxicity. These values of p^o_S were judged as the most appropriate from available reportings in the literature in Chapter 2 of Volume I. They were used in conjunction with Equation (3-4) above to calculate $p°_L$ at 25°C, also shown in Table 3-6. Finally, Table 3-6 gives the p^o_L values at 25°C, which were reported in Eitzer and Hites (1988, 1989).

As seen in Table 3-6, the calculated $p°_L$ were generally less the measured $p°_L$. On the average, the calculated $p°_L$ was 60% of the measured $p°_L$. This assessment will use the measured $p°_L$, which is thought to be preferable to using the modeled values.

These vapor pressures can be corrected to ambient, or any, temperature by the following procedure. The relationship between the liquid sub-cooled vapor pressure and temperature (°K) is (Hinckley, et al., 1990):

$$Log\ p°_L = \frac{-Q_v}{2.303\ R\ T} + b \qquad (3\text{-}8)$$

where:

$p°_L$	=	sub-cooled liquid vapor pressure of the pure compund, Pa
Q_v	=	the latent heat of vaporization, J/mol
R	=	ideal gas constant, 8.314 J/mol-K
T	=	temperature, K
b	=	intercept (related to entropy of vaporization)

The capillary GC method of Eitzer and Hites (1988) provides the temperature coefficient of vapor pressure, expressed by them as the ratio of the heats of vaporization for CDD/Fs to p,p'-DDT: Qv (CDD/Fs)/Qv (DDT). The authors determined these ratios for 14 CDD/F congeners,

including 13 of the ones listed in Table 3-6. For the remaining 4 congeners, it was assumed that Qv (CDD/Fs)/Qv (DDT) were the same as for other members of the same homolog group (e.g., the ratio for 2,3,7,8-TCDD was the same as for 1,2,3,4-TCDD). OCDF was assumed to have the same ratio as OCDD. The value of -Qv/2.303R for p,p'-DDT is -4640 (Hinckley, et al., 1990). This was used with the information given by Eitzer and Hites (1988) to estimate the temperature coefficients of vapor pressure for the CDD/Fs. For example, Eitzer and Hites (1988) give the ratio Qv (2,3,7,8-TCDF)/Qv(DDT) = 0.947. Thus the value of -Qv/2.303R for 2,3,7,8-TCDF = -4640(0.947) = -4394. This quantity can be used as the slope of Equation (3-6) for this congener: log $p°_L$ (2,3,7,8-TCDF) = -4394/T = b.

The next step in the procedure is to estimate the constant, b, of Equation (3-8). This can be accomplished given the slope (as just calculated), and a known (or calculated) $p°_L$, and the temperature associated with that $p°_L$. For example, the measured $p°_L$ of 2378-TCDF at 25 °C, is $1.23*10^{-4}$ Pa (Eitzer and Hites, 1988). Substituting -4394, T = 298 °K, and log p^o_L = -3.910 into Equation (3-6) yields a value for b, 10.83. Therefore, one now has an equation for the vapor pressure of 2378-TCDF as a function of temperature: Log p^o_L (2,3,7,8-TCDF) = 10.83 - 4394/T. In this manner, values of b were derived for all the 17 dioxin-like congeners, and these are shown in Table 3-6. It is importantly noted that all these b were developed from the measured values of the $p°_L$, not the modeled values calculated from the crystalline solid vapor pressure, p^o_S. Therefore, extrapolations to 20 °C are defined as extrapolations from the measured and not the modeled $p°_L$.

At this point, it is now possible to calculate the $p°_L$ as a function of temperature for all the congeners. For estimating the vapor particle partitioning of dioxins, it was assumed that the ambient temperature was 20 °C. The final column in Table 3-6 lists the calculated $p°_L$ at 20°C. Comparing the $p°_L$ at 25 and 20°C, reducing the temperature by 5°C causes the $p°_L$ to be reduced by about a factor of 2.

The Junge-Pankow model, Equation (3-3), was used to estimate particulate percentages for airsheds characterized as clean continental background, average background, background plus local sources, and urban. The particle surface area parameters (θ-values) representative of each airshed were those in Table 3-5. Liquid sub-cooled vapor pressures at 20°C, as derived above, were used, and c = 17.2 Pa-cm was assumed. As an example, the particulate fraction of 1,2,3,7,8-PCDF at 20°C in average background air ($\theta = 1.5 \times 10^{-6}$) is calculated as follows:

a) $p^o_L = 1.98*10^{-5}$ (from Table 3-6)

b) $c\theta = 17.2(1.5 \times 10^{-6}) = 2.58 \times 10^{-5}$

c) $\phi = c\theta/(p^o_L + c\theta) = 2.58 \times 10^{-5}/(1.98*10^{-5} + 2.58 \times 10^{-5}) = 0.57$

Table 3-7 shows the percentage of CDD/Fs predicted to be in the particle phase at 20°C for the seventeen congeners having dioxin-like toxicity.

3.2.4.7. *Comparison of Measured and Modeled Vapor/Particle Distributions for CDD/Fs*

Two factors complicate the comparison of field measurements and predictions of the Junge-Pankow model. One is the problem of sampling artifacts that are inherent with filter-sorbent devices. Parallel collections of PAHs made with filtration samplers and denuders suggest that the more volatile members of a chemical class will be partially lost from the particles on the filter during sampling -- the "blow-off" effect (Gundel et al., 1995; Lewis et al., 1991; Subramanyam et al., 1994). A second difficulty is that very few field measurements of both particulate and gaseous CDD/Fs have been made and presented in such a way that they can be related to model predictions.

The study by Eitzer and Hites (1989) is the best data set for particle/gas partitioning, since a large number of CDD/F congeners were measured on both the glass fiber filter and PUF trap. In their paper, the particle/gas ratios of individual congeners were reported as averages for the entire year, and the average ratios were related to the liquid-phase vapor pressures of the congeners at 25°C. Although their study showed conclusively that vapor pressure controls the distribution of CDD/Fs between the aerosol and gas phases, there is a problem with their method of data treatment. The particle/gas ratio varied greatly with temperature and the average ratio for the year may or may not have been represented by the situation at 25°C.

In his thesis, Eitzer (1989) also presented the particle/gas distributions as functions of the sampling temperature through the equation:

$$Log\ K_p = \frac{Q_d}{2.303\ R\ T} + b \qquad (3\text{-}9)$$

where the heat of desorption, Qd, of individual congeners and the intercept b were estimated by plotting K_p vs. 1/T for all the sampling events. In this form the data allow the particle/gas distributions to be related to event-to-event differences in ambient air temperature.

To relate Eitzer's (1989) data to vapor pressure, his parameters of Equation (3-9) were used to calculate log K_p for individual congeners at 20° C. The K_p values at 20°C were then plotted against the liquid-phase vapor pressures at 20°C according to Equation (3-9) to yield:

$$Log\ K_p = -0.719\ Log\ p^\circ_L - 5.53 \qquad r^2 = 0.962 \tag{3-10}$$

The plot of Equation (3-10) for the 17 dioxin-like CDD/Fs is shown in Figure 3-2a. As seen, there is an excellent correlation between log K_p and log p^o_L. It should be noted that although Equation (3-10) was obtained from values of K_p and p^o_L at 20°C, it applies at any temperature since the variation in partitioning with temperature is accounted for by the temperature effect on vapor pressure. The particulate fraction is related to K_p by:

$$\phi = \frac{K_p\ [\ TSP\ ]}{1 + K_p\ [\ TSP\ ]} \tag{3-11}$$

which follows from Equation (3-5) and the definition of K_p. Comparison of the Eitzer-Hites partitioning data to predictions of the model was done as follows:

a) Field estimates of the particulate fraction (ϕ) were calculated from values of K_p at 20°C by Equation (3-11), scaling to TSP = 60 $\mu g/m^3$ (corresponding to, "background plus local sources", Table 3-5).
b) Model estimates were calculated from Equation (3-3), using $\theta = 3.5 \times 10^{-6}$ (corresponding to, "background plus local sources", Table 3-5).

Plots of measured and modeled particulate percentages vs. log p^o_L at 20°C are shown in Figure 3-2b. Although the Eitzer-Hites partitioning data show a strong dependence on vapor pressure, their measurements fall below the model predictions.

A similar approach was used to evaluate particle/gas distributions for a subset of the other ambient air investigations reviewed earlier. The partitioning data of Hites (1991), Hunt and Maisel (1990, 1992) and Welsch-Paulsch et al. (1995) are given on a homolog basis in Table 3-4. However, because these studies were done at different ambient temperatures, the particulate percentages cannot be directly compared. Therefore, all field data had to be adjusted to a common temperature of 20°C by establishing relationships between the particle/gas distributions and vapor pressure:

a) Values of K_p were calculated from the particulate percentages in Table 3-4 for CDD/Fs which were found to a measurable extent in both the particle and gas phases (i.e., K_p could not be calculated for the 0% and 100% particulate data points). Since these studies were carried out in semi-rural locations, the "background plus local sources" air regime seemed to be the most appropriate, and a value of TSP = 60 $\mu g/m^3$ was assumed in calculating K_p by Equation (3-11).

b) The resulting log K_p values were examined for outliers (only one point was omitted, from the Hites (1991) data set), then regressed against log p^o_L at the ambient sampling temperature (Equations 3-7 and 3-8). The vapor pressure of each homologue group was taken to be the central value for the congeners in that group. Regression parameters of Equation (3-7) are given in Table 3-8 for the various field studies.

c) Values of K_p for each homologue group at 20°C were calculated from the vapor pressure at 20° C, using the regression parameters in Table 3-8.

d) Particulate percentages at 20°C were calculated from K_p by Equation (3-11), assuming TSP = 60 $\mu g/m^3$.

Thus, although the actual field measurements were done under a variety of temperatures, they were normalized to 20°C for comparison. Figure 3-3 shows the particulate percentages from four field studies in comparison to those predicted by the Junge-Pankow model for Whitby's "background plus local sources" air regime. These comparisons are also given in Table 3-9. All of the field data fall substantially below the model curve. For example, the particle-bound percentages of tetrachlorodioxins and furans, which are predicted to be 43-65% at 20°, averaged only 11-18% with the filter-sorbent sampler.

3.2.4.8. *Discussion of Monitored and Modeled Results for CDD/Fs*

The above comparisons show substantial differences between filtration sampling and the Junge-Pankow model for estimating particulate percentages of CDD/Fs. Reasons for these discrepancies may be related to both sampling artifacts and model uncertainties. Blow-off losses during collection are likely to reduce the filter-retained fraction. This artifact is expected to be the most serious for long sampling times, especially if the day-to-night temperature changes are large. However, the Welsch-Paulsch samples, which were collected over two-week integration

times, show only slightly lower particulate values than those of other workers which were obtained over 24-36 h sampling periods. Aside from the Eitzer-Hites data, the measurements of CDD/F vapor/particle distribution in Table 3-4 were based on only a few samples and it is difficult to judge their representativeness. Daily measurements of phase distributions for PAHs and PCBs in Chicago show up to an order of magnitude variation in K_p values, even when normalized for vapor pressure (Cotham and Bidleman, 1995). These variations may be caused by sampling artifacts and kinetic effects, and also by daily differences in aerosol properties.

Limitations of the Junge-Pankow model include uncertainties in the parameters c and θ. Pankow (1987) suggested that optimal values of c might be chosen for different classes of compounds. His reasoning was that the excess heat of desorption (Q_d-Q_v) appeared to be a smaller term for organochlorine compounds than for PAHs. However, this conclusion was based on the very limited field data available at the time Pankow's article was written. It is difficult to extract Q_d information from field data, by plots of Equation (3-7), because such plots involve combining particle/gas distributions for individual air samples which are collected over a range of ambient temperatures, humidities and aerosol properties. Confidence intervals around the Q_d values obtained from such plots are typically large (Pankow, 1991). Moreover, significant differences in Q_d values are obtained by analyzing Equation (3-7) plots by simple linear regression versus regression assuming a constant y-intercept for all compounds (Pankow, 1991). A better approach is to determine Q_d in the laboratory by measuring K_p under equilibrium conditions and at different temperatures, but few of these experiments have been carried out (Cotham and Bidleman, 1992; Falconer and Bidleman, 1994; Storey and Pankow, 1992). The authors of this assessment believe that there is insufficient information at this time to warrant recommending different values of the c-parameter for different compound classes.

The θ-parameter is also subject to uncertainty. It is likely that Whitby's values of θ do not reflect the true surface area distribution, since they were based on the average size spectrum of aerosols and assumed spherical particles. Other limitations of the model are the inability to consider the kinetics of adsorption/desorption (Kamens et al., 1995; Rounds, et al., 1993) and humidity effects (Pankow et al., 1993).

In conclusion, neither the filter-sorbent sampler nor the Junge-Pankow model necessarily give the "correct" vapor/particle distributions. Evidence based on limited field data suggest that the model overestimates the particulate fraction of CDD/Fs relative to the filtration sampler, but it can just as well be stated that the sampler underestimates the particulate fraction relative to the model. Further work needed to improve the state of knowledge of CDD/F partitioning between the aerosol and gas phases includes:

a) Comparative monitoring with filter-sorbent samplers and other speciating devices such as denuders (Coutant et al., 1992; Eatough et al., 1993; Krieger and Hites, 1994; Lane et al., 1988; Lewis et al., 1991; Gundel et al., 1995; Subramanyam et al., 1994; Tang et al., 1994) and diffusion separators (Hornbuckle et al.,1995; Turpin et al., 1993).

b) Laboratory experiments to investigate the kinetics and thermodynamics of the sorption of CDD/Fs and other semivolatile compounds sorption aerosols.

c) Improvements in modeling particle/gas distributions in ambient air.

Despite the differences in the monitored and modeled results, the Junge-Pankow model is the recommended approach for estimating the particle/gas distribution of CDD/Fs at the present time. In addition to reproducing the general trend in partitioning with vapor pressure (Figures 3-2 and 3-3), the Junge-Pankow equation was used in an air-to-beef model validation which is described in Chapter 7. That exercise used the Junge-Pankow model for partitioning dioxins in the air. A key finding of that work was that the transfer of vapor-phase dioxins to plants and subsequently to animals dominated the terrestrial food chain. Also, vapor/particle partition data on other semi-volatile organic compounds are compared in Chapter 7 to model predictions, and the match for these compounds is, in most cases (especially for PAHs), superior to that of the CDD/Fs.

3.2.4.9. *Discussion of Vapor/Particle Partitioning*

This subsection has reviewed stack testing data, ambient air sampling data, and theory rooted in basic physical chemistry that either imply, directly deduce or theoretically calculate the V/P partitioning in the ambient air. From this review it is generally concluded that:

1. Although the sampling methods in use today to characterize stack emissions from combustion sources accurately determine stack gas concentrations of CDD/Fs, these methods do not provide a credible basis for assuming the vapor phase and particle bound partitioning at the point of release. There is no consistent pattern to the interpretation of V/P based on where the CDD/F segregates in the instrument, e.g., the glass fiber filter or the XAD resin. Factors that mostly contributing to this are: (a) The relatively long residence time spent *in situ* during the sampling of stack gases; (b) The fact that the particulate filter housing is kept at a constant temperature, and, (c) The fact that a condensing section (consisting of glass tubing surrounded

by an ice or chilled water bath) is usually located between the particulate trap and the vapor trap to force condensation of vapor-phase organic constituents in the gases.

2. On the other hand, the ambient air sampling methods do give an approximate indication of the V/P ratio that seems to be responsive to changes in temperature, and degree of chlorination of the CDD/Fs. This is in accordance with what would be expected from their individual vapor pressures. There is no artificial heating or cooling of any component of the sampler. The sampler is exposed to actual temperature, pressure, and humidity of the ambient air. This removes the possibility that the vapor phase-particle bound partitioning, operationally defined as the compound segregating to the particulate trap and vapor trap, is actually an artifact induced by artificial heating and cooling within the system. Therefore the methods present a realistic picture of partitioning under variable ambient conditions. However, the method has certain limitations that currently prevent deriving a true measurement of V/P partitioning in the ambient air. Among these limitations are:

a. The glass fiber filter designed to capture and retain particulate matter has filter pours down to 0.1 µm diameter. Particles less than this diameter will pass through the filter and be retained in the polyurethane foam vapor trap downstream. If this is the case, the amount of CDD/Fs observed to be particle bound would be underestimated, and the amount observed to be in vapor phase would be overestimated.

b. The relatively high sampling volume passed through the system (200 to 400 m^3 of air per 24 hours) may redistribute the more volatile congeners from the filter to the absorbent trap by a process known as 'blow-off'.

3. Until sampling methods are improved and modified such that they give results that indicate the true V/P ratio of CDD/Fs in ambient air, the theoretical construct described by Bidleman (1988; and detailed above) is used to calculate the V/P ratio for purposes of air dispersion and deposition modeling of emissions from the hypothetical case demonstrated in Chapter 5. Key advantages to the theoretical approach are that the theoretical construct relies on current adsorption theory, considers the molecular weight and the degree of halogenation of the congeners, uses the boiling points and vapor pressures of the congeners, and uses the availability of surface area for adsorption of atmospheric particles that correspond to a variety of ambient air shed classifications having variable particulate matter densities.

3.2.5. Estimation of the Concentration of Dioxin-Like Compounds in Incineration Ash

The ash that is collected by the particulate matter control device preceding the stack is known conventionally as fly ash. Fly ash is the airborne combustion residue from burning the

fuel. Bottom ash is the ash residue that results from the combustion of the organic solids within the combustion chamber, and usually is collected below a grate system used to convey combustible fuels into the fire zone, or is collected at the bottom of the combustion chamber. In general, there are many factors that may influence the formation of particulate matter known as fly ash from the incineration of organic wastes. Among these factors are: the heating value of the incinerated material (BTU/kg), the percent moisture in the fuel, the furnace temperature and combustion efficiency, and the efficiency of particulate matter capture by the air pollution control device (Brunner, 1984; OTA, 1989). Fly ash, and not the bottom ash, contains most, if not all, the dioxin-like congeners. This can be explained by the synthesis of dioxin that occurs on the reactive surface of fly ash. Therefore, the following estimation of the ash generation rate, and the concentration of dioxin-like compounds in the ash particles, will focus solely on fly ash to the exclusion of bottom ash. Because bottom ash is mostly free of these contaminants, and is about 10 to 100 times the mass of fly ash, the mixing of fly ash with bottom ash will dilute the concentration of dioxin by about a factor of 10 - 100.

Estimation of the mass of fly ash generated, and concentration of dioxin-like compounds can be determined by the following (if no actual data exists):

1. Determine the mass of fly ash generated per day at the facility. This can be estimated from the percent control of particulate matter (PM) of the air pollution control device (APCD) installed at the facility. For example, if a combustor emits 0.5 kg of particulate matter per hour of operation, then 12 kg of PM is released from the stack in one day. If PM is controlled by 99%, then this rate of emission represents one percent of the fly ash generated by the combustion process. The amount of fly ash that is collected by the APCD would be 100 times the amount emitted, or 1200 kg/day.

2. Estimate the congener-specific concentration of CDD/Fs contained in the collected fly ash. This is done by assuming that what is prevented from exiting the stack is contained in the fly ash collected by the pollution control device. If, for example, 10 picograms CDD/F is emitted per gram of PM from the facility per day, and the APCD reduces emissions by 99%, then 100 times more CDD/F concentration, or 1000 picograms CDD/F per gram fly ash, would be in the collected fly ash. If the concentration of dioxin in emitted fly ash and the percent control of dioxin are known, then the concentration of dioxin in the mass of collected fly ash can be estimated. It is important to make such estimations in order to evaluate the potential environmental impact of ash management practices before the operation of the facility, and to select appropriate disposal practices to preclude future adverse conditions from arising.

3. Now estimate total mass, including fly and bottom ash, and final concentrations. If bottom ash mass is estimated at ten times fly ash, than the total ash generated in this example would be 1200 + 1200*10 = 13,200 kg/day. If fly and bottom ash were mixed for disposal, which is common, than the average concentration of the total ash would be one-tenth that estimated for fly ash.

The hypothetical example in Chapter 5 does not assess impacts associated with ash disposal. Section 4.3.5 of Chapter 4 describes procedures for estimating impacts from ash disposal given ash concentrations and mass generated.

3.3. AIR DISPERSION/DEPOSITION MODELING OF THE STACK GAS EMISSIONS OF DIOXIN-LIKE COMPOUNDS

It has been customary for EPA to use air dispersion/deposition models to estimate the atmospheric transport, the deposition flux, and the ambient air concentrations of specific pollutants attributable to smokestack emissions from an industrial combustion source. Air dispersion models are mathematical constructs that approximate the physical and chemical processes occurring in the atmosphere that directly influence the dispersion of gaseous and particulate emissions from smokestacks of stationary combustion sources. These models are computer programs encompassing a series of partial differential and algebraic equations to calculate the dispersion and deposition of the emissions. Concentration and deposition isopleths of the pollutants discharged from the stack are computed at specified distances from the smokestack. These quantities are used to estimate the magnitude of potential exposures to the human receptor.

Numerous dispersion/deposition models have been developed. This document focuses on the Industrial Source Complex 3 Short Term, ISCST3, dispersion model recently developed by EPA to provide modeling outputs useful in the analysis of wet/dry deposition and ambient air concentrations of stack emitted contaminants in all terrain settings (EPA, 1995). The ISC3 was developed as a general replacement to the COMPDEP model first described in EPA (1990b). Modeling enhancements of ISCST3 include more refined small particle dry and wet deposition algorithms than used by the COMPDEP model. The ISCST3 was used to generate the results for the hypothetical incinerator of this assessment. However, the use of ISCST3 is this assessment is not intended to imply that ISCST3 is the only acceptable model to use in the analysis of ambient air concentrations, and wet and dry deposition of dioxin-like compounds.

Subsection 3.3.1 below presents an overview of the dispersion and deposition algorithms in the ISCST3 model. Subsection 3.3.2 discusses dry deposition fluxes, including pertinent

assumptions made in the application of the ISCST3 model for the hypothetical combustor demonstrated in Chapter 5. Subsection 3.3.3 discusses particle size distributions for emitted particles. Subsection 3.3.4 discusses wet deposition, again noting key assumptions for the hypothetical combustor. Subsection 3.3.5. closes the section with guidance indicating that the ISCST3 model should be run with two simultaneous modes of operation: one mode provides estimates of particulate concentrations in air and wet/dry particle deposition flux; the other mode provides for the estimation of vapor phase concentrations of dioxin-like compounds in ambient air.

3.3.1. Basic Physical Principles Used to Estimate Atmospheric Dispersion/Deposition of Stack Emissions

Air dispersion/deposition models mathematically simulate the basic physical processes in the atmosphere to estimate the ground-level air concentrations and deposition flux of contaminants known to be released from the stacks/vents of stationary combustion sources. These processes include advection, turbulent diffusion, and removal of atmospheric particles. Advection describes the physical movement of the air contaminants by the horizontal movement of wind. Turbulent diffusion is the "spreading" of the emissions plume with distance from the stack due to multi-directional fluctuations in air movement. Removal refers to mechanisms which remove emissions from the atmosphere. This can be caused by the force of gravity exerted on the particle mass, Brownian movement of aerosol particles, and scavenging of particles. Scavenging is the removal of particles or vapors by precipitation.

ISCST3 contains modifications of the Industrial Source Complex model (Short-Term version; ISCLT, as described in EPA, 1986b), and COMPLEX I to incorporate algorithms to estimate dispersion, and resulting ambient air concentrations and wet and dry deposition flux. COMPLEX I is a second level screening model applicable to stationary combustion sources located in complex and rolling topography (EPA, 1986a). The ISCST model was developed by EPA to provide estimates of air concentrations and deposition rates of the stack emissions of contaminants from industrial sources located in varied terrain (e.g., from simple to complex terrain). Simple and complex terrain are defined as topography that is either below or above the effective stack height of the source (Turner, 1986). To account for pollutant deposition, the concentration algorithms in COMPLEX 1 were replaced with those from the Multiple Point Source Algorithm with Terrain Adjustments Including Deposition and Sedimentation (MPTER-DS) model (Rao and Sutterfield, 1982). The MPTER-DS algorithms incorporate the gradient transfer theory described by Rao and Sutterfield (1982), and are extensions of the traditional

Gaussian plume algorithms. The dispersion algorithms contained in the ISCST were incorporated to analyze ground-level receptors located below the height of the emission plume (EPA, 1986b). For a steady-state Gaussian plume, the hourly concentrations at downwind distance x (meters) and crosswind distance y (meters) are given by:

$$\chi = \frac{QKVD}{2\pi\mu_s\sigma_y\sigma_z} \exp\left[-0.5\left(\frac{y}{\sigma_y}\right)^2\right] \quad (3\text{-}12)$$

where:

χ	=	the ambient air concentration of the contaminent, $\mu g/m^3$
Q	=	contaminant emissions rate, g/s
K	=	units conversion factor
V	=	vertical term - accounts for the vertical distribution of the Gaussian plume, dimensionless
D	=	plume depletion term relating removal by physical or chemical processes, dimensionless
σ_y, σ_z	=	standard deviation of lateral and vertical concentration distribution, m
μ_s	=	mean wind speed at release height, m/s
y	=	crosswind distance from source to receptor, m

ISCST3 uses the generalized Briggs (1975, 1979) equation to estimate plume-rise and downwind dispersion as a function of wind speed and atmospheric stability. A wind-profile exponent law is used to adjust the observed mean wind speed from the measurement height to the emission height for the plume rise and pollutant concentration calculations. The Pasquill-Gifford curves are used to calculate lateral and vertical plume spread (EPA, 1986a). These curves are based on Pasquill's definitions of atmospheric stability classes, e.g., extremely unstable, moderately unstable, slightly unstable, neutral, slightly stable, and moderately stable, that correspond to various intensities of solar radiation and wind speeds (Seinfeld, 1986). The incorporation of these two basic models into ISCST3 permits analysis of a source located in all types of terrain.

3.3.2. Estimation of Dry Surface Deposition Flux

The dry deposition of particle-bound contaminants is a physical atmospheric removal process that is simulated by the ISCST3 model. Dry deposition refers to the transfer of airborne particulate matter to the Earth's surface (including water, soil, and vegetation) whereby it is removed from the atmosphere. Although the dry gaseous deposition of vapor-phase contaminants is currently considered in the ISCST3 model, this feature has not been calibrated for the estimation of the deposition flux of dioxin-like compounds into vegetation. Until the algorithm has been verified to make reasonably accurate estimates of gaseous deposition of dioxin-like compounds, this guidance will not incorporate examples of it's site-specific application. The focus of the following discussion is directed to the operation of the ISCST3 model to estimate the dry deposition of dioxin-contaminated particles.

The general processes controlling the transfer of particulate from some height above the surface through the surface layer down to the immediate vicinity of the surface are the forces of gravity and turbulent diffusion, followed by diffusion through the laminar sub-layer (defined as a thickness of 10^{-1} to 10^{-2} cm) to the surface (Seinfeld, 1986). The term "deposition flux" is mass concentration of a contaminant sorbed to atmospheric particulates that is delivered to the surface per unit of time by the physical forces of gravity, atmospheric turbulence, and diffusion (Kapahi, 1991). Deposition flux is represented mathematically by F_d. The dry deposition flux, F_d, is defined as the product of the ambient air concentration of the chemical contaminant, C_o, times a deposition velocity(m s^{-1}) of the contaminated particles as in Equation (3-13).

$$F_d = V_d C_o \qquad (3\text{-}13)$$

where:

F_d = dry deposition flux of contaminants sorbed to particles, $\mu g/m^2$-sec
V_d = the particulate depostion velocity, m/sec
C_o = concentration of pollutant on settling particles, $\mu g/m^3$

In general, Chamberlain and Chadwick (1953) first defined the depositon velocity, V_d, as the quotient of the deposition flux, F_d, divided by the airborne concentration, C_o:

$$V_d = - \frac{F_d}{C_o} \quad (3\text{-}14)$$

The value for F_d in Equation (3-14) has a minus sign because the downward flux is negative, whereas the deposition velocity is positive (Sehmel,1980). By this relationship, Chamberlain and Chadwick (1953) first introduced the concept of plume depletion, i.e., as the emission plume is dispersed with downwind distance from the stack, the deposition flux decreases with distance from the source.

The basic dynamics of the physics of modeling dry deposition have not changed significantly since Sehmel's (1980) comprehensive scientific review. The factors that most influence the predicted deposition flux can be divided as being either meteorological influences, or the influences of the properties of the pollutant under analysis. Meteorological influences include the friction velocity, represented as $\mu_{ø}$, and the aerodynamic surface roughness, represented as z_o. These terms are used to describe the wind speed profile above the Earth's surface. In most cases, the analyst uses a graphical procedure to determine values for $\mu_{ø}$ and z_o. If the logarithm of wind speed is plotted for near neutral atmospheric stability as a function of height from the surface, then the values for the constant z_o is fitted to a straight line on a semi-logarithmic scale. This can be described mathematically by Equation (3-15). In most cases, the friction velocity is a percentage of the wind speed.

$$\mu = \left(\frac{\mu*}{\lambda}\right) \ln \left(\frac{z + z_o}{z_o}\right) \quad (3\text{-}15)$$

where:

μ	=	the measured wind speed, cm/sec
μ_*	=	the friction velocity, cm/sec
z	=	the measured height above the surface, cm
z_o	=	surface roughness length, cm
λ	=	von Karman's constant, approx. = 0.4

As a general rule, particles greater than 30 micrometers (μm) in diameter will be removed from the atmosphere primarily by the force of gravity, whereas particles less than 30 μm will be removed primarily by atmospheric turbulence. The deposition flux for the smaller particles is influenced by many factors, including: the distribution of particles by diameter and density; the atmospheric turbulence; the friction of the ground surface and the height of the stack release of emissions. Deposition flux is also affected by the partitioning properties of the pollutant. These properties will determine how much of the pollutant is sorbed to the particle and how much is in the vapor phase. A detailed list of the many factors that can affect dry deposition is shown in Table 3-10.

The ISCST3 estimates dry deposition flux based on empirical associations developed by Sehmel (1980) and Sehmel and Hodgson (1978) relating the deposition flux to the deposition velocity of particles. The downward motion represented by deposition velocity is controlled by the gravitational settling velocity, atmospheric resistance, surface resistance and the atmospheric surface friction layer. This model assumes that a fraction of the particulate comes into contact with the ground surface by the combined processes of gravitational settling, atmospheric turbulence, and Brownian diffusion. The ISCST3 model contains enhancements to calculate dry deposition flux using a dry deposition model developed by Pleim et al. (1984). The Pleim et al. (1984) algorithms represent Sehmel's (1980) empirical relationships for transfer resistances as a function of particle size, density, surface roughness, and friction velocity. In the Pleim et al. (1984) model, integrated resistances to mass transfer are computed within two layers. In the first layer, which extends from one centimeter to one meter above the surface, atmospheric turbulence dominates mass transfer. This is a fully turbulent region where vertical fluxes are nearly constant, and is referred to as the aerodynamic resistance. In the second layer, which lies within one centimeter of the surface, the resistance to mass transfer is derived from particle deposition measurements that were taken in a wind tunnel over various surfaces using mono-dispersed particles (Sehmel,1980; Sehmel and Hodgson,1978). The general approach used by ISCST3 in the resistance methods for estimating the dry deposition velocity of particles is given by:

$$v_d = \frac{1}{r_a + r_d + I_a I_d I_s} + V_g \qquad (3\text{-}16)$$

where:

V_d = the depositon velocity, cm/s

V_g = the gravitaional settling velocity, cm/s
r_a = the aerodynamic resistance, s/cm
r_d = the deposition layer resistance, s/cm

Despite what is currently known about the physical and chemical processes that influence the final deposition flux of particles released from a stationary combustion source, a more thorough understanding of the influence of particle size on deposition velocity is needed. In Sehmel's (1980) review of settling velocities corresponding to particle diameter it was noted that the range of values spanned several orders of magnitude. This complicates efforts to make generalizations of V_d by particle diameter for air modeling purposes. Although dry particle deposition velocities have been estimated from both field studies and laboratory experiments, derived velocities are limited and highly uncertain. This is due largely to the complex and variable array of factors that can influence the rate of deposition (which are summarized in Table 3-10).

In the general classification of particles, particles < 2.5 micrometers (μm) in diameter are referred to a "fine particles", and those > 2.5 μm are "coarse particles". Sehmel (1980) offers the most current review of dry deposition settling velocities for a variety of depositing materials having a broad range of particle diameters. This summary appears in Table 3-11.

For the example application of the ISCST3 model in Chapter 5, particles less than 2 μm were represented by a 1 μm size and were calculated by ISCST3 to deposit at a velocity of $<10^{-2}$ cm/sec. Particles between 2 and 10 μm were represented by a 6.78 μm size and were calculated to deposit at a velocity of < 0.5 cm/sec. Finally, particles greater than 10 μm were represented by a 20 μm size and were calculated to deposit at a velocity of >2.0 < 5.0 cm/sec, although the variable ambient conditions resulted in more variable calculations. The derivation of these particle size representations is given in the next section.

3.3.3. Estimation of the Particle Size Distribution in the Stack Emissions

A distribution of particle size and diameter of the particulate stack emissions must be known before the ISCST3 program can predict deposition flux of the dioxin-like congeners. The diameters of small particles comprising particulate matter in stack emissions are usually measured in units of one millionth of a meter (micrometer, commonly called micron, abbreviated by the letters μm). Unfortunately, few studies have been conducted that describe the distribution of particulate matter entrained in the emissions from various combustion technologies broken down and fractionated by particle diameter. The characterization of particulate matter by

particle diameter will differ from one combustion process to another, and is greatly dependent on such factors as: 1) the efficiency of various air pollution control devices to the remove particles over a broad range of diameters from the gas stream , 2) the composition of the feed/fuel, 3) the design of the combustion chamber, 4) the amount of air used to sustain combustion, and 5) the temperature of combustion. Table 3-12 gives an example of a particle diameter distribution as measured at a stack of an incinerator, and was adopted from USEPA (1980). This example distribution will be assumed for the hypothetical incinerator.

Although the ISCST3 model can simulate up to 10 particle size categories, only three particle sizes are assumed for the model runs of the demonstration in this assessment. These three sizes are generalized from the data in Table 3-12:

- **Category 1:** $\leq$ 2 µm
- **Category 2:** > 2 to $\leq$ 10 µm
- **Category 3:** > 10 µm

After selecting the particle size distribution, it is necessary to calculate the mass emission rate of the particulate-bound congeners of CDD/Fs by particle size category. This is accomplished by calculating the proportion of surface area (available for adsorption of CDD/Fs) for a given particle diameter. The ratio of the surface area to volume is proportional to the ratio of the surface area to weight for a particle with a given radius. Multiplying this proportion times the weight fraction of particles of a specific diameter (µm) gives a value that approximates the amount of surface area available for chemical adsorption. The surface area to volume ratio can be described as follows:

(a) Assume aerodynamic spherical particles.

(b) Specific surface area of a spherical particle with radius,r:

$$S = 4 \pi r^2$$

(c) Volume of spherical particle with radius, r:

$$V = 4/3 \pi r^3$$

(d) The ratio of surface area to volume is:

$$S/V = 4 \pi r^2 / (4/3 \pi r^3)$$

$$S/V = 3/r$$

Dividing the surface area for each particle category by the total available surface area for all particles gives an estimation of the fraction of total area on any size particle. Multiplication of the emission rate of the dioxin-like congener times the fraction of available surface area will estimate the emission rate of the pollutant per particle size. The fraction of total surface area was computed for the three particle size categories. The fraction of total surface areas for the ranges

of particle diameters are summed with each particle size category to represent a single fraction of total surface area for the given particle size category, as follows:

- Particulate category 1: fraction of total surface area = 0.875
- Particulate category 2: fraction of total surface area = 0.095
- Particulate category 3: fraction of total surface area = 0.030

Thus by these assumptions, 87.5% of the emission rate of the dioxin-like congener is calculated to be associated with particles less than $\leq$ 2 µm in diameter, 9.5% of the emission is associated with the particle size of > 2 to $\leq$ 10 µm, and only 3% of the emission is associated with particles greater than 10 µm. To assist in deposition modeling of the emissions from the hypothetical incinerator, the particle size distribution is further simplified by assuming a median particle diameter to represent each broad particle size category, as follows:

- Particulate category 1 = 1 µm particle diameter
- Particulate category 2 = 6.78 µm particle diameter
- Particulate category 3 = 20 µm particle diameter

3.3.4. Estimation of Wet Deposition Flux

Wet deposition occurs by precipitation (rain, hail, snow) physically washing out the chemically contaminated particulate and vapors from the atmosphere. Vapor scavenging is not yet well understood and is not addressed in the ISCST3 model. The remainder of this discussion refers only to the wet deposition of particles.

Wet deposition flux depends primarily on the fraction of the time precipitation occurs and the fraction of material removed by precipitation per unit of time by particle size. Based on these relationships, scavenging coefficients were developed by Jindal and Heinold (1991) for varying types and intensities of precipitation relative to different particle diameters by incorporating the observations of Radke, et al. (1980) in a study of scavenging of aerosol particles by precipitation. The principal assumptions made in computing wet deposition flux are: (1) The intensity of precipitation is constant over the entire path between the source and the receptor; (2) The precipitation originates at a level above the top of the emission plume so that the precipitation passes vertically through the entire plume; (3) The flux is computed on the bases of fraction of the hour precipitation occurs as determined by hourly precipitation measurements compiled by the National Weather Service. The remaining fraction is subject only to dry deposition processes. Thus no dry deposition occurs during hours of steady precipitation, and dry deposition occurs between the periods of precipitation.

Wet deposition flux is estimated by ISCST3 using a scavenging ratio approach. In this approach, the flux of contaminant to the surface (F_w) is the product of the savenging ratio times the contaminant concentration, as in the following equation.

$$F_w = \Lambda \chi \quad (3\text{-}17)$$

where:

F_w = wet deposition flux, g/m^2-sec
Λ = scavenging ratio, sec^{-1}
χ = contaminant air concentration value calculated from the Gaussian plume equation, g/m^3

The scavenging ratio (Λ) is calculated as the product of the scavenging coefficient and precipitation rate (Scire et al., 1990), as follows:

$$\Lambda = \lambda R \quad (3\text{-}18)$$

where:

Λ = scavenging ratio, sec^{-1}
λ = scavenging coefficient, $(sec\text{-}mm/hr)^{-1}$
R = precipitation rate, mm/hr

The scavenging coefficient depends on the size distribution for particles and the nature or form of precipitation, i.e., liquid or frozen.

Across the plume, the total flux to the surface must be approximately equal to the mass lost from the plume. ISCST3 contains a plume wet deposition depletion equation as follows:

$$Q(x) = Q_o e^{-\Lambda x/u} = Q_o e^{-\Lambda t} \quad (3\text{-}19)$$

where:

Q(x) = wet plume depletion factor, dimensionless
Λ = precipitation scavenging ratio, sec^{-1}

t = x/u = the plume travel time, sec

The relationship between the scavenging coefficient, Λ, and the particle size and precipitation intensity was derived from the review of wet deposition studies of aerosol particles by Jindal and Heinold (1991). Table 3-13 displays the scavenging coefficients assigned to the generalized particle size categories and forms of precipitation (liquid rainfall, frozen) used for computing estimates of wet deposition in the application of the ISCST3 for the demonstration scenarios in Chapter 5.

3.3.5. Using ISCST3 to Model Emissions of Particles and Vapors

The ISCST3 model had to be run in two modes in order to provide estimates of ambient air concentrations of vapor-phase and particle-bound dioxins, combined with estimates of wet/dry particle deposition flux. The short-term ISCST3 model can accommodate these estimates in a single run. The user may select any or all of the output types, e.g, air concentration, wet deposition, dry deposition and combined wet and dry deposition, to be generated in a single model run. Instructions for this appear in the User's Guide for the Industrial Source Complex Models (ISC3) (EPA, 1995). To facilitate the modeling exercise, the modeler should assume a "unit emissions release rate" of CDD/Fs from the stack, e.g., 1 g CDD/F congener per second (1 g/s). Results from these unit runs can easily be transformed to final outputs given assumptions on CDD/F emissions in vapor and particle forms. Two assumptions are required. One assumption is the total emission rate of the compound, in units of mass/time (g/s), and the second is the vapor/particle partitioning of this total emission. The two modes are:

- **Mode 1: To estimate vapor-phase concentration of the contaminant in ambient air.**

The first mode assumes that the emissions of dioxin-like compounds are gaseous, e.g., with the wet/dry deposition switches turned to the "off" position. This is to isolate the ambient air concentration of the contaminant in vapor-phase from the calculation of wet and dry particle deposition flux. This inactivates a plume depletion equation that subtracts out losses in ambient air concentration due to particle deposition. What remains is the Gaussian dispersion algorithm to calculate air concentrations.

With the "unitized" emission rate, one can reconstruct the actual predicted ambient air concentration ($\mu g/m^3$) of vapors by multiplying the "actual" vapor-phase emission rate (g/s) by the "unitized" modeling result. For example, let the actual stack gas emission rate of total (vapor

plus particle components) contaminant be $1x10^{-5}$ g/s, and the V/P ratio (expected under ambient conditions) be 60%V/40%P. Then the "actual" emission rate of the vapor-phase portion of the contaminant is calculated to be $6x10^{-6}$ g/s ($1x10^{-5}$ g/s * 0.6). If the "unitized" ambient air concentration at the ground-level receptor is estimated by the ISCST3 model to be $1x10^{-8}$ $\mu g/m^3$ (i.e., this concentration is predicted with a unit emission rate of 1 g/s), then the "actual" predicted air concentration at that receptor can be estimated as:

$$(6x10^{-6} \text{ g/s} \div 1 \text{ g/s}) * 1x10^{-8} \mu g/m^3 = 6x10^{-14} \mu g/m^3$$

- **Mode 2: To estimate wet and dry particle deposition flux, and the ambient air concentration of the contaminant that is particle-bound**.

ISCST3 should be run with the wet/dry particle deposition switches turned to the "on" position, and using a "unit emission rate" of 1 g/s. This second run is considered a simulation of particle-bound contaminant only. Outputs of this run include unitized deposition rate and unitized ambient air concentrations of particles.

Like the vapor-phase run, the "actual" deposition flux (g/m^{-2} -yr) and "actual" particle-phase airborne concentrations can then be determined by multiplying the "actual" emission rate (g/s) of the particle-bound portion of the total contaminant emissions by the "unitized" modeling result at the ground receptor. For example, let the "actual" emission rate of the particle-bound portion of the contaminant be $4x10^{-6}$ g/s, and the "unitized" dry deposition flux at the ground receptor be $1x10^{-5}$ g/m^2-yr. Then the "actual" predicted dry deposition flux is $4x10^{-11}$ g/m^2 ($4x10^{-6}$ g/s ÷ 1 g/s * $1x10^{-5}$ g/m^2-yr). Using this same procedure, this second run provides the airborne concentration of contaminants bound to particles ($\mu g/m^3$).

There are two meteorological preprossesors used by ISCST3 model program to access local conditions necessary to compute model concentrations in both modes of operation: PCRAMMET (Catalano et al., 1987) and MPRM (Irwin and Paumier, 1990). These files contain hourly data for the wind speed, wind direction, stability class, mixing height, ambient air temperature, precipitation, and surface friction velocity.

Inhalation exposures are estimated as the sum of vapor and particle phase concentrations. Air-to-plant transfers require the vapor phase concentrations for vapor transfers and the particle-phase depositions. The air-to-soil algorithm requires particle phase depositions.

3.4. RESULTS OF THE AIR DISPERSION MODELING OF CONGENER-SPECIFIC EMISSIONS FROM THE HYPOTHETICAL ORGANIC WASTE INCINERATOR

The preceding subsections have presented general procedures for conducting air modeling of the emissions of dioxin-like compounds from the stack to the ground, starting with estimation of emission factors, vapor/particle partitioning at the stack, and proceeding to atmospheric dispersion and deposition using EPA's ISCST3 model. Where appropriate, previous subsections have also included discussion on the assumptions and the selection of parameters for the hypothetical incinerator which is demonstrated in Chapter 5. For example, Section 3.2.3 provided the emission factors that were used in this demonstration. This section will provide all other details of the hypothetical incinerator and provide the final results of the ISCST3 model simulations.

To reiterate, the purpose of the hypothetical construct is to help readers understand how to apply these principles to the air dispersion modeling and analysis of dioxin emissions from the source. Therefore, generalizations should not be made on the basis of this example regarding the magnitude of the emissions release and associated environmental impact.

A completely hypothetical incinerator was devised to serve as the example. Accordingly, a hypothetical, but realistic, incineration technology, facility size, stack height, and geographical location was selected. The hypothetical incineration facility has an assumed total daily capacity of 200 metric tons of organic waste materials. The emission rates of specific congeners of PCDD/Fs were derived from the stack testing and monitoring of emissions from a modern incinerator of this size. These emissions are expressed in units of g/sec, and are shown for the hypothetical incinerator in Table 3-14.

In constructing the hypothetical case, the following was defined: stack height; stack diameter; exit velocity of the gaseous emissions from the stack; and temperature of the exhaust gases characteristic of incineration facilities of this size. In order to access historical meteorological data for air modeling purposes, the hypothetical facility was located in a specific geographical area having specific meteorological conditions. To simplify the ambient air modeling and deposition, the hypothetical organic waste incinerator was assumed to exist in a simple terrain setting (e.g., flat terrain). By definition, simple terrain refers to an area where the terrain features are all lower in elevation than the top of the stack of the stationary source under analysis.

The dispersion and deposition computations performed by the ISCST3 model require data on wind speed, wind direction, wind profile above the surface, and hourly precipitation data.

When performing a regulatory analysis, e.g., to set air quality permit conditions, EPA's *Guideline on Air Quality Models* (EPA, 1986a) recommends the use of five consecutive years of representative meteorological data. However, in this example analysis of only one year of meteorological data was used as compiled at the Denver-Stapleton International Airport by the National Weather Service (NWS), because this was not intended as a regulatory analysis. Hourly measurements of wind speed, wind direction, temperature, and precipitation were used as a basis of computing annual average ground-level concentrations of dioxin in ambient air, and as a basis for the estimation of the dry and wet deposition flux. The Pasquill-Gifford (P-G) stability categories, were used as defined in the Modeling Guidelines. The specifications of stability categories depending on wind speed, cloud cover and mixing heights were established by Pasquill (1961), and later modified by Turner (1964). Reference is made here to Tables 9-3 and 9-4 on pages 9-21,22 of the Modeling Guidelines which gives a method for estimating P-G Stability Categories for daytime and nighttime conditions based on surface roughness and the wind speed profiles distributed in the United States.

To summarize, inputs for the ISCST3 model included hourly meteorological data, source characteristics and receptor features. Hourly meteorological data requirements are the mean wind speed, the direction from which the wind is blowing, the wind-profile exponent, the ambient air temperature, the Pasquill stability category, the vertical potential temperature gradient with height, the mixing layer height, and the frequency distribution of hourly precipitation. Source input data requirements included the congener-specific mass emission rate partitioned by vapor and particulate; the physical stack measurements, e.g., diameter, base elevation of the stack, and exit velocity and temperature of the stack gas, and settling parameters for particulate matter for both dry and wet deposition. Table 3-14 is a review of the congener-specific emissions data, and Table 3-15 is a review of the modeling parameters used in the air quality modeling of the hypothetical incinerator.

The output of the ISCST3 model for both surface deposition and ambient air impacts is a concentration array for 160 ground-level receptors around the incinerator, e.g., 10 receptor points along each of the 16 wind directions every 22.5° on the polar azimuth. Vapor and particle phase concentrations are in units of grams per cubic meter of air (g/m^3), and particle-bound depositions are in units of grams per square meter of surface area per year (g/m^2-yr). Results for both ambient air and surface deposition were estimated at concentric radial distances from the incinerator of 0.2, 0.5, 0.8, 0.9, 1.0, 2.0, 5.0, 10, 20, 30, 40, and 50 kilometers. The maximum annual average ground-level vapor and particle-phase air concentrations of all modeled congeners is estimated to occur 900 meters from the center of the stack. Tables 3-16 and 3-17

display the annual average vapor-phase and particle-phase air concentrations of dioxin-like congeners at various distances in the direction of the maximum impact. Tables 3-18 and 3-19 display the dry and wet deposition fluxes of dioxin-like compounds at various distances in the direction of maximum impact. The maximum annual average dry deposition flux occurs 800 meters from the center of the stack, although there is no significant difference from the 900 m distance where the maximum annual average ambient air concentration occurs. The maximum annual average wet deposition occurs 200 meters from the center of the stack, which is what is expected from the algorithm (refer to subsection 3.3.4. Estimation of Wet Deposition Flux).

3.5. REVIEW OF PROCEDURES FOR ESTIMATING SITE-SPECIFIC IMPACTS FROM A STACK EMISSION SOURCE

This chapter has detailed a procedure for evaluating site-specific impacts from stack emission sources. For purposes of demonstration, a hypothetical incinerator was defined, and using the ISCST3 model, estimates of vapor-phase concentrations and particle phase depositions at points around the stack were made. Three major points for estimating impacts of dioxin-like compounds using the ISCST3 or other models are as follows:

1. Characterize the emissions on a congener-specific basis: Although much of the information available on stack emission sources in on a TEQ or a homologue group basis, and not a congener-specific basis, the approach in this assessment, and the recommendation made here, is to conduct site-specific assessments using specific congener emissions. This is because fate and transport parameters, and bioconcentration/biotransfer parameters, are different for the various congeners. Assuming one set of such parameters for TEQ emissions can lead to a different estimated exposure media TEQ concentration than assuming congener-specific parameters and then, given estimated congener-specific concentrations, calculating TEQ exposure media concentrations with the TEF scheme. Emission factors were used in this assessment to describe source and site-specific emissions. These are defined as the mass of contaminant emitted per mass of feed material combusted. Procedures to convert other emission data, such as mass per time emitted or concentration emitted, are presented.

2. Estimate the vapor/particle partitioning for atmospheric transport and deposition modeling: Vapors are dispersed assuming Gaussian plume dispersion algorithms, and particles are transported and deposited via wet and dry deposition. The principal output of the atmospheric transport model, ISCST3, used for further exposure analysis are the vapor and particle phase concentrations, and the wet and dry deposition totals at sites of exposure. There is some thought that the partitioning between the vapor and particle phases at the stack differs from

the partitioning in ambient air. Such a difference might be due to the difference in temperature at the stack versus temperature of ambient air. If so, then deposition and dispersion trends in the close vicinity of the stack may differ from such trends further from the stack. Currently the data to support such a hypothesis is lacking; the earlier review of stack vapor/particle partitioning was inconclusive. Also, modeling approaches for such differences are unavailable. Instead, the approach in this chapter is to assume one partitioning scheme (separate V/P partitioning for individual congeners) for atmospheric transport and dispersion modeling. The scheme adopted in this assessment is based on a theoretical approach described by Bidleman (1988).

3. Conduct atmospheric dispersion and deposition modeling: The ISCST3 model is used in this assessment to estimate vapor and particle-phase concentrations, and wet and dry deposition totals for points around the stack emission source. Key inputs are vapor phase and particulate phase emission rates (rather than emission factor units, atmospheric transport models require emission rates in units of mass/time, or g/sec), stack descriptors (stack height, exit temperature, etc.), atmospheric transport parameters (particle size distributions, dry deposition velocity), meteorological data (hourly rainfall, windspeeds, etc.), and terrain descriptions. Procedures to translate the final model outputs of concentrations and deposition fluxes into exposure media concentrations is given in Chapter 4, Section 4.4.

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Table 3-1. The number of dioxin-like and total congeners within dioxin, furan, and coplanar PCB homologue groups.

Homologue Group	n: Number of Dioxin-Like Congeners	N: Number of Total Congeners	1/N
I. Dioxins			
Tetra-CDD	1	22	0.022
Penta-CDD	1	14	0.071
Hexa-CDD	3	10	0.100
Hepta-CDD	1	2	0.500
Octa-CDD	1	1	1.000
II. Furans			
Tetra-CDF	1	38	0.026
Penta-CDF	2	28	0.036
Hexa-CDF	4	16	0.063
Hepta-CDF	2	4	0.250
Octa-CDF	1	1	1.000
III. Mono-ortho coplanar PCBs			
Tetrachloro-PCBs	1	42	0.024
Pentachloro-PCBs	5	46	0.022
Hexachloro-PCBs	4	42	0.024
Heptachloro-PCBs	3	24	0.042

Table 3-2. Emission factors and average emissions used for the hypothetical incinerator.

Congener	Emission Factors, ng/kg			Emissions, g/sec
	Test 1	Test 2	Test 3	
2378-TCDD	0.052	0.031	0.037	$9.3*10^{-11}$
Other TCDD	0.826	0.870	0.913	$2.0*10^{-9}$
12378-PCDD	0.148	0.056	0.048	$1.9*10^{-10}$
Other PCDD	1.390	0.322	0.783	$1.9*10^{-9}$
123478-PCDD	0.104	0.165	0.056	$2.5*10^{-10}$
123678-PCDD	0.157	0.187	0.130	$3.6*10^{-10}$
123789-PCDD	0.148	0.165	0.117	$3.3*10^{-9}$
Other HxCDD	2.440	0.670	1.040	$3.2*10^{-9}$
1234678-HpCDD	2.350	0.957	0.957	$3.3*10^{-9}$
Other HpCDD	4.040	1.650	2.170	$6.0*10^{-9}$
OCDD	4.260	1.390	30130	$6.7*10^{-9}$
2378-TCDF	3.300	2.390	2.170	$6.0*10^{-9}$
Other TCDF	20.00	15.70	14.30	$3.8*10^{-8}$
12378-PCDF	0.435	0.165	0.226	$6.3*10^{-10}$
23478-PCDF	0.243	0.139	0.122	$3.9*10^{-10}$
Other PCDF	6.280	4.480	3.480	$1.1*10^{-8}$
123478-HxCDF	0.478	0.365	0.357	$9.2*10^{-10}$
123678-HxCDF	0.478	0.343	0.313	$8.7*10^{-10}$
123789-HxCDF	0.357	0.165	0.226	$5.7*10^{-10}$
234678-HxCDF	0.243	0.117	0.074	$3.3*10^{-10}$
Other HxCDF	1.490	0.313	0.943	$2.1*10^{-9}$
1234678-HpCDF	0.243	0.565	0.696	$1.2*10^{-9}$
1234789-HpCDF	0.391	0.096	0.165	$5.0*10^{-10}$
Other HpCDF	241.0	2.380	2.180	$5.4*10^{-9}$
OCDF	1.579	0.478	0.971	$2.2*10^{-9}$

Table 3-3. Percent distribution of dioxins and furans between vapor-phase (V) and particulate-phase (P) as interpreted by various stack sampling methods (4-D = tetraCDD; 4-F = tetraCDF).

Citation	V/P	4-D	5-D	6-D	7-D	8-D	4-F	5-F	6-F	7-F	8-F
Cavellaro et al., 1982	V	95	91	94	99	89	NR	NR	NR	NR	96
	P	5	9	6	1	11	NR	NR	NR	NR	4
Cavallaro et al, 1982	V	9	38	69	57	14	59	NR	NR	NR	60
	P	91	62	31	43	86	41	NR	NR	NR	40
Cavallaro et al., 1982	V	99	99	99	99	99	99	NR	NR	NR	99
	P	1	1	1	1	1	1	NR	NR	NR	1
Cavellaro et al., 1982	V	85	92	99	98	99	99	NR	NR	NR	99
	P	15	8	1	2	1	1	NR	NR	NR	1
Cavellaro et al., 1982	V	97	90	63	82	59	80	NR	NR	NR	97
	P	3	10	37	18	42	20	NR	NR	NR	3
Cavellaro et al., 1982	V	100	99	99	100	99	100	NR	NR	NR	100
	P	0	1	1	0	1	0	NR	NR	NR	0
Benfenati et al., 1986	V	94	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P	6	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tiernan et al, 1984	V	75	68	67	55	64	75	70	64	69	86
	P	25	32	33	45	36	25	30	36	31	14
Tiernan et al, 1984	V	95	90	88	85	98	86	98	89	88	98
	P	5	10	12	15	2	14	2	11	12	2
Tiernan et al, 1984	V	91	91	89	77	56	92	89	91	72	65
	P	9	9	11	23	44	8	11	9	28	35
Tiernan et al, 1984	V	17	22	45	84	85	7	10	22	63	77
	P	83	78	55	16	15	93	90	78	37	23
Clement et. al., 1985	V	98	92	96	93	73	97	96	98	98	94
	P	2	8	4	7	27	3	4	2	2	6
Clement et. al., 1985	V	84	55	54	72	20	95	73	70	52	68
	P	16	45	46	28	80	5	27	30	48	32

Table 3-3. Cont'd.

Citation	V/P	4-D	5-D	6-D	7-D	8-D	4-F	5-F	6-F	7-F	8-F
Clement et. al., 1985	V	100	99	98	93	95	100	100	99	99	98
	P	0	1	2	7	5	0	0	1	1	2
Hagenmaier et al., 1986	V	62	42	25	20	20	68	55	40	25	0
	P	38	58	75	80	80	32	45	60	75	100
Battelle 1988	V	90	NR	NR	NR	NR	NR	NR	NR	NR	NR
	P	10	NR	NR	NR	NR	NR	NR	NR	NR	NR
US EPA, 1990a	V	56	42	30	26	18	62	56	45	37	21
	P	44	58	70	74	82	38	44	55	63	79
Radian 1986	V	16	16	16	20	16	16	14	17	16	17
	P	84	84	84	80	84	84	84	83	84	83
AVERAGE	**V**	**76**	**70**	**71**	**73**	**63**	**76**	**66**	**64**	**62**	**73**
	P	**24**	**30**	**29**	**27**	**37**	**24**	**34**	**36**	**38**	**27**

Table 3-4. Review of air monitoring data on the percentage of measured dioxins and furans which are in the particle phase (4-D = tetraCDD; 4-F = tetraCDF).

Reference	4-D	5-D	6-D	7-D	8-D	4-F	5-F	6-F	7-F	8-F
1, T=20°C	23	37	66	87	96	14	31	64	87	91
2, T=3°C	40	87	100	100	100	100	60	88	100	98
2, T=18°C	8	28	45	88	100	ND	28	30	93	100
2, t=28°C	5	13	45	60	100	ND	0	38	78	98
3	21	20	24	70	85	23	26	29	59	94
3	3	5	12	64	90	7	12	15	43	91
4, T=18°C	NR	NR	92	100	78	14	42	73	100	100
4, T=18°C	NR	NR	100	100	100	5	43	100	100	NR
5	ND	0	65	82	100	20	71	100	100	100
5	ND	ND	100	100	100	ND	ND	ND	ND	ND
6, T=18°C	10	28	45	77	93	9	22	48	77	89
AVERAGE	16	27	63	84	95	24	32	59	84	96

Notes: - For references, 1 = Eitzer & Hites (1989) and Eitzer (1989). Average distribution at 20°C based on plots of log Kp vs 1/T from their data; see Section 3.2.4.7. and Figure 3-2a).; 2 = Hites, 1991; 3 = Harless & Lewis, 1992; 4 = Hunt, et al 1990; 5 = Bobet, et al 1990; 6 = Welsch-Pausch, et al, 1995;
- For dioxin columns, 4D = tetra dioxin congener group; 5F = penta furan congener group, etc.
- NR = not reported; ND = not detected; NR and NDs not included in average estimation
- Welsch-Pausch, et al (1995) does not include V/P data, but it was sent by authors
- Harless and Lewis (1992) do not calculate V/P, rather V/P calculated here is based on isotopically labeled CDD/F spiked onto the filter and recovered from the filter and PUF trap.

Table 3-5. Values of θ, V_T, and TSP in different air regimes.

Airshed type	θ cm^2 aresol/cm^3 air	V_T cm^3 aerosol/cm^3 air	TSP $\mu g/m^3$
Clean continental background	$4.2*10^{-7}$	$6.5*10^{-12}$	9
Average background	$1.5*10^{-6}$	$3.0*10^{-11}$	42
Background plus local sources	$3.5*10^{-6}$	$4.3*10^{-11}$	60
Urban	$1.1*10^{-5}$	$7.0*10^{-11}$	98

Sources: Bidleman (1988), Whitby (1978)

Table 3-6. Data for calculation of the liquid subcooled vapor pressure, $p°_L$, at 20 °C, and final $p°_L$ for the dioxin-like congeners.

Congener	EPA $p°_S$ (25°C)	EPA $p°_L$ (25°C)	E-H $p°_L$ (25°C)	Slope	Int.	E-H $p°_L$ (20°C)
2378-TCDD	$2.00*10^{-7}$	$1.18*10^{-4}$	$1.14*10^{-4}$	-4417*	10.88	$6.34*10^{-5}$
12378-PCDD	$5.87*10^{-8}$	$7.87*10^{-6}$	$1.74*10^{-5}$	-4779	11.28	$9.30*10^{-6}$
123478-HxCDD	$5.07*10^{-9}$	$1.47*10^{-6}$	$3.96*10^{-6}$	-5058	11.57	$2.03*10^{-6}$
123678-HxCDD	$4.80*10^{-9}$	$1.80*10^{-6}$	$3.96*10^{-6}$	-5058	11.57	$2.03*10^{-6}$
123789-HxCDD	$6.53*10^{-9}$	$9.37*10^{-7}$	$3.96*10^{-6}$	-5058*	11.57	$2.03*10^{-6}$
1234678-HpCDD	$7.47*10^{-10}$	$1.73*10^{-7}$	$1.02*10^{-6}$	-5280*	11.73	$5.10*10^{-7}$
OCDD	$7.10*10^{-10}$	$1.02*10^{-7}$	$2.77*10^{-7}$	-5526	11.99	$1.34*10^{-7}$
2378-TCDF	$2.00*10^{-6}$	$2.00*10^{-4}$	$1.23*10^{-4}$	-4394	10.83	$6.81*10^{-5}$
12378-PCDF	$2.27*10^{-7}$	$2.16*10^{-5}$	$3.64*10^{-5}$	-4608	11.02	$1.98*10^{-5}$
23478-PCDF	$3.47*10^{-7}$	$1.71*10^{-5}$	$2.17*10^{-5}$	-4728	11.20	$1.17*10^{-5}$
123478-HxCDF	$3.20*10^{-8}$	$3.12*10^{-6}$	$8.09*10^{-6}$	-4877	11.27	$4.25*10^{-6}$
123678-HxCDF	$2.93*10^{-8}$	$3.35*10^{-6}$	$8.09*10^{-6}$	-4877	11.27	$4.25*10^{-6}$
123789-HxCDF	$3.73*10^{-8}$	$6.01*10^{-6}$	$4.99*10^{-6}$	-4983	11.42	$2.58*10^{-6}$
234678-HxCDF	$2.67*10^{-8}$	$3.50*10^{-6}$	$4.99*10^{-6}$	-4983	11.42	$2.58*10^{-6}$
1234678-HpCDF	$4.67*10^{-9}$	$5.71*10^{-7}$	$2.24*10^{-6}$	-5099	11.46	$1.14*10^{-6}$
1234789-HpCDF	$1.43*10^{-8}$	$1.27*10^{-6}$	$1.31*10^{-6}$	-5192	11.54	$6.58*10^{-7}$
OCDF	$5.00*10^{-10}$	$1.01*10^{-7}$	$2.60*10^{-7}$	-5526*	11.96	$1.24*10^{-7}$

Column 1: $p°_S$: crystalline solid phase vapor pressure at 25°C, Pa. Assigned based on analysis of available literature; see Volume II, Chapter 2

Column 2: $p°_L$: sub-cooled liquid vapor pressure at 25°C, Pa, calculated from $p°_S$ in Column 1 and the use of Equation (3-2)

Column 3: $p°_L$: l iquid sub-cooled vapor pressure at 25°C, as measured by Eitzer and Hites (1988, 1989)

Column 4: slope: the slope of Equation (3-6), equal to $Q_v/2.303R$

Column 5: b: intercept b of Equation (3-6)

Column 6: $p°_L$: liquid sub-cooled vapor pressure calculated at 20°C using the slope and intercept in Columns 4 and 5, and Equation (3-6)

* numbers without asterisks were based on ratios of Qv (CDD/Fs)/Qv (DDT) measured by Eitzer and Hitest (1989). Numbers with asterisks were assumed to be the same as for other members of the homologue group. OCDF was assumed to have the same ratio as OCDD.

Table 3-7. Particle fractions, ϕ, in four airsheds at 20°C for the dioxin-like congeners.

Congener	Clean Continental	Average Background	Background Plus Local Sources	Urban
2378-TCDD	0.10	0.29	0.49	0.75
12378-PCDD	0.44	0.74	0.87	0.95
123478-HxCDD	0.78	0.93	0.97	0.99
123678-HxCDD	0.78	0.93	0.97	0.99
123789-HxCDD	0.78	0.93	0.97	0.99
1234678-HpCDD	0.93	0.98	0.99	0.997
OCDD	0.98	0.995	0.998	0.999
2378-TCDF	0.09	0.27	0.47	0.73
12378-PCDF	0.27	0.57	0.75	0.91
23478-PCDF	0.38	0.69	0.84	0.94
123478-HxCDF	0.63	0.86	0.93	0.98
123678-HxCDF	0.63	0.86	0.93	0.98
123789-HxCDF	0.74	0.91	0.96	0.99
234678-HxCDF	0.74	0.91	0.96	0.99
1234678-HpCDF	0.86	0.96	0.98	0.99
1234789-HpCDF	0.92	0.98	0.99	0.997
OCDF	0.98	0.995	0.998	0.999

Table 3-8. Regression parameters slope m and intercept b for Equation (3-5), Log K_p = m Log $p°_L$ + b, based on field measurements of particle/gas distributions for CDD/Fs.

Reference	Slope, m	Intercept, b	r^2
Eitzer and Hites (1989), congeners	-0.775	-5.72	0.96
Hites (1991), homologues	-0.988	-6.87	0.87
Hunt and Maisel (1992), homologues	-0.620	-5.00	0.61
Weslch-Pausch, et al. (1995), homologues	-0.707	-5.73	0.99

Table 3-9. Comparison of monitored and modeled particulate percentage for CDD/F homologues at 20°C.

Homologue	Monitored (see below for study identification)				Modeled*
	1	2	3	4	
TCDD	23	10	19	10	49
PCDD	37	30	36	22	87
HxCDD	66	67	59	45	97
HpCDD	87	91	80	72	99
OCDD	96	98	91	90	99.8
TCDF	14	8	16	8	47
PCDF	31	24	31	18	79
HxCDF	63	64	57	43	93
HpCDF	87	90	79	71	99
OCDF	97	98	92	90	99.8

Study identification: 1 = Eitzer (1989); Eitzer and Hites (1989); 2 = Hites (1991); 3 = Hunt, et al. (1988); Hunt and Maisel (1992); 4 = Welsch-Pausch, et al. (1995)
* by Equation (3-1), $\theta = 3.5*10^{-6}$ cm^2 aerosol/cm^3 air, c = 17.2 Pa-cm

Table 3-10. Factors that influence the dry deposition removal rate in the atmosphere.

Micrometeorological Variables	Characteristics of Particles	Characteristics of Gases	Surface Variables
Aerodynamic roughness	Agglomeration	Chemical activity	Accommodation
Mass transfer of particles gases Heat transfer Momentum transfer Atmospheric stability Diffusion Friction velocity	Diameter Diffusion Effects Brownian Eddy Particle Momentum Heat Electrostatic effects	Diffusion effects Brownian Eddy Partial pressure in equilibrium with the surface Solubility	Edudates Trichomes Pubescence Wax Biotic surface Canopy growth Dormant Expanding
Inversion layer Pollutant concentration Relative humidity Seasonal variation Solar radiation Surface heating Temperature Terrain effects Turbulence Wind velocity Zero plane Displacement Effect Mass transfer of particles	Attraction Repulsion Gravity settling Hygroscopicity Impaction Interception Momentum Physical properties Resuspension Solubility Thermophoresis		Senescent Canopy structure Areal density Bark Bole Leaves Porosity Soils Stem Type Electrostatic properties Water Pollutant
Gases Heat transfer Momentum transfer			Penetration of canopy

Table 3-11. A summary of dry deposition velocities for particles.

Depositing Material	Particld Diameter (μm)	Deposition Surface	Deposition Velocity (cm/s)
Particles	0.03-30	grassland	10^{-3} - 40
Pollen	20 32-35 90-100	grassland grassland grassland	4.5 9.9 20
Natural aerosol Pb auto exhaust	1-10	grass shard	0.8

Source: Sehmel (1980).

Table 3-12. Generalized particle size distribution (μm), and proportion of available surface area, in particulate emissions from incineration.

Particle Diameter (μm)[a]	Particle Radius (μm)	Surface Area/ Volume	Fraction of Total Weight	Proportion Available Surface Area	Fraction of Total Surface Area
>15.0	7.50	0.400	0.128	0.0512	0.0149
12.5	6.25	0.480	0.105	0.0504	0.0146
8.1	4.05	0.741	0.104	0.0771	0.0224
5.5	2.75	1.091	0.073	0.0796	0.0231
3.6	1.80	1.667	0.103	0.1717	0.0499
2.0	1.00	3.000	0.105	0.3150	0.0915
1.1	0.55	5.455	0.082	0.4473	0.1290
0.7	0.40	7.500	0.076	0.5700	0.1656
<0.7	0.40	7.500	0.224	1.6800	0.4880

Total surface area: 3.4423 μm^2

Notes: a. Geometric mean diameter in a distribution. Distribution from EPA (1980).

Table 3-13. Unit wet deposition scavenging coefficients per particle diameter category (micrometers) used in the example ISCST3 analysis, expressed as 1/(sec-mm/hr).

Form of Precipitation	Particle Diameter Category (µm)		
	1	6.78	20
Liquid (rain)	0.43×10^{-4}	0.46×10^{-3}	0.66×10^{-3}
Frozen (snow)	0.14×10^{-4}	0.16×10^{-3}	0.22×10^{-3}

Table 3-14. Emission of CDD/Fs (g/sec) from the hypothetical incinerator.

Congener	Emission rate, g/sec	Vapor emissions, g/sec	Particulate emissions, g/sec	V/P ratio
2378-TCDD	$9.23 * 10^{-11}$	$4.71 * 10^{-11}$	$4.52 * 10^{-11}$	0.51/0.49
Other TCDD	$2.00 * 10^{-9}$	$1.02 * 10^{-9}$	$9.00 * 10^{-10}$	0.51/0.49
12378-PCDD	$1.93 * 10^{-10}$	$2.51 * 10^{-11}$	$1.68 * 10^{-10}$	0.13/0.87
Other PCDD	$1.91 * 10^{-9}$	$2.49 * 10^{-10}$	$1.66 * 10^{-9}$	0.13/0.87
123478-HxCDD	$2.50 * 10^{-10}$	$7.50 * 10^{-12}$	$2.43 * 10^{-10}$	0.03/0.97
123789-HxCDD	$3.63 * 10^{-10}$	$1.09 * 10^{-11}$	$3.52 * 10^{-10}$	0.03/0.97
123678-HxCDD	$3.30 * 10^{-10}$	$9.90 * 10^{-12}$	$3.20 * 10^{-10}$	0.03/0.97
Other HxCDDs	$3.19 * 10^{-9}$	$9.56 * 10^{-11}$	$3.09 * 10^{-9}$	0.03/0.97
1234678-HpCDD	$3.27 * 10^{-9}$	$3.27 * 10^{-11}$	$3.23 * 10^{-9}$	0.01/0.99
Other HpCDDs	$6.03 * 10^{-9}$	$6.03 * 10^{-11}$	$5.97 * 10^{-9}$	0.01/0.99
OCDD	$6.73 * 10^{-9}$	$1.35 * 10^{-11}$	$6.72 * 10^{-9}$	0.002/0.998
2378-TCDF	$6.03 * 10^{-9}$	$3.20 * 10^{-9}$	$2.84 * 10^{-9}$	0.53/0.47
Other TCDFs	$3.83 * 10^{-8}$	$2.03 * 10^{-8}$	$1.80 * 10^{-8}$	0.53/0.47
23478-PCDF	$6.33 * 10^{-10}$	$1.01 * 10^{-10}$	$5.32 * 10^{-10}$	0.16/0.84
12378-PCDF	$3.87 * 10^{-10}$	$9.67 * 10^{-11}$	$2.90 * 10^{-10}$	0.25/0.75
Other PCDFs	$1.09 * 10^{-8}$	$2.73 * 10^{-9}$	$8.19 * 10^{-9}$	0.25/0.75
123478-HxCDF	$9.20 * 10^{-10}$	$6.44 * 10^{-11}$	$8.56 * 10^{-10}$	0.07/0.93
123678-HxCDF	$8.70 * 10^{-10}$	$6.09 * 10^{-11}$	$8.09 * 10^{-10}$	0.07/0.93
123789-HxCDF	$5.73 * 10^{-10}$	$2.29 * 10^{-11}$	$5.50 * 10^{-10}$	0.04/0.96
234678-HxCDF	$3.33 * 10^{-10}$	$1.33 * 10^{-11}$	$3.20 * 10^{-10}$	0.04/0.96
Other HxCDFs	$2.10 * 10^{-9}$	$8.41 * 10^{-11}$	$2.02 * 10^{-9}$	0.04/0.96
1234678-HpCDF	$1.15 * 10^{-9}$	$2.31 * 10^{-11}$	$1.13 * 10^{-9}$	0.02/0.98
1234789-HpCDF	$5.00 * 10^{-10}$	$5.00 * 10^{-12}$	$4.95 * 10^{-10}$	0.01/0.99
Other HpCDFs	$5.35 * 10^{-9}$	$5.35 * 10^{-11}$	$5.29 * 10^{-9}$	0.01/0.99
OCDF	$2.23 * 10^{-9}$	$4.47 * 10^{-12}$	$2.23 * 10^{-9}$	0.002/0.998

Table 3-15. Modeling parameters used in the ISCST3 modeling of CDD/F emissions from the hypothetical incinerator.

Description	Value
General	Modeled after actual organic waste incinerator
Rate of organic waste combustion	200 metric tons per day
Air pollution control system	dry scrubber combined with a baghouse (fabric filters) resulting in 99% reduction of CDDs/CDFs
Model Options: Terrain adjustments	Yes
Stack downwash	No
Gradual Plume Rise	Yes
Buoyancy induced dispersion	Yes
Gravitational settling/deposition	Yes
Wet deposition	Yes
Calm winds processing option	Yes
Building wake effects	No
Stack height	30.48 m
Stack diameter	1.52 m
Anemometer height	10 m
Terrain	simple
Stack temperatre	400 °K
Stack exit velocity	8.9 m/sec
Source elevation	0 m
Z minutes	10 m
Exponents for power law wind increase with height:	0.07, 0.07, 0.10, 0.15, 0.35, 0.55
Particle size categories for dry/wet deposition analysis	
Category 1	$\leq$ 2 µm represented by 1.0 µm diameter
Category 2	>2 - $\leq$ 10 µm represented by 6.78 µm
Category 3	>10 µm represented by 20.0 µm
Particle density	1.4 g/cm^3
Fraction of CDD/F particle bound emission by particle size category: Category 1	0.88
Category 2	0.09
Category 3	0.03
Dry deposition velocities predicted by the CARB algorithm: 1.0 µm	7.11 *10^{-3} cm/sec
6.78 µm	2.87 * 10^{-1} cm/sec
20.0 µm	2.47 cm/sec
Wet deposition scavenging coefficients	Table 3-13
National Weather Service data	Denver-Stapleton Airport: 1989
Grid System	Polar

Table 3-16. Predicted average vapor-phase concentrations of CDD/Fs (pg/m^3; columns are downwind distance in km).

Congener	0.2	0.5	0.8	0.9	1	2	5	10	20	30	40	50
2378-TCDD	$4.34*10^{-7}$	$7.02*10^{-6}$	$9.14*10^{-6}$	$9.19*10^{-6}$	$9.10*10^{-6}$	$6.06*10^{-6}$	$2.94*10^{-6}$	$1.10*10^{-6}$	$4.57*10^{-7}$	$2.73*10^{-7}$	$1.91*10^{-7}$	$1.45*10^{-7}$
Other TCDD	$9.40*10^{-6}$	$1.52*10^{-4}$	$1.98*10^{-4}$	$1.99*10^{-4}$	$1.97*10^{-4}$	$1.31*10^{-4}$	$5.40*10^{-5}$	$2.37*10^{-5}$	$9.90*10^{-6}$	$5.92*10^{-6}$	$4.13*10^{-6}$	$3.14*10^{-6}$
12378-PCDD	$2.32*10^{-7}$	$3.75*10^{-6}$	$4.88*10^{-6}$	$4.91*10^{-6}$	$4.86*10^{-6}$	$3.23*10^{-6}$	$1.33*10^{-6}$	$5.85*10^{-7}$	$2.44*10^{-7}$	$1.46*10^{-7}$	$1.02*10^{-7}$	$7.74*10^{-8}$
Other PCDD	$2.29*10^{-6}$	$3.71*10^{-5}$	$4.83*10^{-5}$	$4.86*10^{-5}$	$4.81*10^{-5}$	$3.20*10^{-5}$	$1.32*10^{-5}$	$5.79*10^{-6}$	$2.42*10^{-6}$	$1.44*10^{-6}$	$1.01*10^{-6}$	$7.66*10^{-7}$
123478-HxCDD	$6.92*10^{-8}$	$1.12*10^{-6}$	$1.46*10^{-6}$	$1.46*10^{-6}$	$1.45*10^{-6}$	$9.65*10^{-7}$	$3.97*10^{-7}$	$1.74*10^{-7}$	$7.28*10^{-8}$	$4.35*10^{-8}$	$3.04*10^{-8}$	$2.31*10^{-8}$
123789-HxCDD	$1.00*10^{-7}$	$1.63*10^{-6}$	$2.11*10^{-6}$	$2.13*10^{-6}$	$2.11*10^{-6}$	$1.40*10^{-6}$	$5.77*10^{-7}$	$2.54*10^{-7}$	$1.06*10^{-7}$	$6.32*10^{-8}$	$4.41*10^{-8}$	$3.36*10^{-8}$
123678-HxCDD	$9.13*10^{-8}$	$1.48*10^{-6}$	$1.92*10^{-6}$	$1.93*10^{-6}$	$1.91*10^{-6}$	$1.27*10^{-6}$	$5.24*10^{-7}$	$2.30*10^{-7}$	$9.61*10^{-8}$	$5.74*10^{-8}$	$4.01*10^{-8}$	$3.05*10^{-8}$
Other HxCDD	$8.81*10^{-7}$	$1.43*10^{-5}$	$1.85*10^{-5}$	$1.87*10^{-5}$	$1.85*10^{-5}$	$1.23*10^{-5}$	$5.06*10^{-6}$	$2.22*10^{-6}$	$9.28*10^{-7}$	$5.54*10^{-7}$	$3.87*10^{-7}$	$2.94*10^{-7}$
1234678-HpCDD	$3.01*10^{-7}$	$4.87*10^{-6}$	$6.34*10^{-6}$	$6.38*10^{-6}$	$6.31*10^{-6}$	$4.20*10^{-6}$	$1.73*10^{-6}$	$7.60*10^{-7}$	$3.17*10^{-7}$	$1.89*10^{-7}$	$1.32*10^{-7}$	$1.01*10^{-7}$
Other HpCDD	$5.56*10^{-7}$	$9.00*10^{-6}$	$1.17*10^{-5}$	$1.18*10^{-5}$	$1.17*10^{-5}$	$7.76*10^{-6}$	$3.19*10^{-6}$	$1.40*10^{-6}$	$5.86*10^{-7}$	$3.50*10^{-7}$	$2.44*10^{-7}$	$1.86*10^{-7}$
OCDD	$1.24*10^{-7}$	$2.01*10^{-6}$	$2.61*10^{-6}$	$2.63*10^{-6}$	$2.60*10^{-6}$	$1.73*10^{-6}$	$7.13*10^{-7}$	$3.13*10^{-7}$	$1.31*10^{-7}$	$7.81*10^{-8}$	$5.45*10^{-8}$	$4.15*10^{-8}$
2378-TCDF	$2.95*10^{-5}$	$4.77*10^{-4}$	$6.20*10^{-4}$	$6.24*10^{-4}$	$6.18*10^{-4}$	$4.11*10^{-4}$	$1.69*10^{-4}$	$7.44*10^{-5}$	$3.10*10^{-5}$	$1.85*10^{-5}$	$1.30*10^{-5}$	$9.85*10^{-6}$
Other TCDF	$1.87*10^{-4}$	$3.03*10^{-3}$	$3.94*10^{-3}$	$3.97*10^{-3}$	$3.93*10^{-3}$	$2.61*10^{-3}$	$1.08*10^{-3}$	$4.73*10^{-4}$	$1.97*10^{-4}$	$1.18*10^{-4}$	$8.23*10^{-5}$	$6.26*10^{-5}$
23478-PCDF	$9.34*10^{-7}$	$1.51*10^{-5}$	$1.97*10^{-5}$	$1.98*10^{-5}$	$1.96*10^{-5}$	$1.30*10^{-5}$	$5.36*10^{-6}$	$2.36*10^{-6}$	$9.84*10^{-7}$	$5.88*10^{-7}$	$4.10*10^{-7}$	$3.12*10^{-7}$
12378-PCDF	$8.91*10^{-7}$	$1.44*10^{-5}$	$1.88*10^{-5}$	$1.89*10^{-5}$	$1.87*10^{-5}$	$1.24*10^{-5}$	$5.12*10^{-6}$	$2.25*10^{-6}$	$9.39*10^{-7}$	$5.61*10^{-7}$	$3.92*10^{-7}$	$2.98*10^{-7}$
Other PCDF	$2.52*10^{-5}$	$4.07*10^{-4}$	$5.29*10^{-4}$	$5.33*10^{-4}$	$5.27*10^{-4}$	$3.51*10^{-4}$	$1.44*10^{-4}$	$6.35*10^{-5}$	$2.65*10^{-5}$	$1.58*10^{-5}$	$1.10*10^{-5}$	$8.40*10^{-6}$
123478-HxCDF	$5.94*10^{-7}$	$9.60*10^{-6}$	$1.25*10^{-5}$	$1.26*10^{-5}$	$1.24*10^{-5}$	$8.29*10^{-6}$	$3.41*10^{-6}$	$1.50*10^{-6}$	$6.25*10^{-7}$	$3.74*10^{-7}$	$2.61*10^{-7}$	$1.98*10^{-7}$
123678-HxCDF	$5.61*10^{-7}$	$9.08*10^{-6}$	$1.18*10^{-5}$	$1.19*10^{-5}$	$1.18*10^{-5}$	$7.84*10^{-6}$	$3.22*10^{-6}$	$1.42*10^{-6}$	$5.91*10^{-7}$	$3.53*10^{-7}$	$2.47*10^{-7}$	$1.88*10^{-7}$
123789-HxCDF	$2.11*10^{-7}$	$3.42*10^{-6}$	$4.45*10^{-6}$	$4.48*10^{-6}$	$4.43*10^{-6}$	$2.95*10^{-6}$	$1.21*10^{-6}$	$5.33*10^{-7}$	$2.23*10^{-7}$	$1.33*10^{-7}$	$9.29*10^{-8}$	$7.06*10^{-8}$
234678-HxCDF	$1.23*10^{-7}$	$1.99*10^{-6}$	$2.59*10^{-6}$	$2.60*10^{-6}$	$2.58*10^{-6}$	$1.72*10^{-6}$	$7.06*10^{-7}$	$3.10*10^{-7}$	$1.29*10^{-7}$	$7.73*10^{-8}$	$5.40*10^{-8}$	$4.11*10^{-8}$
Other HxCDF	$7.76*10^{-7}$	$1.25*10^{-5}$	$1.63*10^{-5}$	$1.64*10^{-5}$	$1.63*10^{-5}$	$1.08*10^{-5}$	$4.45*10^{-6}$	$1.96*10^{-6}$	$8.17*10^{-7}$	$4.88*10^{-7}$	$3.41*10^{-7}$	$2.59*10^{-7}$
1234678-HpCDF	$2.13*10^{-7}$	$3.44*10^{-6}$	$4.47*10^{-6}$	$4.50*10^{-6}$	$4.46*10^{-6}$	$2.97*10^{-6}$	$1.22*10^{-6}$	$5.37*10^{-7}$	$2.24*10^{-7}$	$1.34*10^{-7}$	$9.34*10^{-8}$	$7.10*10^{-8}$
1234789-HpCDF	$4.61*10^{-8}$	$7.46*10^{-7}$	$9.70*10^{-7}$	$9.76*10^{-7}$	$9.66*10^{-7}$	$6.43*10^{-7}$	$2.65*10^{-7}$	$1.16*10^{-7}$	$4.86*10^{-8}$	$2.90*10^{-8}$	$2.03*10^{-8}$	$1.54*10^{-8}$
Other HpCDF	$4.93*10^{-7}$	$7.97*10^{-6}$	$1.04*10^{-5}$	$1.04*10^{-5}$	$1.03*10^{-5}$	$6.88*10^{-6}$	$2.83*10^{-6}$	$1.24*10^{-6}$	$5.19*10^{-7}$	$3.10*10^{-7}$	$2.17*10^{-7}$	$1.65*10^{-7}$
OCDF	$4.12*10^{-8}$	$6.66*10^{-7}$	$8.67*10^{-7}$	$8.72*10^{-7}$	$8.63*10^{-7}$	$5.75*10^{-7}$	$2.36*10^{-7}$	$1.04*10^{-7}$	$4.34*10^{-8}$	$2.59*10^{-8}$	$1.81*10^{-8}$	$1.38*10^{-8}$

Table 3-17. Predicted average particle-phase concentrations of CDD/Fs (pg/m^3 ; columns are downwind distance in km).

Congener	0.2	0.5	0.8	0.9	1	2	5	10	20	30	40	50
2378-TCDD	$4.16*10^{-7}$	$6.71*10^{-6}$	$8.70*10^{-6}$	$8.75*10^{-6}$	$8.66*10^{-6}$	$5.76*10^{-6}$	$2.36*10^{-6}$	$1.03*10^{-6}$	$4.22*10^{-7}$	$2.49*10^{-7}$	$1.72*10^{-7}$	$1.29*10^{-7}$
Other TCDD	$8.28*10^{-6}$	$1.33*10^{-4}$	$1.73*10^{-4}$	$1.74*10^{-4}$	$1.72*10^{-4}$	$1.14*10^{-4}$	$4.69*10^{-5}$	$2.04*10^{-5}$	$8.40*10^{-6}$	$4.95*10^{-6}$	$3.42*10^{-6}$	$2.57*10^{-6}$
12378-PCDD	$1.55*10^{-6}$	$2.49*10^{-5}$	$3.24*10^{-5}$	$3.25*10^{-5}$	$3.22*10^{-5}$	$2.14*10^{-5}$	$8.76*10^{-6}$	$3.82*10^{-6}$	$1.57*10^{-6}$	$9.25*10^{-7}$	$6.39*10^{-7}$	$4.81*10^{-7}$
Other PCDD	$1.53*10^{-5}$	$2.47*10^{-4}$	$3.20*10^{-4}$	$3.22*10^{-4}$	$3.19*10^{-4}$	$2.12*10^{-4}$	$8.67*10^{-5}$	$3.78*10^{-5}$	$1.55*10^{-5}$	$9.16*10^{-6}$	$6.33*10^{-6}$	$4.76*10^{-6}$
123478-HxCDD	$2.23*10^{-6}$	$3.59*10^{-5}$	$4.66*10^{-5}$	$4.69*10^{-5}$	$4.64*10^{-5}$	$3.08*10^{-5}$	$1.26*10^{-5}$	$5.50*10^{-6}$	$2.26*10^{-6}$	$1.33*10^{-6}$	$9.22*10^{-7}$	$6.94*10^{-7}$
123789-HxCDD	$3.24*10^{-6}$	$5.22*10^{-5}$	$6.78*10^{-5}$	$6.82*10^{-5}$	$6.75*10^{-5}$	$4.48*10^{-5}$	$1.84*10^{-5}$	$8.00*10^{-6}$	$3.2*10^{-6}$	$1.94*10^{-6}$	$1.34*10^{-6}$	$1.01*10^{-6}$
123678-HxCDD	$2.94*10^{-6}$	$4.74*10^{-5}$	$6.16*10^{-5}$	$6.19*10^{-5}$	$6.13*10^{-5}$	$4.07*10^{-5}$	$1.67*10^{-5}$	$7.27*10^{-6}$	$2.99*10^{-6}$	$1.76*10^{-6}$	$1.22*10^{-6}$	$9.15*10^{-7}$
Other HxCDD	$2.84*10^{-5}$	$4.58*10^{-4}$	$5.95*10^{-4}$	$5.98*10^{-4}$	$5.92*10^{-4}$	$3.93*10^{-4}$	$1.61*10^{-4}$	$7.02*10^{-5}$	$2.88*10^{-5}$	$1.70*10^{-5}$	$1.17*10^{-5}$	$8.84*10^{-6}$
1234678-HpCDD	$2.98*10^{-5}$	$4.79*10^{-4}$	$6.22*10^{-4}$	$6.26*10^{-4}$	$6.19*10^{-4}$	$4.11*10^{-4}$	$1.69*10^{-4}$	$7.34*10^{-5}$	$3.02*10^{-5}$	$1.78*10^{-5}$	$1.23*10^{-5}$	$9.25*10^{-6}$
Other HpCDD	$5.50*10^{-5}$	$8.85*10^{-4}$	$1.15*10^{-3}$	$1.16*10^{-3}$	$1.14*10^{-3}$	$7.60*10^{-4}$	$3.11*10^{-4}$	$1.36*10^{-4}$	$5.57*10^{-5}$	$3.29*10^{-5}$	$2.27*10^{-5}$	$1.71*10^{-5}$
OCDD	$6.18*10^{-5}$	$9.96*10^{-4}$	$1.29*10^{-3}$	$1.30*10^{-3}$	$1.29*10^{-3}$	$8.55*10^{-4}$	$3.50*10^{-4}$	$1.53*10^{-4}$	$6.27*10^{-5}$	$3.70*10^{-5}$	$2.55*10^{-5}$	$1.92*10^{-5}$
2378-TCDF	$2.61*10^{-5}$	$4.20*10^{-4}$	$5.45*10^{-4}$	$5.49*10^{-4}$	$5.43*10^{-4}$	$3.61*10^{-4}$	$1.48*10^{-4}$	$6.44*10^{-5}$	$2.65*10^{-5}$	$1.56*10^{-5}$	$1.08*10^{-5}$	$8.11*10^{-6}$
Other TCDF	$1.66*10^{-4}$	$2.67*10^{-3}$	$3.47*10^{-3}$	$3.49*10^{-3}$	$3.45*10^{-3}$	$2.2*10^{-3}$	$9.39*10^{-4}$	$4.09*10^{-4}$	$1.68*10^{-4}$	$9.91*10^{-5}$	$6.85*10^{-5}$	$5.15*10^{-5}$
23478-PCDF	$4.89*10^{-6}$	$7.89*10^{-5}$	$1.02*10^{-4}$	$1.03*10^{-4}$	$1.02*10^{-4}$	$6.77*10^{-5}$	$2.77*10^{-5}$	$1.21*10^{-5}$	$4.96*10^{-6}$	$2.93*10^{-6}$	$2.02*10^{-6}$	$1.52*10^{-6}$
12378-PCDF	$2.67*10^{-6}$	$4.30*10^{-5}$	$5.58*10^{-5}$	$5.61*10^{-5}$	$5.55*10^{-5}$	$3.69*10^{-5}$	$1.51*10^{-5}$	$6.58*10^{-6}$	$2.71*10^{-6}$	$1.60*10^{-6}$	$1.10*10^{-6}$	$8.29*10^{-7}$
Other PCDF	$7.53*10^{-5}$	$1.21*10^{-3}$	$1.57*10^{-3}$	$1.58*10^{-3}$	$1.57*10^{-3}$	$1.04*10^{-3}$	$4.27*10^{-4}$	$1.86*10^{-4}$	$7.64*10^{-5}$	$4.50*10^{-5}$	$3.11*10^{-5}$	$2.34*10^{-5}$
123478-HxCDF	$7.87*10^{-6}$	$1.27*10^{-4}$	$1.65*10^{-4}$	$1.66*10^{-4}$	$1.64*10^{-4}$	$1.09*10^{-4}$	$4.46*10^{-5}$	$1.94*10^{-5}$	$7.98*10^{-6}$	$4.71*10^{-6}$	$3.25*10^{-6}$	$2.45*10^{-6}$
123678-HxCDF	$7.44*10^{-6}$	$1.20*10^{-4}$	$1.56*10^{-4}$	$1.57*10^{-4}$	$1.55*10^{-4}$	$1.03*10^{-4}$	$4.22*10^{-5}$	$1.84*10^{-5}$	$7.55*10^{-6}$	$4.45*10^{-6}$	$3.07*10^{-6}$	$2.31*10^{-6}$
123789-HxCDF	$5.06*10^{-6}$	$8.16*10^{-5}$	$1.06*10^{-4}$	$1.06*10^{-4}$	$1.05*10^{-4}$	$7.00*10^{-5}$	$2.87*10^{-5}$	$1.25*10^{-5}$	$5.14*10^{-6}$	$3.03*10^{-6}$	$2.09*10^{-6}$	$1.57*10^{-6}$
234678-HxCDF	$2.94*10^{-6}$	$4.74*10^{-5}$	$6.16*10^{-5}$	$6.19*10^{-5}$	$6.12*10^{-5}$	$4.07*10^{-5}$	$1.67*10^{-5}$	$7.26*10^{-6}$	$2.99*10^{-6}$	$1.76*10^{-6}$	$1.22*10^{-6}$	$9.15*10^{-7}$
Other HxCDF	$1.84*10^{-5}$	$2.99*10^{-4}$	$3.88*10^{-4}$	$3.91*10^{-4}$	$3.86*10^{-4}$	$2.57*10^{-4}$	$1.05*10^{-4}$	$4.58*10^{-5}$	$1.88*10^{-5}$	$1.11*10^{-5}$	$7.67*10^{-6}$	$5.77*10^{-6}$
1234678-HpCDF	$1.04*10^{-5}$	$1.68*10^{-4}$	$2.17*10^{-4}$	$2.19*10^{-4}$	$2.16*10^{-4}$	$1.44*10^{-4}$	$5.89*10^{-5}$	$2.57*10^{-5}$	$1.05*10^{-5}$	$6.22*10^{-6}$	$4.30*10^{-6}$	$3.23*10^{-6}$
1234789-HpCDF	$4.55*10^{-6}$	$7.37*10^{-5}$	$9.52*10^{-5}$	$9.58*10^{-5}$	$9.47*10^{-5}$	$6.30*10^{-5}$	$2.58*10^{-5}$	$1.12*10^{-5}$	$4.62*10^{-6}$	$2.72*10^{-6}$	$1.88*10^{-6}$	$1.42*10^{-6}$
Other HpCDF	$4.87*10^{-5}$	$7.85*10^{-4}$	$1.05*10^{-3}$	$1.02*10^{-3}$	$1.01*10^{-3}$	$6.73*10^{-4}$	$2.76*10^{-4}$	$1.20*10^{-4}$	$4.94*10^{-5}$	$2.91*10^{-5}$	$2.01*10^{-5}$	$1.51*10^{-5}$
OCDF	$2.05*10^{-5}$	$3.30*10^{-4}$	$4.29*10^{-4}$	$4.31*10^{-4}$	$4.27*10^{-4}$	$2.84*10^{-4}$	$1.16*10^{-4}$	$5.06*10^{-5}$	$2.08*10^{-5}$	$1.23*10^{-5}$	$8.47*10^{-6}$	$6.37*10^{-6}$

Table 3-18. Predicted annual dry deposition of particle-bound CDD/Fs (pg/m^2-yr; columns are downwind distance in km).

Congener	0.2	0.5	0.8	0.9	1	2	5	10	20	30	40	50
2378-TCDD	0.028	0.444	0.584	0.578	0.561	0.315	0.097	0.035	0.010	0.005	0.003	0.002
Other TCDD	0.558	8.84	11.6	11.5	11.2	6.26	1.93	0.666	0.207	0.099	0.063	0.045
12378-PCDD	0.104	1.65	2.17	2.15	2.09	1.17	0.360	0.124	0.039	0.019	0.012	0.008
Other PCDD	1.03	16.3	21.5	21.3	20.6	11.6	3.56	1.23	0.393	0.183	0.117	0.083
123478-HxCDD	0.150	2.38	3.13	3.10	3.01	1.69	0.519	0.179	0.059	0.027	0.017	0.012
123789-HxCDD	0.219	3.46	4.55	4.50	4.37	2.45	0.754	0.261	0.081	0.039	0.024	0.018
123678-HxCDD	0.198	3.14	4.13	4.09	3.97	2.23	0.685	0.237	0.074	0.035	0.024	0.016
Other HxCDD	1.92	30.4	39.9	39.5	38.3	21.5	6.61	2.29	0.711	0.340	0.216	0.155
1234678-HpCDD	2.01	31.8	41.7	41.3	40.1	22.5	6.92	2.39	0.744	0.356	0.226	0.162
Other HpCDD	3.70	58.7	77.1	76.3	74.1	41.6	12.8	4.42	1.37	0.657	0.418	0.299
OCDD	4.17	66.0	86.7	85.9	83.3	46.8	14.4	4.97	1.55	0.739	4.70	0.336
2378-TCDF	1.76	27.8	36.6	36.2	35.2	19.7	6.07	2.10	0.652	0.312	0.198	0.142
Other TCDF	11.2	177.0	232.0	230.0	223.0	125.0	38.6	13.3	4.12	1.98	1.26	0.903
23478-PCDF	0.330	5.22	6.86	6.80	6.60	3.70	1.14	0.394	0.122	0.059	0.037	0.027
12378-PCDF	0.182	2.85	3.74	3.71	3.60	2.02	0.621	0.215	0.067	0.032	0.020	0.015
Other PCDF	5.07	80.4	106.0	105.0	101.0	57.0	17.5	6.06	1.88	0.900	0.573	0.409
123478-HxCDF	0.530	8.40	11.0	10.9	10.6	5.95	1.83	0.633	0.197	0.094	0.060	0.043
123678-HxCDF	.0502	7.95	10.4	10.3	10.0	5.63	1.73	0.599	0.186	0.089	0.057	0.041
123789-HxCDF	0.341	5.40	7.10	7.03	6.82	3.83	1.18	0.407	0.127	0.061	0.039	0.028
234678-HxCDF	0.198	3.14	4.13	4.09	3.97	2.23	0.685	0.237	0.074	0.035	0.022	0.016
Other HxCDF	1.25	19.8	26.0	25.8	25.0	14.1	4.32	1.49	0.464	0.222	0.141	0.101
1234678-HpCDF	0.701	11.1	14.6	14.4	14.0	7.87	2.42	0.836	0.260	0.124	0.079	0.057
1234789-HpCDF	0.307	4.86	6.39	6.33	6.14	3.45	1.06	0.366	0.114	0.054	0.035	0.025
Other HpCDF	3.28	52.0	68.3	67.6	65.6	36.8	11.3	3.92	1.22	0.582	0.371	0.265
OCDF	1.38	21.9	28.8	28.5	27.6	15.5	0.477	0.165	0.051	0.245	0.156	0.111

Table 3-19. Predicted annual wet deposition of particle-bound CDDs/Fs (pg/m^2-yr; columns are downwind distance in km).

Congener	0.2	0.5	0.8	0.9	1	2	5	10	20	30	40	50
2378-TCDD	1.80	0.684	0.406	0.356	0.315	0.143	0.046	0.019	0.007	0.004	0.003	0.002
Other TCDD	35.9	13.6	8.07	7.07	6.27	2.81	0918	0.369	0.144	0.081	0.054	0.036
12378-PCDD	6.71	2.54	1.51	1.32	1.17	0.525	0.172	0.069	0.027	0.015	0.010	0.007
Other PCDD	66.4	25.2	14.9	13.1	11.6	5.19	1.70	0.683	0.266	0.150	0.100	0.067
123478-HxCDD	9.67	3.66	2.18	1.91	1.69	0.757	0.247	0.099	0.039	0.022	0.015	0.010
123789-HxCDD	14.1	5.33	3.16	2.77	2.46	1.10	0.359	0.144	0.056	0.032	0.021	0.014
123678-HxCDD	12.8	4.84	2.87	2.52	2.23	0.999	0.327	0.131	0.051	0.029	0.019	0.013
Other HxCDD	123.0	46.7	27.7	24.3	21.5	9.64	3.15	1.27	0.495	0.278	0.185	0.124
1234678-HpCDD	129.0	48.9	29.0	25.4	22.5	10.1	3.30	1.33	0.517	0.291	0.194	0.129
Other HpCDD	238.0	90.3	53.6	46.9	41.6	18.6	6.09	2.45	0.956	0.538	0.358	0.239
OCDD	268.0	102.0	60.3	52.8	46.8	21.0	6.85	2.76	10.8	0.605	0.403	0.269
2378-TCDF	113.0	42.8	25.4	22.3	19.8	8.85	2.89	1.16	0.454	0.255	0.170	0.113
Other TCDF	719.0	272.0	162.0	142.0	126.0	56.2	18.4	7.39	2.88	1.62	1.08	0.721
23478-PCDF	21.2	8.04	4.77	4.18	3.71	1.66	0.543	0.218	0.085	0.048	0.032	0.021
12378-PCDF	11.6	4.38	2.60	2.28	2.02	0.905	0.296	0.119	0.046	0.026	0.017	0.012
Other PCDF	326.0	124.0	73.4	64.3	57.0	25.5	8.35	3.36	1.31	0.737	0.491	0.327
123478-HxCDF	34.1	12.9	7.67	6.73	5.96	2.67	0.873	0.351	0.137	0.077	0.051	0.034
123678-HxCDF	32.3	12.2	7.26	6.36	5.64	2.52	0.825	0.332	0.129	0.073	0.049	0.032
123789-HxCDF	22.0	8.32	4.94	4.33	3.84	1.72	0.561	0.226	0.088	0.049	0.033	0.022
234678-HxCDF	12.8	4.84	2.87	2.52	2.23	0.998	0.326	0.131	0.051	0.029	0.019	0.013
Other HxCDF	80.5	30.5	18.1	15.9	14.1	6.30	2.06	0.828	0.323	0.182	0.121	0.081
1234678-HpCDF	45.1	17.1	10.1	8.88	7.88	3.53	1.15	0.463	0.181	0.102	0.068	0.045
1234789-HpCDF	19.7	7.48	4.44	3.89	3.45	1.54	0.505	0.203	0.079	0.045	0.029	0.020
Other HpCDF	211.0	80.0	47.5	41.6	36.9	16.5	5.40	2.17	0.847	0.476	0.318	0.212
OCDF	88.9	33.7	20.0	17.5	15.5	6.95	2.27	0.914	0.357	0.201	0.134	0.089

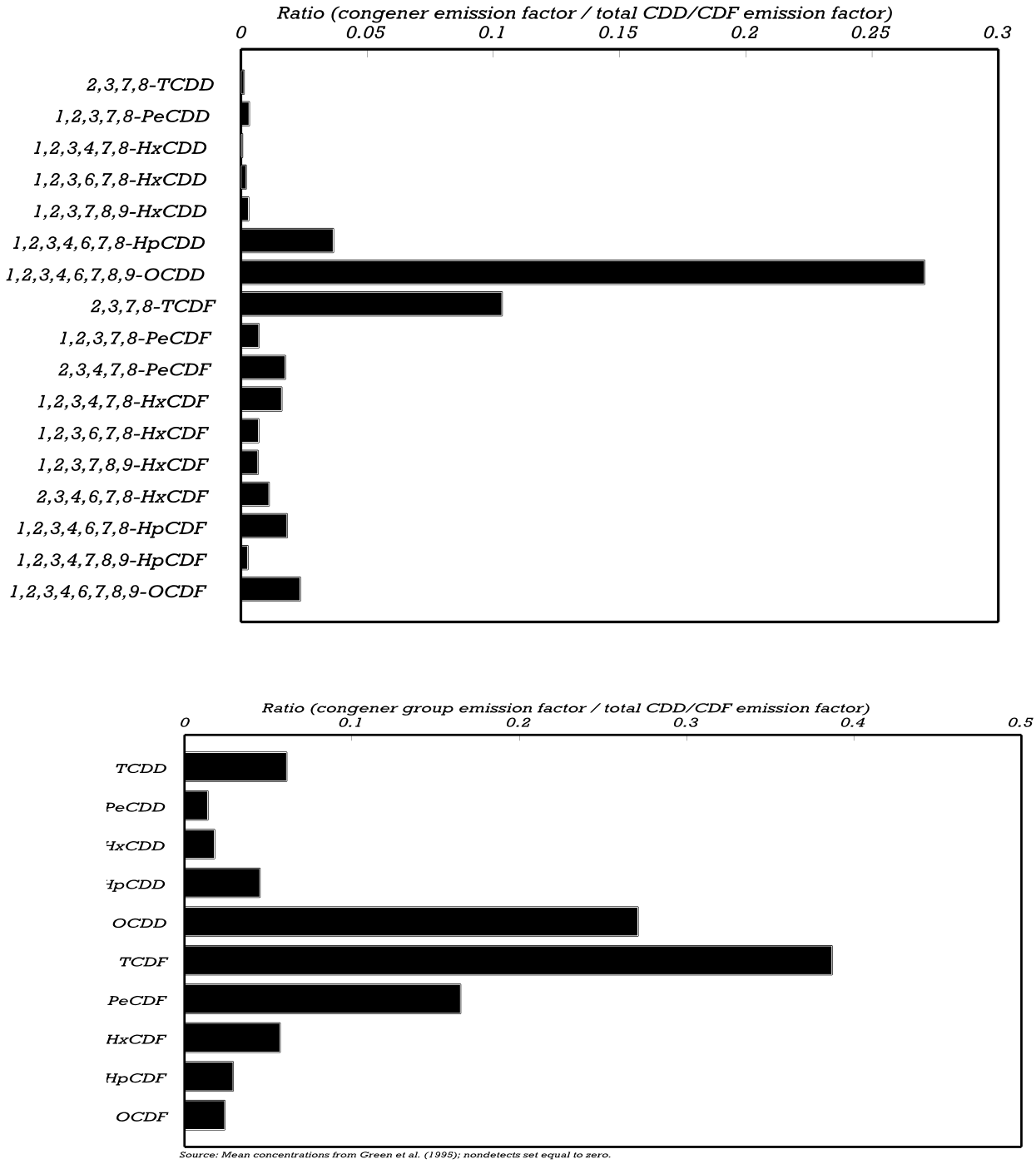


Figure 3-1. Example of a congener and a homologue profile from a sewage sludge incinerator

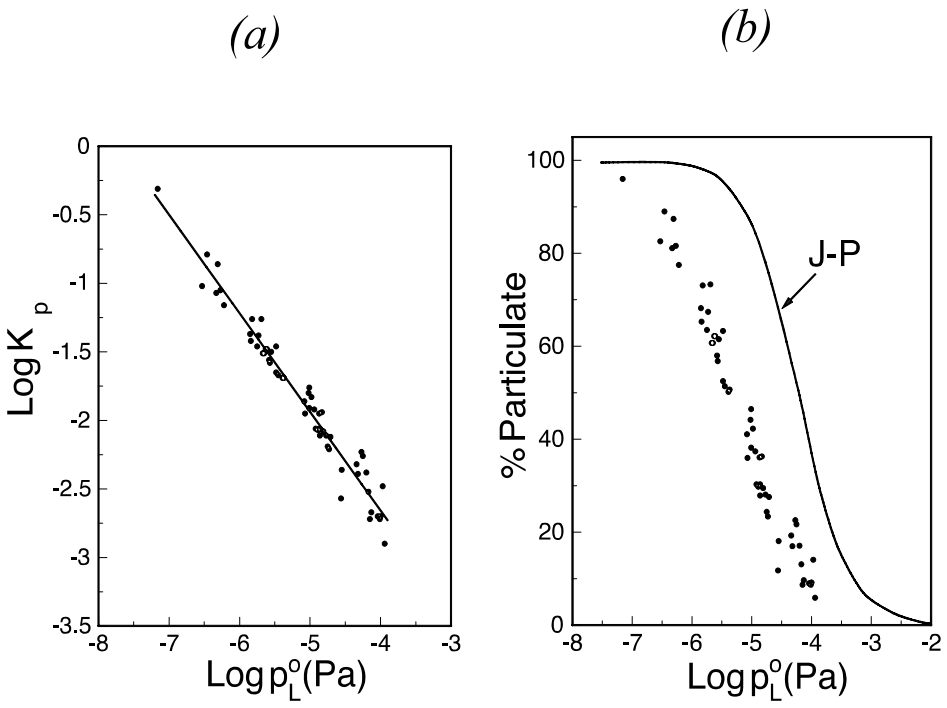
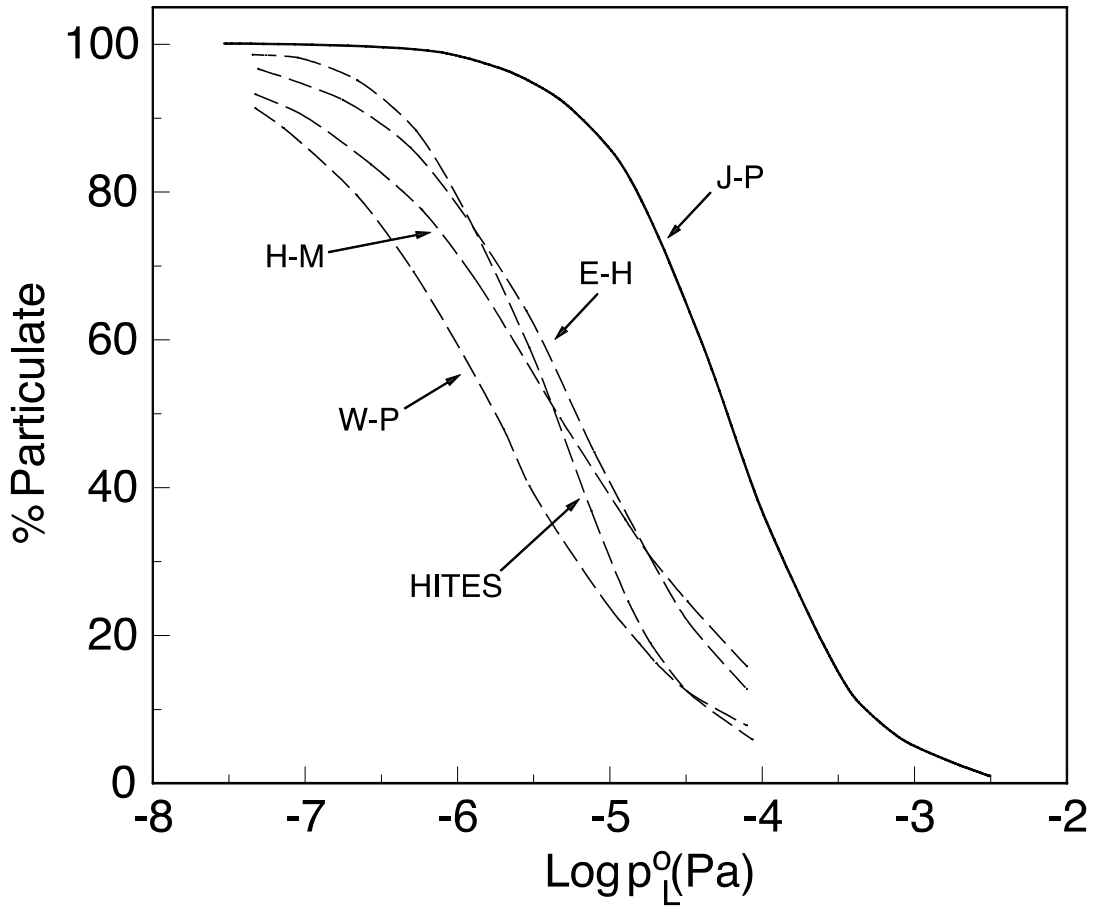


Figure 3-2. The relationships between the log of liquid sub-cooled vapor pressure, $p_L°$,0 and the particle-gas partition coefficient, K_p, (figure (a)), and between $p_L°$ and modeled (as indicated by "J-P" in figure (b)) and measured percent particulate-phase in the ambient air (measurements from Eitzer & Hites (1989)).



KEY: E-H = Eitzer and Hites (1989); HITES = Hites (1991)
H-M = Hunt and Maisel (1990); Hunt and Maisel (1992)
W-P = Welsch-Pausch, et al. (1995)

Figure 3-3. Comparison of measured particulate percentages of PCDD/F on a homolog basis to predictions of the Junge-Pankow model as a function of the sub-cooled liquid vapor pressure, $p°_L$, of the homolog groups.

4. ESTIMATING EXPOSURE MEDIA CONCENTRATIONS

4.1. INTRODUCTION

The purpose of this chapter is twofold. First, it describes the algorithms used to determine exposure media concentrations of the dioxin-like compounds. Discussion of the algorithms are structured around three "source categories." These categories roughly translate to beginning points, or origins, of contamination. The source categories are also the basis for the example scenarios described in Chapter 5. Second, it provides information about all the model parameters and justification for the values selected for the demonstration of methodologies in Chapter 5. Parameter discussions appear immediately following descriptions of modeling methodologies.

Section 4.2 provides an introduction to the type of modeling used in this assessment. Section 4.3 describes the algorithms used for the first source category, soil contamination, where the dioxin-like compounds occur in surface soils. The exposures could occur at the site of contamination or the exposures could occur off the site of contamination. Section 4.3 describes the differences in modeling for these two. Section 4.4 describes algorithms to determine exposure media concentrations resulting from stack emissions, the second source category. Chapter 3 laid the groundwork for this section by describing the use of air dispersion/deposition models as applied to a point source to generate two key quantities: air-borne contaminant vapor phase concentrations at a site of exposure, and particulate phase deposition rates. Section 4.4 describes how modeled concentrations and depositions translate to soil, vegetative, and water concentrations. Section 4.5 concludes the chapter with a discussion of algorithms specific to the third source category, point-source effluent discharges into surface water bodies.

Algorithms are presented which estimate exposure media concentrations for: 1) surface soils, 2) surface water impacts: suspended and bottom sediment and dissolved phase concentrations, 3) air including the vapor phase and in particulate form, and 4) biota including beef, milk, fruit and vegetables, and fish.

4.2. BACKGROUND FOR SOLUTION ALGORITHMS

Literally hundreds of fate and transport models have been published which differ widely in their technical sophistication, level of spatial or temporal resolution, need for site specific parameterization, and so on. This can make selection of the most appropriate one for any particular situation difficult. Relatively simple, screening level models are used to model fate, transport, and transfer of dioxin-like compounds from the source to the exposure media in this

assessment. Simple assumptions are often made in order to arrive at the desired result, which is long-term average exposure media concentrations. Perhaps the most critical of the assumptions made is the assumption that the source strength remains constant throughout the period of exposure: the initial soil concentration of dioxin-like compound remains the same for that exposure period, and stack emissions and effluent discharges remain steady throughout this period.

It is important to understand that EPA is not endorsing the algorithms of this assessment as the best ones for use in all dioxin assessments. They are suggested as reasonable starting points for site-specific or general assessments, and as will be discussed shortly, most multi-media exposure modeling has included similar screening level approaches. The assumptions behind models are described carefully throughout this chapter. If these assumptions do not apply to a particular situation, or where assessors require more spatial or temporal resolution, more complex models should be selected. References to other models are made in this and other sections throughout the chapter. Also, Chapter 7 compares the models of this assessment to alternate models for several of the algorithms.

Finally, it cannot be overemphasized that measured concentrations are generally more reliable than modeled ones. Assessors should use measured concentrations if available and if such measurements can be considered spatially and temporally representative for the exposed populations.

The first examples of similar multimedia compartment modeling were probably the "fugacity" models proposed by Mackay (1979) and Mackay and Paterson (1981, 1982). Fugacity in this context is defined as the tendency for a chemical to escape from one environmental media compartment into another. The fugacity of a chemical present in an environmental media compartment is modeled using common fate and transport parameters such as octanol water partition coefficients, Henry's Constants, water solubilities, and so on. The fugacity concept is based on the fact that at equilibrium, equal fugacities are established in all compartments of a system. Examples of fugacity modeling include the transfer of nonionic organic chemicals between the atmosphere and surface water (Mackay, et al., 1986), between the atmosphere and plants (Riederer, 1990), and for food chain modeling (Travis and Hattemer-Frey, 1987). A regional fugacity model being used in regulatory risk assessment forums is the CALTOX (DTSC, 1993) model. Mackay (1991) authored a comprehensive, though somewhat dated, text on multimedia compartment modeling using the fugacity approach.. A key difference between fugacity modeling and the modeling in this assessment is that for fugacity modeling, movement between compartments is considered for both directions - from compartment A to compartment

B and also compartment B to compartment A. The modeling in this assessment is essentially one way - air to leaf, air to soil, vegetation to terrestrial animal, and so forth. This is thought to be reasonable for dioxins under the circumstances for which the models are being promoted - which is the circumstance of the source strength being constant over the period of exposure. Also, because the persistence and adsorptive tendencies of the dioxin-like compounds, movement from one compartment to another tends to be more one-way than it is for less persistent or more volatile organic compounds.

One possible drawback for the fugacity approach applied to the types of source categories discussed in this assessment is that it does not consider spatial variability of concentrations within a compartment. For example, air concentrations vary depending on the distance from a source of air emissions, such as a stack or a site of soil contamination. The fugacity approach would typically treat air as a single compartment with a uniform concentration. This would be a concern for a regional model such as the CALTOX model.

The transfer of contaminants between compartments and multimedia modeling approaches have been extensively studied at the National Center for Intermedia Transport at the University of California, Los Angeles. Their multimedia compartment model, MCM (Cohen and Ryan, 1985), provides several useful algorithms for intermedia transfer factors that would have application for dioxin-like compounds. Later on, this group introduced the spatial multimedia compartment model (Cohen, et al., 1990), which allows for non-uniformity in some compartments. Such a model would be more suitable for the types of source categories of this assessment, since there is non-uniformity within a compartment as noted above in the air compartment example.

An early approach which merged simplistic multimedia modeling with human exposure was termed the exposure commitment method, developed by Bennett (1981). An exposure commitment is defined as a contaminant concentration in human tissue. Exposure commitments are calculated from transfer factors that are estimated as the ratios of the steady-state concentrations of a contaminant in adjoining compartments of an exposure pathway. An example of adjoining compartments is air to plants to livestock to diet. This method has been applied to both PCBs (Bennett, 1983) and 2,3,7,8-TCDD (Jones and Bennett, 1989). These applications have required measured concentrations of the contaminants in different compartments in order to estimate the transfer factors. The retrospective nature of this approach limits its usefulness for general applications.

One of the early multimedia models which also had human exposure as the endpoint, but did not require retrospective data, was the GEOTOX model (McKone and Layton, 1986). This

model had air (vapor and particle phases), water (surface and ground water, including bottom sediments of surface water bodies), soil (soil gas, water, and solid subcompartments), and biomass (eggs, milk, meat, fish, and vegetation including food crops) compartments. The most recent evolution of this model can be found in McKone and Daniels (1991).

Multimedia modeling approaches have been extensively used to evaluate the exposure to dioxins. Paustenbach, et al. (1992) evaluated the exposure and risk to humans from residential and industrial soil contamination by 2,3,7,8-TCDD. Simple models were used to estimate the concentrations of 2,3,7,8-TCDD in air-borne suspended particulates and fish that reside in nearby streams impacted by the contaminated soil. Together with concentrations in contaminated soil, Paustenbach evaluated human exposures via soil ingestion, dermal contact, particulate inhalation, and fish consumption. They also used Monte Carlo techniques on exposure parameters (in contrast to using Monte Carlo on fate and transport parameters) to determine a range of residential and industrial soil concentrations that would result in a specified risk level. The risk level chosen for their demonstration was 10^{-5}, which was determined by multiplication of the Lifetime Average Daily Doses (LADDs in mg/kg-day) and the cancer slope factor for 2,3,7,8-TCDD of 9700 $(mg/kg\text{-}day)^{-1}$ derived by Keenan, et al. (1991). Residential soil concentrations less than 20 ppb did not pose a lifetime cancer risk greater than 10^{-5}. For industrial sites, concentrations in soil that could pose a 10^{-5} risk ranged between 131 and 582 ppb, depending on the amount of time the industrial worker spend outdoors under typical exposure conditions.

Travis and Hattemer-Frey (1991) evaluated human exposure to 2,3,7,8-TCDD from a broader perspective. The principal assumption of the Fugacity Food Chain model used for Travis' human exposure assessment is that atmospheric concentrations of 2,3,7,8-TCDD can be empirically linked to water, soil, and vegetative concentrations, which in turn are linked to agricultural produce, meat, milk, eggs, and fish concentrations. Simple models for atmospheric depositions onto plants, air-to-leaf transfers of vapor phase 2,3,7,8-TCDD onto plants, transfers to cattle beef and milk, and other models, are presented. They also compared their model predictions of exposure media concentrations to literature values, and concluded that their approaches resulted in concentrations comparable to those found in the literature. This effort by Travis and Hattemer-Frey is examined in more detail in Section 5.6 of Chapter 5.

Exposure to 2,3,7,8-TCDD using simplistic multimedia models has also been assessed for specific sources. Goeden and Smith (1989) evaluated the impact to fish and subsequent human exposure by consumption of fish to dioxins and furans emitted by a resource-recovery facility. Surface water sediment concentrations in a lake were estimated as a simple weighted average of concentrations on three kinds of particles entering the lake: soil via erosion whose concentration

was estimated given contaminated particle depositions onto soil (and considering mixing and soil half-lives), deposition of background uncontaminated suspended particulates directly onto the lake, and direct deposition of contaminated particles onto the lake. Fries and Paustenbach (1990) also evaluated the impact of incinerator emissions of 2,3,7,8-TCDD, but they evaluated human exposure via consumption of food crops, meat, and milk. EPA (1990d) used a simple dilution model to evaluate the impact of pulp and paper mill effluent discharges of 2,3,7,8-TCDD and 2,3,7,8-TCDF into surface water bodies.

The air-plant interface has been the subject of numerous fugacity and related modeling efforts for the dioxin-like compounds. This is because it is recognized that this pathway is critical to the terrestrial animal food chain; little soil-to-plant transfer occurs for these highly sorbed class of compounds. Trapp and Matthies (1995) present a comprehensive air/soil-to-plant modeling system, and in their application of this approach to 2,3,7,8-TCDD, they neglect the soil-to-above ground portion of their model. The importance of the vapor phase dioxins has been recognized in numerous modeling efforts, particularly for the lower chlorinated congeners (Lorber, 1995; McLachlan, et al., 1995). McLachlan, et al. (1995) developed a fugacity approach while the empirical air-to-plant transfer factor approach for vapor-phase dioxins in Lorber (1995) is advocated in the methodology.

This is only a cursory summary of the wealth of multimedia modeling approaches that are available, and the application of such modeling approaches for evaluating human exposure to dioxins. While there are many similarities and differences among the approaches, they all share one characteristic in common - they have all been described as "screening level models". Without attempting a definition of the qualifier, "screening level", such a qualifier for these models seems to imply the following types of common features: assumptions of equilibrium and/or steady state conditions between compartments, lack of substantial (if any) spatial or temporal resolution, the use of biotransfer or bioconcentration concepts which simply relate an environmental concentration (air or water concentration, e.g.) to a biomass concentration (plant or fish concentrations), and so on.

A counterpoint to screening level models might be what are termed "mechanistic" models. Such models are more theoretically sophisticated, contain more spatial and temporal resolution, attempt to simulate actual mechanisms of fate and transport rather than depend on empirical relationships developed from data, could involve complex food chain approaches to model biomass concentrations (to counter the simple biotransfer or bioconcentration approaches), and generally are highly parameterized requiring site-specific data that is often not readily available.

Because of the complexity of the multimedia environment, modeling of contaminant fate in such an environment has tended to remain simple. However, there are complex models which can be applied to smaller subsets of the multimedia environment, and which have been applied to assessments of dioxin-like compounds. One example is the ISCST3 model, which was used in this assessment to evaluate the impact of stack emissions of dioxin-like compounds. That model allows for complexities of terrain, varying weather patterns, vapor/particle partitioning, etc., to be considered. It relies on hourly meteorological data to simulate years of atmospheric transport and deposition, and summarizes the results of its simulation as long term average concentrations and depositions. That model is further described in Chapter 3. Another example of more complex modeling was the use of the WASP4 model in a comprehensive evaluation of bioaccumulation of 2,3,7,8-TCDD in Lake Ontario (EPA, 1990b). That application required a substantial amount of site-specific parameterization. Gobas, et al. (1999) describes the application of EcoFate to 2,3,7,8-TCDD and 2,3,7,8-TCDF pulp and paper mill discharges to the Fraser-Thompson River system in British Columbia, Canada from 1988 to 1995. This is a time-dependent, multimedia mass balance simulation of the environmental distribution and food-chain accumulation of organic contaminants in aquatic ecosystems. In this framework, modeled river systems are segmented, and within each segment, numerous compartments are modeled including the bed sediment (an accessible and an inaccessible bed layer), one or several water column compartments, the atmosphere, and one or more aquatic organism trophic levels (algae/zooplankton, benthic filter filters and detritivores, and fish). They were able to demonstrate a successful application of this model to predicted the two dioxin congener concentrations in bottom sediments, rocky mountain white fish, and rainbow trout.

With the exception of the ISCST3 model, the models used for this assessment are better described as screening level rather than mechanistic. Many of the algorithms used are the same or very similar to the ones found in references above. Except for the effluent discharge source category, which uses a non-spatially resolved dilution model for surface water impacts, the algorithms do consider spatial differences between the source and site of impact or site of exposure. For example, the algorithm estimating surface water impacts from a site of soil contamination, while simple in its framework, does incorporate the following: the area of the site that is contaminated, the area of the watershed which drains into the water body, the erosion rates of the site of contamination as well as the rest of the watershed, the proximity of the site to the water body, the concentration of the contaminant at the site of contamination as well as within the watershed other than the contaminated site, the lipid content of the fish, and the organic carbon fractions of the suspended and bottom sediments of the water body. Assignments

for all these parameters impact water and fish concentrations, and it is certainly arguable that they are all site-specific parameters. From this perspective, it could be argued that most of the algorithms of this assessment are generally screening level in their theoretical sophistication, but site specific in their application.

Sections in other chapters of this volume address key issues relating to the use and credibility of the algorithms described in this chapter. Chapter 5, which demonstrates the methodology, makes observations concerning exposure media concentrations. Chapter 6, on user considerations for use of the models and algorithms of this assessment, discusses categorization of model parameters and conducts sensitivity analysis exercises on key fate, transport, and transfer algorithms. Chapter 7 discusses applications of these models in validation exercises, and also compares the models of this assessment to others available for dioxin-like compounds. Chapter 8 on Uncertainty has critical discussions on parameter assignment and algorithm uncertainties.

Figures 4-1 through 4-3 are flow diagrams showing interim compartment concentrations modeled, and principal processes modeled and assumptions made in the intermedia transfer. Sections 4.3. through 4.5 describe the algorithms for the three source categories considered in this assessment, and background and assignment of parameters for the demonstration scenarios of Chapter 5.

4.3. ALGORITHMS FOR THE SOIL CONTAMINATION SOURCE CATEGORY

As earlier noted, exposures to contaminated soils can occur both at the site of the soil contamination or away from the site of soil contamination. Examples of on-site exposure would be worker exposures to Superfund or similar sites, or unique circumstances such as Times Beach where soil at the site of a residence or a playground becomes contaminated. Examples of off-site exposure include exposures at residences, farms, play or school areas, and so on, that are located near, but not at, the site of soil contamination. There are two primary differences with regard to modeling when exposure is on-site versus off-site. One is in the modeling of the dispersion of dioxin residues which have been suspended via volatilization or dust suspension. Models are presented below for on-site dispersion and off-site dispersion. The second difference is that, for on-site exposures, the initial soil concentration is assumed to remain constant throughout the period of exposure. For off-site exposures, the soil concentration at the site of exposure is assumed to build up over time from an initial level of zero before the site became contaminated to a level when exposure begins and then to a second level when exposure ends. The average soil concentration during the period of exposure is estimated as the midpoint between the two

latter concentrations noted. Otherwise, all other algorithms for the soil contamination source category, including the algorithms for surface water impacts and for biota calculations, are the same whether the exposure to the soil contamination is on-site of off-site.

Sections 4.3.1 through 4.3.4 describe the algorithms for estimating concentrations of the dioxin-like compounds in: bottom sediment, suspended solids, and in the dissolved phase in the water column of surface water bodies (4.3.1), exposure site soil concentrations (4.3.2.), in the air in the vapor and particulate phases (4.3.3), and in biota including fish (4.3.4.1), home-grown vegetables and fruit (4.3.4.2), beef and milk (4.3.4.3), and chicken and eggs (4.3.4.4). Section 4.3.5 describes some key characteristics of specific cases of soil contamination.

4.3.1. Surface Water and Sediment Contamination

The principal assumption in the algorithm estimating the impact to surface water and surface water sediments (suspended and bottom sediments) from an area of contaminated soil is that such an impact is correlated to surface soil concentrations at that site as well as surface soil concentrations within a larger area draining into the water body. This drainage area is commonly referred to as a watershed. Further, the impact to the water body is assumed to be uniform. This tends to be more realistic for smaller water bodies as compared to large river systems. Other key assumptions in the surface water impact algorithm are:

- Soil erosion estimates, coupled with sediment delivery ratios, can be used to describe the impact of a contaminated site relative to other soils in the watershed which contribute sediments to the water body;
- The sorption of dioxin-like compounds onto surface soil, suspended solids and bottom sediments is principally a function of the contaminant's organic carbon partition coefficient, Koc, and the organic carbon content of soils and sediments;
- The concentration of contaminants in soil eroding from a site are initially higher than the concentrations at the site itself - it is "enriched" with contaminants. This enrichment occurs because some processes of transport, such as wind erosion or soil erosion, favor lighter soils (silts and clays) which have higher surface area to volume ratios (more binding sites) as well as higher organic matter contents on the average (which also favors more binding of organic chemicals). Other processes such as volatilization or degradation may counteract the enrichment noted at the edge of a site - concentrations on soil entering a water body may be less than those leaving the site;
- The concentration of contaminants in sediment suspended in the water column exceeds the concentration in bottom sediments. Similar reasoning as the above enrichment

argument applies: particulates which remain in suspension tend to be lighter and more enriched with organic matter as compared to particulates which settle to the bottom of water bodies. It should be noted that suspended solids, in this algorithm, are simply a reservoir into which dioxin-like compounds sorb; more complex models consider sorption onto more than one reservoir of suspended materials including suspended particulates and dissolved organic matter;

- Suspended and bottom sediments originate principally as soil erosion; a mass balance is maintained such that a part of the soil reaching the water body through erosion remains as suspended particulates, and a part settles to bottom sediments.
- A steady state is achieved between concentrations in the dissolved phase in the water column, concentrations in the sorbed phase in the water column, and concentrations in bottom sediments;
- Volatilization out of the water body or degradation of residues in the water body are not modeled. Neglecting these dissipation processes has the net effect of overestimating water body impact. On the other hand, bottom sediment resuspension is not modeled. Not modeling resuspension would have a net effect of underestimating water column impacts; and
- Estimating the average impact to the water body, rather than a localized impact which may be the case if the contaminated soil is very near the water body, is suitable for purposes of this assessment procedure.

Concentrations in bottom sediment are desired because fish concentrations are estimated as a function of bottom sediment concentrations (see Section 4.3.4.1). Concentrations in suspended solids are desired because they are used to estimate bottom sediment concentrations, and dissolved phase concentrations are needed for estimating drinking water exposures.

The solution begins with the mass balance statement:

The mass of contaminant entering the water body	=	An amount which remains as dissolved in the water column + An amount which remains sorbed to suspended materials + An amount which remains sorbed to particles settling to the bottom

This can be described mathematically as:

$$C_{swb}\ ER_{w} = C_{wat}\ V_{wat} + C_{ssed}\ M_{ssed} + C_{sed}\ M_{sed} \quad (4\text{-}1)$$

where:

C_{swb} = concentration on soil entering water body, mg/kg
ER_w = total watershed annual soil erosion, kg/yr
C_{wat} = dissolved-phase concentration in water column, mg/L
V_{wat} = water body annual volume, L/yr
C_{ssed} = concentration on suspended sediment, mg/kg
M_{ssed} = mass of suspended sediment introduced per year, kg/yr
C_{sed} = concentration on sediment settling to bottom, mg/kg
M_{sed} = mass of bottom sediment introduced per year, kg/yr

Other equations based on assumptions stated above and needed for this solution are:

1) mass balance of soil is maintained:

$$ER_w = M_{ssed} + M_{sed} \quad (4\text{-}2)$$

$$M_{ssed} = f_s \, ER_w \quad (4\text{-}3)$$

$$M_{sed} = (1 - f_s) \, ER_w \quad (4\text{-}4)$$

where:

f_s = fraction of annual erosion remaining as suspended materials, unitless

2) equilibrium between sorbed and dissolved phases is maintained; suspended sediments are enriched in comparison to bottom sediments:

$$C_{wat} = \frac{C_{ssed}}{Kd_{ssed}} \quad (4\text{-}5)$$

$$C_{sed} = C_{ssed} \frac{OC_{sed}}{OC_{ssed}} \quad (4\text{-}6)$$

where:

Kd_{ssed} = soil-water partition coefficient for contaminant in suspended sediment, L/kg

OC_{ssed} = fraction organic carbon in suspended sediment, unitless

OC_{sed} = fraction organic carbon in bottom sediment, unitless

Now, Equations (4-2) through (4-6) can be substituted into the right hand side of Equation (4-1) so that this side can be function a one concentration, C_{ssed}, and one erosion amount, ER_w. Factoring out C_{ssed} then gives:

$$C_{swb}\, ER_w = C_{ssed} \left\{ \frac{V_{wat}}{Kd_{ssed}} + f_s\, ER_w + \frac{OC_{sed}}{OC_{ssed}} \left(1 - f_s \right) ER_w \right\} \quad (4\text{-}7)$$

The bracketed quantity in the right hand side of Equation (4-7) can be termed ϕ, so that C_{ssed} can be solved as $(C_{swb}\, ER_w)/\phi$. Now, the numerator in this term can be expanded to describe contaminant contributions by a site of contamination and contaminant contributions by the rest of the watershed. Included in this solution is the assumption made above that soils eroding into water bodies are "enriched":

$$C_{swb}\, ER_w = C_s\, SL_s\, A_s\, E\, SD_s + C_w\, SL_w \left(A_w - A_s \right) E\, SD_w \quad (4\text{-}8)$$

where:

C_{swb} = concentration on soil entering water body, mg/kg

ER_w = total watershed erosion, kg/yr

C_s = contaminated site soil concentration of dioxin-like compound, mg/kg

E = enrichment ratio, unitless

SL_s = unit soil loss from contaminated site area, kg/ha-yr

A_s = area of contaminated site, ha

SD_s = sediment delivery ratio for soil eroding from contaminated site to water body, unitless

C_w = average concentration of dioxin-like compound in effective area of watershed not including contaminated site, mg/kg

SL_w = average unit soil loss for land area within watershed not including contaminated site, kg/ha-yr

A_w = effective drainage area of watershed; the area contributing sediment which mixes with the sediment originating from A_s, ha

SD_w = sediment delivery ratio for watershed, unitless

Finally, the right hand side of Equation (4-8) can be termed, ρ, and the concentration in suspended sediment, C_{ssed}, is equal to ρ/ϕ. All the terms in ρ/ϕ are input parameters or can be solved as a function of input parameters. Other water body concentration terms, C_{wat} and C_{sed}, can now be solved using Equations (4-5) and (4-6). Note that this solution is applicable to both stationary water bodies such as ponds or lakes and moving water bodies such as streams or rivers. The differences in the two water systems can be expressed in the parameters, effective watershed area, A_w, water body volume, V_{wat}, and organic carbon contents of suspended solids and bottom sediments, OC_{ssed} and OC_{sed}. Guidance on these terms and assignment of values for the demonstration scenarios in Chapter 5 is now given.

- **C_s and C_w:** These are concentrations of dioxin-like compounds in the contaminated site soil, C_s, and the average within the effective area of the watershed, C_w. The contaminated site concentrations drive the concentrations assumed for most exposures, and is a principal user input. The simplest assumption for C_w is that it is 0.0. However, examination of soil data from around the world shows that, where researchers have measured concentration in what they described as "background" or "rural" settings, soil concentrations of CDD/Fs are in the non-detect to low ng/kg (ppt) range. Chapter 3 of Volume II of these Dioxin Exposure Reassessment Documents describes studies measuring dioxins in rural parts of America and calculates a TEQ_{DFP}-WHO_{98} of 4 pg/g (ppt). Example Scenarios 1 and 2 in Chapter 5 demonstrate the methodologies in this chapter in what are termed “background” settings. For these example scenarios, the 17 dioxin-like CDD/Fs are initialized to values that have been measured in an actual background setting.

● **E:** Enrichment refers to the fact that erosion favors the lighter soil particles, which have higher surface area to volume ratios and are higher in organic matter content. Therefore, concentrations of organic contaminants, which are a function of organic carbon content of sorbing media, would be expected to be higher in eroded soil as compared to in-situ soil. While enrichment is best ascertained with sampling or site-specific expertise, generally it has been assigned values in the range of 1 to 5 for organic matter, phosphorous, and other soil-bound constituents of concern (EPA, 1977). The enrichment ratio would be expected to be higher in sandy soils as compared to silty or loamy soils because the finer silt particles which erode from a soil generally characterized as sandy are more a deviation from the norm compared to silt particles which erode from a soil generally characterized as silty or loamy. The example scenarios in Chapter 5 modeled mid-range agricultural loam soils (as modeled with organic carbon fractions, soil loss parameters as discussed below). The enrichment ratio will therefore be assigned a value of 3.0 in all circumstances.

Two data bases have been found which justify the use of the enrichment ratio in this context. One is the data base from Connecticut which involved the sampling of surface soils and sediments from several rural locations in Connecticut (CDEP, 1992). Enrichment ratios were calculated from individual sites and for three dioxin-like compounds as the ratio of the concentration measured in sediment to the concentration measured in nearby surface soil samples. Enrichment ratios ranged from 0.33 to 12.3 with overall averages for the three dioxin-like compounds of 1.58 (for 2,3,4,7,8-PCDF), 2.59 (2,3,7,8-TCDF), and 3.86 (2,3,7,8-TCDD). Further details on this data are found in Chapter 7. A first set of results from another research study on the Hudson River was described in Smith, et al. (1995). Using modeling, they concluded that the concentration of dioxins in surficial sediment layers of the Hudson River were principally caused by soil erosion: 76% of the total deposition of CDD/Fs to bottom sediments were caused by surface erosion, with other causes including anthropogenic waste (sewer outflows; 20%), and direct atmospheric input (4%). To model the concentrations in the Hudson river surficial sediments, they used an enrichment ratio of 1.6 (defined as here as the ratio of the sediment concentration to the surficial soil concentration), based on an earlier analysis of particle sources of the Hudson river and its tributaries. The data presented in Smith, et al. (1995) on surface soils and sediments also show the disparity between surface soils and sediments - sediment concentrations are higher than surface soil concentration and sometimes substantially higher. However, since the Hudson River watershed is fairly complex and includes important sources other than soil erosion, it would be inappropriate to estimate enrichment ratios from the data as was done for the Connecticut data.

- **SL_s and SL_w:** These are the unit soil loss, in kg/ha, from the exposure site and the average from the effective land area draining into the surface water body. In the simplest case, the unit losses can be considered equal. In the most complicated solution, the effective drainage area can be broken up into "source areas", where each source area can be unique in terms of the erosion potential, concentration of contaminant, and so on. The total contribution equals the sum of contributions from each source area, as: $\sum C_j * SL_j * A_j * E_j * SD_j$ for the right hand side of Equation (4-8) for j number of source areas not including the exposure site. For direct input into Equation (4-8), the terms C_j, SL_j, A_j, E_j, and SD_j, should be determined and C_w, SL_w, E_w, and SD_w should be estimated as weighted averages over all source areas, A_j. The effective drainage area, A_w, would be the sum of all source areas, A_j.

For the example scenarios in Chapter 5 demonstrating the "background" settings, SL_s and SL_w are assumed equal. This generally assumes that erosion parameters for the site of exposure mirror the averages for the drainage area. Also, the enrichment ratio, E, is assumed to be constant for all watershed soils. For the demonstration of the soil contamination source category, the site of contamination is assumed to have different erosion characteristics. The following is offered as general guidance and background for estimation of unit soil losses in this assessment.

The unit soil loss is commonly estimated using the Universal Soil Loss Equation. This empirical equation estimates the amount of soil eroding from the edge of a field (Wischmeier and Smith, 1965):

$$SL = R\ K\ LS\ C\ P \qquad (4\text{-}9)$$

where:

SL	=	average annual soil loss, Eng. tons/acre-year
R	=	rainfall/runoff erosivity index, t-ft/ac-yr
K	=	soil erodibility factor, t/ac-(unit of RF)
LS	=	topographical factor, unitless
C	=	cover and management practice, unitless
P	=	supporting practices factor, unitless.

Several references are available to evaluate USLE factors for agricultural and non-agricultural settings (EPA, 1977; USDA, 1974; Wischmeier, 1972; Novotny and Chesters, 1981). For this assessment, values for these terms will based on assumptions about contaminated sites and rural

soils. Justification and assumptions are given below. It should be noted that more sophisticated models are available for estimating erosion rates (i.e., CREAMS as described in Knisel, 1980), and should be considered in actual site-specific assessments.

- **Rainfall/erosivity index, R:** The R term represents the influence of precipitation on erosion, and is derived from data on the frequency and intensity of storms. This value is typically derived on a storm-by-storm basis, but it has been compiled regionally for the development of average annual values (EPA, 1977). Annual values range from less than 50 for the arid western United States to greater than 300 for the Southeast. The value used in this assessment will be 160, which is typical of rainfall patterns seen in much of the midwestern United States.

- **Soil erodibility, K:** The soil erodibility factor reflects the influence of soil properties on erosion, with values ranging from less than 0.05 for non-erodible sandy soils to greater than 0.50 for highly erodible silty soils. The value used in this assessment will be 0.30, which is typical of, for example, sandy or silty loam soils with 2% - 4% organic matter contents.

- **Length-slope factor, LS:** The topographic factor reflects the influence of slope steepness and length of the field in the direction of the erosion. Steeper slopes and longer lengths lead to higher LS values, with a range of 0.1 for slopes less than 1.0% and lengths less than 100 ft to greater than 2.0 for slopes generally greater than 10%. The two key considerations for its assignment, therefore, are the size of the field for which erosion estimates are being made, and the slope of that field. The example scenarios in Chapter 5 had field sizes of 0.4 ha (1 ac) for a rural residence, 4 ha (10 ac) for a small rural farm, and 10 ha (25 ac) for a soil contamination site. Guidance for use of the Universal Soil Loss Equation stops short of defining appropriate sizes of field for which unit estimates are to be derived, except that the USLE was developed for agricultural "fields" where cover, slope, soil type, etc. are assumed to be uniform. For purposes of estimating erosion losses in this assessment, a field of 4 ha for estimating the LS factor will be used. In a rural watershed with agricultural and non-agricultural settings, this would be a reasonable average area of uniformity. If square shaped, a 4 ha area translates to a side length of 200 m. For purposes of assignment of the LS factor, it will be assumed that the contaminated site has a 2% slope. EPA (1977) (and other references as noted above) show nomagraphs giving the LS factor as a function of slope length and slope. With a 200 meter slope length and a 2%

slope, the LS factor is approximately 0.20. This factor will be used for all soil loss estimates required in this assessment.

- **Support practice factor, P:** The support practice factor reflects the use of surface conditioning, dikes, or other methods to control runoff/erosion. P can be no greater than 1.0. However, values less than 1.0 should only be assigned when specific practices are employed which are designed to reduce erosion. For the example scenarios in Chapter 5, it will be assumed that no such practices are in place at the site of concern or throughout the watershed to control erosion. Therefore, a value of 1.0 will be assumed.

- **Management practice factor, C:** The final term in the USLE is the cover and management practice factor, C, which primarily reflects how vegetative cover and cropping practices, such as planting across slope rather than up and down slope, influences erosion. C values can be no greater than 1.0, with this value appropriate for bare soils. A C value of 1.0 is an appropriate choice for active landfills or sites of high soil contamination (like Superfund sites) mostly devoid of vegetation. For an inactive landfill with grass cover or any area with dense vegetative cover such as grass, a value of 0.1 or less is appropriate. Values greater than 0.1 but less than 0.7 are appropriate for agricultural row crops, which offer more protection than bare soil, but not as much protection as dense vegetation.

Three erosion estimates are required for scenarios demonstrated in Chapter 5. One is for areas of high soil contamination, or the scenario demonstrating the soil contamination source category. It will be assumed that the contaminated site is largely devoid of vegetation in this case, and a value of 1.0 will be assumed. A second erosion estimate is needed to characterize average unit soil loss throughout a watershed draining into a surface water body. The example scenarios are based on a rural setting which has agricultural and non-agricultural (i.e., rural residences) areas. The C value in this circumstance will be assumed to be 0.3. Finally, a soil erosion estimate is needed in the algorithm transporting contaminated soil from an area of high soil contamination to a nearby site of contamination, as part of the algorithms developed for the soil contamination source category. In this case, the land between a site of soil contamination and the nearby site of exposure will be assumed to be covered with dense vegetation, such as grass. In this case, the C value will be 0.1.

As just described, three unit soil loss estimates are required for this estimates and the difference between the three will be expressed in the C term. Multiplication of the five USLE

terms gives unit soil loss estimates of 9.60 (with C = 1.0), 0.96 (with C = 0.1), and 2.88 (with C = 0.3) t/ac-yr. The value of SL_s and SL_w for the demonstration of the background setting scenarios in Chapter 5 is 2.88 t/ac-yr. Since Equation (4-8) and other uses of unit soil loss estimates are needed in kg/ha-yr, these unit losses are easily converted to 21515, 2152, and 6455 kg/ha-yr.

- **A_s and A_w:** These are the area terms, including the area of the contaminated site, and the effective drainage area of the watershed, both in ha. The scenarios demonstrated in Chapter 5 have assumed 0.4 ha (1 acre roughly) for exposure sites described as rural residences, 4 ha (10 acres) for farms, and 10 ha (25 acres) for the site of soil contamination. If the soil contamination site is at the site of exposure, as in the "on-site" source category, then A_s should be assigned an area equaling the site of exposure (and the concentration term, C_s, should equal the average soil concentration over this site of exposure). If the area of contamination is away from the site of exposure, A_s should equal the total area of contamination (and again C_s should equal the average soil concentration over this area).

The total area impacting a river system has been termed a watershed. For purposes of this assessment, an "effective" drainage area will almost always be less than the total area of a watershed. A "watershed" includes all the land area which contributes water to a river system. For large river systems, this area is in the order of thousands of square miles and includes several tributaries and smaller streams feeding into the main branch of the river. Each stream and tributary has its own sub-basin, whose sediment originates from a land area much smaller than thousands of square miles. If the contaminated site lies within that sub-basin, that it would be appropriate to include only the area within that sub-basin as the effective drainage area. This is one circumstance where an "effective drainage area" would be less than a total watershed area. Another consideration for determining the effective drainage area is the positioning of the contaminated site with respect to the point where water is extracted for drinking and fish are caught for consumption. If these points are significantly upstream in the river system in relation to the contaminated site, there is no reason to conclude that sediments or water near where the water is extracted are impacted by the contaminated site. If these withdrawal points are downgradient of the contaminated site, then there is reason to believe that sediments and water are impacted. However, if they are downgradient from the contaminated site but not at the bottom of the watershed, then sediment and water quality further downgradient from the withdrawal points is not of concern and land draining into these downgradient portions would not be part of the "effective drainage area". One further possible consideration is how far upgradient

in the watershed one should go when determining the size of the effective drainage area. While sediments introduced at the furthest points may eventually work their way down to the mouth of the watershed, this may take geologic time and not recent historic time. Therefore, sediment quality near a site of contamination need not consider these far reaches.

For a standing water body such as a lake or a pond substantially fed by ground water recharge, an assumption that probably should be made using the simple framework of this assessment is that all sediments within the lake/pond are completely mixed. Therefore, the effective area should equal all area around the lake/pond contributing sediment, and, as in the above discussion on river systems, a part of the land area contributing sediments to streams or rivers which may feed the standing water body.

From this discussion, it is clear that determination of an effective drainage area depends on site specific considerations, but it will likely be less than the total watershed area. The demonstrations in Chapter 5 assume a reasonably large watershed area draining into a river that can support a fish population suitable for recreational fishing. The effective drainage area of this watershed, A_w, will be assumed to be 100,000 hectares ($1*10^9$ m^2, $1*10^3$ km^2, 250,000 acres, 385 mi^2). Furthermore, it will be assumed that the water body in question is a river, which mainly impacts the assignment of the total suspended solids parameter, TSS (as discussed below). This assignment is not based on any specific sites that have been studied. As noted , it is justified as being a reasonable size to drain into a river large enough to support recreational fishing

A useful data source for this term and the suspended sediment term below, for specific sites in the United States, is Appendix F in Mills, et al. (1985). This appendix includes a compilation of data from river and reservoir sediment deposition surveys, including total drainage area, water body volumes, and rates of sediment deposition (mass/area-time). A caution in using this and similar data bases when evaluating specific sites is that, again, these total drainage areas are just that, <u>total</u> areas. Water bodies in this data base are located in the 48 conterminous states. An estimate of suspended sediment concentrations can be made using the water volume and the sediment deposition rates from this data, and an assumption on sediment deposition velocity. The specific weight of sediments in the water body, also supplied in this appendix, can be used to estimate sediment deposition velocity.

- **SD_s and SD_w:** These are the sediment delivery ratios applied to the exposure site and the watershed as a whole. Such a ratio is required because not all the soil which erodes from an area deposits into the receiving water body. The following delivery ratio was proposed for construction sites (EPA, 1977):

$$SD_s = (3.28\ DL)^{-0.22} \quad (4\text{-}10)$$

where:

SD_s = sediment delivery ratio for soil eroding from contaminated site to water body, unitless

DL = distance from contaminated site to receiving water body, m

3.28 = converts m to ft (empirical equation was developed for units of ft).

Note that the sediment delivery empirical equation simplifies all land features pertinent to erosion to a function only of length. The equation was developed to estimate sediment loads from construction sites to nearby surface water bodies, and from distances up to 250 m (800 ft, roughly). Without specific information on the sites from which it was developed, it is assumed that the land area between the construction sites and the receiving water body is "average" and this relationship can be used for applications other than construction sites.

As noted in previous bullets, the example scenarios demonstrating the background setting assumed $C_s = C_w$, and $SL_s = SL_w$. The impacted water body was assumed to be 150 meters away from the site of exposure for this demonstration setting. This distance translates to a delivery ratio of 0.26. Site-specific conditions could result in a larger (steeper slope, e.g.) or smaller proportion of the eroded soil being delivered to the water body than would be estimated with this equation.

Figure 4-4 shows a watershed delivery ratio as a function of watershed size. As seen, the ratio decreases as land area increases. The total watershed size, A_w, assumed for the example scenarios in Chapter 5 was 1000 km^2. From Figure 4-4, this translates to a watershed delivery ratio, SD_w, of 0.06. If the watershed is larger than about 2000 km^2, which is the extent of coverage of this figure from Vanoni (1975), the following empirical equation was found to satisfactorily extend the relationship seen in Figure 4-4:

$$SD_w = 0.6\ (A_w)^{-0.125} \quad (4\text{-}11)$$

where:

SD_w = sediment delivery ratio for a watershed, unitless

A_w = effective drainage area of watershed; the area contributing sediment which mixes with the sediment originating from the contaminated site, m^2

- **f_s:** As soil erodes into the water body, it will settle onto the bottom to become bottom sediment. Part of the settled material will become resuspended because of turbulent flow. The finest materials in eroded soil may not settle for a long time, and essentially always be in suspension. One way to arrive at the fraction of annually eroding material which remains in suspension ("remains in suspension" for purposes of discussion - in reality, little, if any, will remain in suspension, but will rather deposit and resuspend) involves complex modeling. A wealth of such models exist, such as those described in Wang (1989). The approach used here is more simple than those in Wang (1989).

If an average level of suspended material in the water were specified, in units of mg/L, what would be known with otherwise required parameters is the total amount of erosion reaching the water body (as discussed above) as well as the annual water volume (discussed below). A required parameter for this assessment will therefore be the level of suspended solids in the water body, TSS. With this parameter and the annual water flow volume, V_{wat}, the total suspended load equals, TSS (mg/L) * V_{wat} (L/yr). The assignment of these two terms are 10 mg/L and $4.8*10^{11}$ L/yr, leading to a total suspended load of $4.8*10^{12}$ mg/yr, or $4.8*10^{6}$ kg/yr. Total erosion into the water body, in similar units, equals, $A_s * SL_s * SD_s + (A_w - A_s) * SL_w * SD_w$. With parameter assignments as discussed above, the total annual erosion equals 1.29×10^{7} kg/yr. Therefore, the fraction of total load that is suspended is 0.36 ($4.8*10^{6}/1.3*10^{7}$).

Given this formulation, the f_s term is not a model input value, but is solved on the basis of the other parameters noted.

- **TSS:** This is the total suspended sediment in the water body. This value will be lower for standing water bodies such as ponds or lakes as compared to streams or rivers. The more turbulent flow in rivers will suspend sediments to a greater degree than a relatively calm lake. A complex modeling exercise evaluating the impact of 2,3,7,8-TCDD to Lake Ontario assumed a suspended sediment concentration of 1.2 mg/L (EPA, 1990b). For use in pond or lake settings, an assumption of a suspended sediment concentration of 1-2 mg/L is reasonable. All example scenarios in Chapter 5 assume that the 100,000 ha watershed drains into a river suitable for supporting fish for consumption and water for drinking purposes. General guidance offered for the potential for pollution problems in rivers and streams as a function of average suspended sediment concentration are: 10 mg/L or less - no problem, 100 mg/L or less - potential problem,

and greater than 100 mg/L - probable problem. A cutoff concentration for protection of aquatic life is 80 mg/L (Mills, et al., 1985). The value assumed for TSS for all example scenarios in Chapter 5 is 10 mg/L, indicating no turbidity problems and a river supportive of fish for consumption.

- **V_{wat}:** The stream in the example scenarios will be assumed to derive its annual flow only from the effective drainage area, A_w. Given the area of drainage, one way to estimate annual flow volume is to multiply total drainage area (in length squared units) times a unit surface water contribution (in length per time). The *Water Atlas of the United States* (Geraghty et al., 1973) provides maps with isolines of annual average surface-water runoff, which they define as all flow contributions to surface water bodies, including direct runoff, shallow interflow, and ground-water recharge. The range of values shown include 5-15 in/yr throughout the Midwest cornbelt, 15-30 in/yr in the South and Northeast, 1-5 in/yr in the desert Southwest, and a wide range of 10-40 in/yr in the far West. For this assessment, an assumed 19 in/yr is used to estimate the annual flow volume. Over a 100,000 hectare drainage area, total flow volume equals 4.8 x 10^{11} L/yr (19 in/yr * 0.0254 m/in * 100,000 ha * 10,000 m^2/ha * 1000 L/m^3).

- **Kd_{ssed}:** This adsorption partition coefficient describes the partitioning between suspended sediment and the water column. For numerous applications for organic contaminants, particularly for estimating the partitioning between soil and soil water, this partition coefficient has been estimated as a function of the organic carbon partition coefficient and the fraction organic carbon in the partitioning media:

$$Kd_{ssed} = Koc \quad OC_{ssed} \qquad (4\text{-}12)$$

where:

Kd_{ssed} = soil-water partition coefficient for contaminant in suspended sediment, L/kg

Koc = organic carbon partition coefficient for contaminants, L/kg or cm^3/gm

OC_{ssed} = fraction organic carbon content of suspended sediment, unitless.

The organic carbon partition coefficient, Koc, can be a measured value or it can be estimated. Chapter 2 of Volume II of this dioxin exposure reassessment reviewed the available

literature on Koc for 2,3,7,8-TCDD. Based on available studies measuring the Koc, a log Koc value of 6.6 was recommended for this congener. Recommendations could not be made for the other dioxin-like congeners because of few measured data points, and when available, the data sometimes showed considerable differences.

In the absence of measured values, the Koc can be estimated from a chemical's octanol water partition coefficient, Kow. Empirical equations relating Kow to Koc are listed in Lyman, et al. (1982). Of six different equations listed in that reference, the following derived by Karickhoff, et al. (1979) is used to estimate the Koc for the example compounds in Chapter 5:

$$\log Koc = \log (Kow) - 0.21 \quad (4\text{-}13)$$

where:

Koc = organic carbon partition coefficient, L/kg
Kow = octanol water partition coefficient, unitless

This equation was empirically developed from a limited number of hydrophobic contaminants (n=10, $R^2 = 1.00$). It implies that Koc is very similar to Kow for strongly sorbed compounds such as the dioxin-like compounds. Using the log Kow of 6.8 recommended in Chapter 2, Volume II of this assessment for 2,3,7,8-TCDD, the estimate of log Koc is 6.59. This is essentially the same as the recommendation for log Koc of 6.6 for 2,3,7,8-TCDD based on measurement studies. This relationship will be used to estimate the Koc for all other dioxin-like compounds.

- **OC_{sed}, OC_{ssed}:** The organic carbon content of solids and sediments of water bodies are generally higher than organic carbon contents of the surrounding lands. Furthermore, organic carbon contents of suspended organic materials and solids are typically greater than those of bottom sediments. A significant sink for strongly hydrophobic contaminants such as the dioxin-like compounds is thought to be suspended, or non-settling, organic material. In modeling 2,3,7,8-TCDD in Lake Ontario (EPA, 1990b) using the WASP4 model, a compartment separate from suspended solids termed "non-settling organic matter" served as a permanent sink. For purposes of this assessment, a single reservoir of suspended materials onto which incoming dioxin-like compounds sorb is principally characterized by OC_{ssed}, and the values selected for OC_{sed} and OC_{ssed} should reflect the relative partitioning behavior of suspended and bottom materials. As noted above, these water body carbon contents are also related to the organic

carbon contents of surrounding soils. The model parameter, OC_{sl}, is the soil organic carbon fraction and is required for modeling of soil contamination by dioxin-like compounds. Foth (1978) lists the organic nitrogen content of several soil types ranging from sand and sandy loam to clay. The range from that list is 0.0002 - 0.0024 on a fractional basis. Assuming a carbon to nitrogen ratio of 10 (Brady, 1984; who notes that C:N ratios vary from 8 to 15, with the typical range of 10 to 12), organic carbon ranges from 0.002 to 0.024. A soil organic carbon fraction, OC_{sl}, is assumed to be 0.01 for all example settings in Chapter 9, which is in the middle of this range. The organic carbon content of bottom sediments, OC_{sed}, will be higher at 0.03. Bottom sediments originate as erosion from surrounding land, but also include decay of organic materials within water bodies. The organic carbon content of suspended materials can approach 0.20, but OC_{ssed} will be assumed to be 0.05 for the example settings in Chapter 5.

4.3.2. Exposure Site Soil Concentrations

If the soil contamination occurs at the site of exposure, than the exposure site soil concentration is simply the soil concentration as initialized by the model user. As described in the Section 4.3.1 above, a key assumption for the simplistic models used in this assessment is that the source strength does not vary over the course of the exposure. Therefore, the soil concentration as initialized remains unchanged during the exposure period. An example of a situation where the contaminated soil is at the site of exposure is a residential property impacted similar to the properties at Times Beach, Missouri, where residential soils were impacted by the spraying of waste oils for dust suppression. Another example would be the analysis of worker exposures on a Superfund site contaminated by dioxin-like compounds.

A more typical application of the methodologies for soil contamination, however, would be the circumstance where sites of exposure are near, but not at, the site of soil contamination. For example, residences or farms near a Superfund site would be the scenario of concern for the contaminated soil source category. This section describes methodologies for estimating the soil concentration at an exposure site near a contaminated soil site.

The key assumptions for the solution strategy estimating exposure site soil concentrations resulting from an off-site soil contamination source are: 1) the exposure site soil becomes contaminated due to erosion of contaminated soil from the source to the exposure site, 2) the amount of soil at the exposure site does not increase, which means that soil delivered to the site via erosion is matched by an equal amount which leaves the site, and 3) not only does soil erode off the contaminated site en route to the exposure site, but soil between the contaminated site and the exposure site also erodes to the exposure site.

The second and third assumption translate to:

$$D_1 + D_2 = SR \quad (4\text{-}14)$$

where:

D_1 = mass of soil delivered from off-site contaminated source, kg

D_2 = mass of soil delivered from land area between contaminated source and exposure site, kg

SR = mass of soil removed from exposure site, kg.

The mass balance equation for exposure site soil concentrations can now be qualitatively stated as (with "ΔC" used as shorthand for change in exposure site soil concentration over time):

ΔC = (the incremental addition to C resulting from the change in erosion of contaminated soil) - (the incremental substraction of C resulting from removal of now contaminated soil from the exposure site) - (the incremental substraction of C resulting from dissipation of residues at the exposure site)

This can be expressed mathematically as:

$$\frac{dC_e}{dt} = \frac{D_1 C_s}{M} - \frac{SR C_e}{M} - k_s C_e \quad (4\text{-}15)$$

where:

C_e = the exposure site soil concentration, mg/kg

D_1 = mass of soil delivered from off-site contaminated source, kg/yr

C_s = contaminated site soil concentration of dioxin-like compound, mg/kg

M = mass of soil at exposure site into which contaminant mixes, kg

SR = mass of soil removed from exposure site, kg/yr

k_s = first order soil dissipation rate constant, 1/yr.

Assuming that the contaminant concentration at the exposure site, C_e, is initially 0, Equation (4-15) can be solved to yield:

$$C_e = \frac{D_1 C_s}{SR + k_s M} \left[1 - e^{-(\frac{SR}{M} + k_s) t} \right] \quad (4\text{-}16)$$

which computes C_e as a function of time, t (in years since k is in years). This can be solved for various increments of time starting from a time when the exposure or contaminated site initially became contaminated, or it can be simplistically assumed that the contamination has existed at the contaminated site for a reasonably large amount of time such that the exponential term approaches zero. The rate at which the exponential term approaches zero is a function of the value of k, the first-order dissipation constant. The smaller the value of k (i.e., the longer the half-life of dioxins transported to a nearby site), the longer it will take for the system to reach steady state. The algorithms of this assessment, such as the surface water algorithms described above and the calculation of the biota calculations as described below, have simplistically assumed that steady state has occurred by the time any exposure has occurred. This simplicity will be continued here. Generally, assuming steady state will lead to conservative results - i.e., overall impacts over time will be less if the systems modeled have not reached steady state (or close enough to it) by the time exposure begins. At steady state, the exponential term drops out, and C is estimated as:

$$C_e = \frac{D_1 C_s}{SR + k_s M} \quad (4\text{-}17)$$

One final note on this solution is that, unlike the solution for estimating water body impacts, there is not an assumption that the eroded soil is enriched in comparison to the soil at the site of contamination; an enrichment ratio was used in the surface water algorithm, but not for this algorithm. The foundation for enrichment of sediments was the arrival of finer textured soils with higher concentrations of constituents of concerns (organic contaminants, inorganic nutrients) at water bodies. This theory is well founded and there is data on the enrichment of dioxin-like compounds in sediments as compared to surface soils. On the other hand, there is no

similar evidence or foundation for assuming enrichment for dioxin-like compounds in soil when the transport is to a nearby site instead of a more distant water body.

Equation (4-17) was used to estimate exposure site concentrations resulting from the erosion of contaminated soil in the demonstration of the soil contamination source category in Chapter 5. Guidance for estimation of these terms including justification for their values as selected in the example settings are:

- **k_s:** For soil residues at the site of soil contamination, the assumption is made that residues do not degrade or dissipate to the point of reducing the concentration of the "initial" soil levels. This was partly based on information indicating generally low rates of biological or chemical degradation for the dioxin-like compounds of this assessment, coupled with the assumption that the soil contamination was sufficiently deep implying a reservoir of contaminant that would remain available during a period of exposure. These assumptions are less likely to be valid for residues which have migrated over the surface to deposit on the exposure site. The deposition is likely to result in only a thin layer of contaminated soil. Though very small, surface-related dissipation mechanisms such as photolysis, volatilization, or degradation, might reduce surface soil contaminant concentrations. For these reasons, a "dissipation" rate constant is assumed to apply to delivered contaminant, where the precise mechanisms of dissipation are not specified, but could include transport (volatilization, erosion) and degradation (photolysis) mechanisms.

Fries and Paustenbach (1990) suggested the use of a half-life of at least 10 years, and used a 15 year half-life in their example scenarios on the impact of air-borne deposition of 2,3,7,8-TCDD originating from stack emissions. In a later publication, Paustenbach, et al. (1992) reviewed the literature on the environmental half-life in soil. For surface soils, they cited the evidence from Eglin Air Force Base (Young, 1983) suggesting a half-life of 10 to 12 years for 2,3,7,8-TCDD, and the work of Cerlesi, et al. (1989), who estimated a soil half-life of 9.1 years for 2,3,7,8-TCDD in Seveso soil. Paustenbach, et al. (1992) also discussed the fact that the loss of TCDD from soil is predominantly through volatilization and photodegradation of residues at the soil surface, and that loss mechanisms are minimal below the soil surface. They suggested that ultraviolet radiation penetrates only about the surface 0.1 cm, which implies that photodegradation could be limited below that depth. They concluded that their review supported the concept that TCDD probably has a half-life of 9-15 years in surface soil and 25-100 years in subsurface soils. McLachlan, et al. (1996) reported on an analysis of soil taken from experimental plots which had been amended with sewage sludge in 1968 and sampled in 1972,

76, 81, 85, and 90. These archived samples were analyzed for all 17 dioxin-like CDD/Fs, and based on an analysis of results, McLachlan and coworkers concluded that half-lives were on the order of 20 years, with dioxin removal from the plots being mainly physical removal processes (overland runoff, wind erosion). Furthermore, their results suggested that all congeners had been removed at roughly the same rate, which is why they concluded that removal processes were mainly physical and very little in-situ degradation appeared to be occurring.

This assessment assumes that residues transported from a site of soil contamination to a site of exposure mix in a soil layer extending 2 cm. This will be discussed below. Therefore, the reservoir of dioxin-like compounds includes a surficial component and what could be considered a subsurface component. This suggests that the average half-life of residues within this depth might be greater than the 9-15 year estimate for surface soils by Paustenbach, et al. (1992), but less than the 25-100 year estimate made by these researchers. This assessment will assume a half-life of 25 years for the 2-cm reservoir of transported dioxins, which translates to a k_s of 0.0277 yr^{-1}. Ideally, half-lives should be assigned to individual dioxin-like congeners as many of the other contaminant-specific parameters such as Kow or bioconcentration parameters. However, the data for 2,3,7,8-TCDD was not definitive, and based on McLachlan's findings with sewage sludge amended soils, it appears reasonable to assign the same half-life to all congeners. The uniform rate of degradation, k_s, for all CDD/Fs, and PCBs, will be 0.0277 yr^{-1}.

- **M:** The delivered contaminant mixes to a shallow depth at the exposure site. The mixing depth depends on activities which disturb the surface, such as construction, plowing, vehicle traffic, movement of cattle or other animals, burrowing action of animals, other biological activity, normal leaching, and raindrop splash. Mixing depths for fallout plutonium have been found to be 20 cm on cultivated land and 5 cm on uncultivated forest and rangeland (Foster and Hakonson, 1987). Fries and Paustenbach (1990) suggested a depth of 15 cm for agricultural tillage, but assumed values of 1 and 2 cm for various sensitivity tests. However, they did not need to make a distinction between tilled and untilled situation because vegetation (pasture grass and forage for estimating beef and milk fat concentration; above ground fruits and vegetables for human consumption) was assumed to be impacted only by particulate deposition and not root uptake. In another assessment on indirect impacts from incinerator emissions, EPA (1990a) estimated vegetation concentrations as a function of particulate depositions, root uptake, and air-to-leaf transfer from the vapor phase. Different mixing depths for untilled and tilled concentration estimation was required. For root uptake estimation for vegetable and other crops, the estimated soil concentrations assuming a tillage mixing depth of 20 cm. For soil

concentrations in untilled situations, they assumed a mixing depth of 1 cm. This mixing depth of 1 cm was retained in a later addendum to this methodology (EPA, 1993a). An earlier version of these dioxin exposure methodologies assumed a 1 cm depth for untilled soils and a 20 cm depth for tilled soils (EPA, 1994).

The methodology of this assessment uses 2 cm for the untilled and 20 cm for the tilled conditions for the off-site soil source category. A principal justification for the increase from the 1 cm depth of the earlier dioxin exposure assessment methodologies (EPA, 1994) to the current 2 cm depth for surface soils comes from Brzuzy and Hites (1995). Their data on soil concentrations of dioxin congener groups as a function of depth show definite migration of residues below the surface. Soil core results were described and concentration versus depth was displayed for 6 cores. The cores were undisturbed, and were taken in background settings with high vegetative cover so that the introduction of dioxins was speculated to be due only to atmospheric depositions - not pesticides or in an oily matrix. Briefly, the results did show a relationship between leaching and percent organic carbon - more residues near the surface soil at higher organic carbon content. For the 6 cores displayed: 1) a peak at the 1-2 cm depth was found in only one core, 2) there was essentially uniform concentrations for 3 cores to 5 cm with dropoffs thereafter, and 3) in two cores which had low organic carbon, there was a steadily rising concentration to peaks at 45 and 55 cm. The authors speculated that downward movement was due to movement of soil particles. They also did suggest that based on their sediment core information that deposition to these soils had been occurring for 60 years. This is not likely to be analogous to the situation of soil eroding from a site of soil contamination both because of the time involved and the mechanism of transport. Still, it would appear from this data that a 1 cm depth may not be justifiable. Based on this evidence, an untilled depth assumed for the soil contamination source will be 2.0 cm.

A tilled depth will be assumed to be 20 cm, as in earlier assessments (EPA, 1990a; EPA, 1993a; EPA, 1994). This assumption is made because tilling gardens is assumed to distribute surface residues to the 20-cm depth. Soil concentrations for dermal contact, soil ingestion, and pasture grass and soil intake for cattle grazing will assume a depth of 2 cm. These activities are assumed to occur on soil which has not been tilled. As will be described in Section 4.5, tilled and untilled depths of mixing are also required for the stack emission source category. For that source category, the untilled and tilled mixing depths are also assumed to be 2 and 20 cm, respectively.

Given the area of the exposure site, the mass of soil into which the eroded contaminant is mixed can be calculated as:

$$M_u = A_{es} B_{soil} d \quad (4\text{-}18)$$

where:

M_u = mass of soil for contaminant mixing per unit depth, kg/m
A_{es} = area of exposure site, m^2
B_{soil} = soil bulk density, kg/m^3
d = depth of mixing, m

- **D_1 and D_2:** The first step in deriving both these amounts of soil is to use the Universal Soil Loss Equation (USLE). This approach was described above. Justification was given for an assumption of unit soil loss from the contaminated site of 9.6 t/ac-yr in Section 4.3.1. D_1 equals this unit loss times the area of contamination times a sediment delivery ratio. The example scenario in Chapter 5 assumed that the exposure site was 150 meters from the contaminated site, and using Equation (4-10), the sediment delivery ratio is 0.26. The unit loss assumed for the area between the contaminated site and the exposure site is 0.96 t/ac-yr. Since this area is adjacent to the exposure site, there is no sediment delivery, and D_2 equals this unit loss times the area between the contaminated and exposure sites.

D_1 and D_2 can now be expressed as:

$$D_1 = 0.224 \; SL_1 \; SD_1 \; A_S \quad (4\text{-}19a)$$

$$D_2 = 0.224 \; SL_2 \; SD_2 \; A_{BLE} \quad (4\text{-}19b)$$

where:

$D_{1,2}$ = mass of soil delivered from off-site contaminated source, D_1, and from the land area between contaminated source and exposure site, D_2, kg/yr,
$SL_{1,2}$ = average annual unit soil loss, Eng. tons/acre-year, equal to 9.6 t/ac-yr for SL_1 and 0.96 t/ac-yr for SL_2
$SD_{1,2}$ = sediment delivery ratios, unitless, 0.26 for SD_1 (with distance = 150 meters) and 1.00 for SD_2

A_S/A_{BLE} = land area of contaminated site, A_S, and of area between contaminated site and exposure site, A_{BLE}, m^2

0.224 = converts t/ac-yr to kg/m^2-yr.

An adjustment is made to the sediment delivery ratio, SD_1, considering the size discrepancies between the contaminated site and the exposure site. For example, if the contaminated site is larger than the exposure site, then the amount of eroded soil delivered 150 meters downgradient would not all mix with soil at the exposure site. On the other hand, if the contaminated site were smaller than the exposure site, than the full amount of eroded soil delivered 150 meters downgradient would be contained within the exposure site. A simple correction factor, equaling the ratio of a side length of the exposure site (assumed square-shaped) and a side length of the contaminated site size (also assumed square shaped), is used to adjust the sediment delivery ratio:

$$SD_{1a} = SD_1 \quad CF_{SD} \tag{4-20}$$

where:

SD_{1a} = adjusted sediment delivery ratio corresponding to SD_1, unitless

SD_1 = sediment delivery ratio reducing the amount eroding from the contaminated site to be delivered to the exposure site, unitless

CF_{SD} = sediment delivery correction factor, unitless

= $A_{ES}^{0.5}/A_S^{0.5}$ if $A_{ES} < A_S$

= 1 if $A_{ES} > A_S$

A_{ES} = area of exposure site, m^2

A_S = area of contaminated site, m^2

Similar considerations are pertinent to the land area between the contaminated and exposure site. Remember that the algorithm assumed that some "clean" (D_2) and some "contaminated" soil (D_1) erodes onto the exposure site, and that a similar amount of soil entering the exposure site (R, which equals $D_1 + D_2$) leaves the exposure site so as to maintain a mass balance. The amount of clean soil eroding from upgradient sources mixing with exposure site soil can be larger than the amount of contaminated soil if the exposure site is larger than the

contaminated site. If the exposure site is smaller than the contaminated, and similar to the solution for SD_{1a} above, then only the small corridor defined by the size of the exposure site contributes clean soil. Either way (i.e., the exposure site is larger or smaller than the contaminated site), the size of the land area contributing clean soil is defined by the size of the exposure site. A_{BLE} can be estimated as the product of the distance between the exposure and contaminated site, and the side length of the exposure site:

$$A_{BLE} = DLCE \quad SLE \tag{4-21}$$

where:

A_{BLE} = land area between contaminated and exposure site, m^2
DLCE = distance from contaminated site to exposure site, m
SLE = side length of exposure site, m
= $(A_{es})^{0.5}$
A_{es} = area of exposure site, m^2

4.3.3. Vapor- and Particle-Phase Air Concentrations

The algorithms for estimating vapor- and particle-phase concentrations of contaminants were presented and derived in Hwang, et al. (1986), EPA (1985b), Hwang (1987), and Turner (1970). The algorithms, in general, entail estimation of the flux of vapor phase and particle bound dioxin-like compounds, and then the estimation of the dispersion of fluxes to arrive at appropriate air concentrations. The flux calculations for emissions of vapor phase and particle bound dioxin-like compounds is the same if the soil contamination occurs at the site of exposure or away from the site of exposure. However, the dispersion algorithms differ, depending on whether the site of exposure is at the site of contamination or away from the site. Discussions below begin with the procedure for calculating the soil fluxes, the volatile flux and the wind erosion flux, of dioxin-like compounds, and then to the two different dispersion algorithms.

The procedures for estimating volatile flux were developed for soil surface and subsurface contamination with polychlorinated biphenyls, PCBs. The models are based on the assumptions that: 1) PCBs move through the soil primarily by vapor phase diffusion, i.e., leaching is not considered, 2) PCB vapor in the soil matrix reaches a local equilibrium with pore air, 3) degradation processes for PCBs were not considered , and 4) the PCB contamination

occurs at the surface and extends down infinitely. These assumptions are similar to the general types of assumptions that have been made for all the algorithms estimating exposure media concentrations in this assessment. The procedures in that PCB assessment were also used for this assessment. Details of the derivation are presented in Hwang, et al. (1986).

The average flux rate over an exposure duration of ED can be estimated as:

$$FLUX_V = \frac{(2)\ (E_{slp})\ (D_{ea})\ (C_s)\ (H)\ (41)\ (10^{-6})}{Kd_s\ [\ (\pi)\ (I)\ (ED)\ ]^{0.5}} \qquad (4\text{-}22)$$

where:

$FLUX_V$ = average volatilization flux rate of contaminant from soil, g/cm^2-s
E_{slp} = soil pore porosity, unitless
D_{ea} = effective diffusivity of contaminant in air, cm^2/s
C_s = contaminant concentration in soil, ppm or mg/kg
H = Henry's Constant of contaminant, atm m^3/mol
Kd_s = soil/water partition coefficient, cm^3/g
ED = exposure duration, s
I = interim undefined term for calculation, cm^2/s
= $[\ D_{ea}\ E_{slp}\ ] / [\ E_{slp} + P_{soil}\ (1\text{-}E_{slp})\ [Kd_s/(41\ H)]\ ]$
P_{soil} = particle bulk density of soil, g/cm^3

The effective diffusivity, D_{ea}, is solved as a function of contaminant diffusivity in air, and soil pore porosity:

$$D_{ea} = D_c\ E_{slp}^{0.33} \qquad (4\text{-}23)$$

where:

D_{ea} = effective diffusivity of contaminant in air, cm^2/s
D_c = molecular diffusivity of contaminant in air, cm^2/s
E_{slp} = soil pore porosity, unitless.

The soil adsorption partition coefficient, Kd_s, is given as:

$$Kd_s = Koc \quad OC_{sl} \tag{4-24}$$

where:

Koc = contaminant organic partition coefficient, L/kg

OC_{sl} = fraction organic carbon in soil, unitless.

It is noted in Hwang, et al. (1986) that this procedure would tend to overestimate emissions and resulting exposures in situations involving small spills which would not involve deep contamination. It is also noted that the average flux rate is inversely proportional to the square root of the duration of exposure - the longer the duration of exposure, the lower will be the average flux rate. Whereas this solution assumes an unlimited reservoir of contaminant, it is an unsteady state solution (unlike most other solution strategies) and is essentially an average flux rate over an amount of time defined by the exposure duration. Inherent in the solution was the consideration that residues dissipate by volatilization at the surface layers, resulting in contaminants diffusing upwards from deeper soil layers over time. With this longer path of diffusion, volatilized amounts decrease, and hence the average flux over time also decreases.

The method for determining the flux of soil particles due to wind erosion for on-site conditions was developed in EPA (1985b) based on Gillette's (1981) field measurements of highly erodible soils. A key assumption for this solution is that the soil surface is assumed to be exposed to the wind, uncrusted, and to consist of finely divided particles. This creates a condition defined by EPA (1985b) as an "unlimited reservoir" and results in maximum dust emissions due to wind only. This solution will, in essentially all cases, overestimate the amount of dioxin-like compounds being emitted by wind erosion. This is because the soil conditions to which it applies, uncrusted and consisting of finely divided particles, are conditions that, at the very least, are disrupted by rainfall or anthropogenic activities (plowing, walking, etc.). The degree of overestimation is less in the situation of most concern - mostly unattended sites of high soil contamination. An alternate, less conservative solution, is one described as a “limited” reservoir solution. This model is presented in EPA (1989). A major problem with this model for application in the current framework is that it requires site-specific daily rainfalls and windspeeds, and it should be run for a period of time, at least a year, in order to estimate average

daily flux. To be consistent with all other methodologies of the soil contamination source category, and to be conservative regarding dust emissions, the "unlimited" reservoir solution is used here. This wind erosion flux for the unlimited reservoir approach is given as (EPA, 1985b):

$$E_e = 0.036 \quad (1 - V) \quad (U_m/U_t)^3 \quad F(x) \qquad (4\text{-}25)$$

where:

E_e	=	total dust flux of <10 μm particle due to wind erosion, g/m^2-hr
V	=	fraction of vegetation cover, unitless
U_m	=	mean annual wind speed, m/s
U_t	=	threshold wind speed, m/s
F(x)	=	a function specific to this model.

EPA (1985b) provides details allowing for the application of this equation under a variety of circumstances. Specific parameter assignments for the application of this equation to the example scenarios in Chapter 5 are given below.

The unit dust flux is easily converted to a contaminant flux by multiplying by soil concentration:

$$FLUX_{WE} = (2.8 \times 10^{-17}) \quad C_s \quad E_e \qquad (4\text{-}26)$$

where:

$FLUX_{WE}$	=	contaminant wind erosion flux from soil, g/cm^2-s
E_e	=	total dust flux of <10 μm particle due to wind erosion, g/m^2-hr
C_s	=	contaminant concentration in soil, ppb or ng/g
$2.8*10^{-17}$	=	converts ng/m^2-hr to g/cm^2-sec.

Like for vapor-phase dioxin-like compounds, the flux is converted to a concentration by the use of a dispersion term. Hwang (1987) describes an algorithm for the dispersion of contaminants emitted from an area source. Vapor- and particle-phase concentrations along the

center (y=0.0) of this area source are used to estimate concentrations when the site of exposure is at the site of contamination:

$$C_{vp} = \frac{(2/\pi)^{0.5} \quad FLUX \quad a \quad 10^{10} \quad erf(e)}{u_m \; S_z} \quad (e^{-0.5\,(z/S_z)^2}) \qquad (4\text{-}27)$$

where:

C_{vp}	=	vapor- or particle-phase concentration of contaminant in air, µg/m^3
FLUX	=	average volatilization or wind erosion flux rate ($FLUX_V$ or $FLUX_{WE}$) of contaminant from soil, g/cm^2-s
a	=	side length of contaminated site parallel to the wind direction, m
U_m	=	mean annual wind speed, m/s
S_z	=	vertical dispersion coefficient in air, m
z	=	height of the exposed individual, m
erf	=	error function
e	=	error function term, unitless
	=	b/(2*(2*S_y)$^{.5}$)
b	=	side length perpendicular to the wind direction, m
S_y	=	horizontal dispersion coefficient in air, m
10^{10}	=	converts g/cm^2-m to µg/m^3.

The dispersion terms, S_z and S_y can be estimated using site-specific wind rose data. In the absence of data, these terms can be estimated assuming the most common stability class, D, as:

$$S_y = 0.1414 \quad X^{0.894} \qquad (4\text{-}28a)$$

$$S_z = 0.222 \quad X^{0.725} \qquad (4\text{-}28b)$$

where:

$S_{y,z}$	=	horizontal and vertical dispersion coefficient, m

X = distance upwind of the contaminated site, m

Estimating the dispersion and resulting exposure site concentrations of air-borne contaminants, originating at a site of contamination which is near but not at the site of exposure, requires a different solution than this solution for the concentrations along the center line of an area source. A simplified solution, given as a virtual point source model, can be found in Turner (1970). This model approximates the dispersion that occurs from an area source by using an imaginary point source. This point is located upwind of the actual source at a distance calculated to create a lateral dispersion at the site equal to its width:

$$C_{vp} = \frac{2.03 \quad FLUX \quad A_{sc} \quad FREQ \quad 10^{10}}{VD \quad S_z \quad U_m} \qquad (4\text{-}29)$$

where:

C_{vp} = vapor or particle phase concentration of contaminant in air, $\mu g/m^3$

FLUX = average volatilization or wind erosion flux rate ($FLUX_V$ or $FLUX_{WE}$) of contaminant from soil, g/cm^2-s

A_s = area of contaminated site, m^2

FREQ = frequency wind blows from source to receptor, unitless

VD = virtual distance, source center to receptor, m

S_z = vertical dispersion coefficient, m

U_m = average wind speed, m/s

10^{10} = converts g/cm^2 to $\mu g/m^2$.

The term, FREQ, in not in the original Turner (1970) solution. It has been added to this equation to appropriately account for changing wind directions, and hence, obtain a more accurate annual average air concentration. The vertical dispersion, S_z, is estimated as an empirical function of the distance from the source center to receptor:

$$S_z = 0.222 \quad x^{0.725} \quad - \quad 1.7 \quad , \quad x \quad < 1000 \ m \qquad (4\text{-}30a)$$

$$S_z = 1.260\ x^{0.516} - 13.0\ ,\ x > 1000\ m \qquad (4\text{-}30b)$$

where:

S_z = vertical dispersion coefficient, m

X = actual distance from source center to receptor, m.

The virtual distance, VD, is an empirical function of the width of the contaminated area and the actual distance from source center to receptor:

$$VD = 2.514\ b + x \qquad (4\text{-}31)$$

where:

VD = virtual distance, source center to receptor, m

b = width of contaminated area perpendicular to wind direction - defined previously as side length for assumed square-shaped contaminated area, m

X = actual distance from source center to receptor, m.

Background on Koc and OC_{sl} were given in Section 4.3.1. above. Guidance for other terms in the four algorithms - volatile flux, wind erosion, on-site dispersion, off-site dispersion, now follow.

- **E_{slp}:** Porosity is defined as the pore space in soils occupied by air and water, and for sandy surface soils show a range of 0.35-0.50. Medium to fine-textured soils (loams, clays, etc.) show a higher range of 0.40-0.60 (Brady, 1984). Soil porosities in the example settings were 0.50.

- **H:** Henry's Constants were discussed in Volume 3, Chapter 2. The values of H used for the three example compounds were: for 2,3,7,8-TCDD - $3.29*10^{-5}$ atm-m^3/mole; for 2,3,4,7,8-PCDF - $4.98*10^{-6}$ atm-m^3/mole; and for 2,3,3',4,4',5,5'-HPCB - $6.65*10^{-5}$ atm-m^3/mole.

- **P_{soil}:** Particle bulk density is defined as the mass of a volume of soil solids. This contrasts the more common parameter, bulk density, which is the mass of a unit of dry soil, which includes both pores and solids. Particle bulk density, P_{soil}, has a narrow range of 2.60 to 2.75, and for general calculation purposes, Brady (1984) recommends a value of 2.65 for average mineral surface soils, the value used for the example settings.

- **ED:** The exposure duration is simply the amount of time individuals are exposed. Two exposure durations were used in the demonstration scenarios, 9 years for "central" and 30 years for "high end" exposures. Used in this algorithm, and as discussed earlier, longer exposure durations translate to lower average volatilization fluxes. This presumes a soil concentration assumed to be uniform over depth starting at time zero, and to become depleted over time. The selected exposure durations of 9 ($2.83*10^8$ sec) and 30 years ($9.46*10^8$ sec) was used.

- **D_c:** Molecular diffusivities in air of the example compounds could not be found in the literature. However, diffusivities of one compound can be estimated from another with the following (Thibodeaux, 1979):

$$\frac{D_a}{D_b} = \left(\frac{MW_b}{MW_a}\right)^{0.5} \qquad (4\text{-}32)$$

where:

$D_{a,b}$ = Molecular diffusivities of compounds a and b, cm^2/s

$MW_{a,b}$ = Molecular weights of compounds a and b, g/mole

Thibodeaux (1979) lists the molecular diffusivity of diphenyl at 25 °C at 0.068. Given the molecular weight of diphenyl of 154 g/mole, the diffusivities of the example compounds are: 2,3,7,8-TCDD (MW = 322) = 0.047; 2,3,4,7,8-TCDF (MW = 340) = 0.046; and 2,3,3',4,4',5,5'-HPCB (MW = 396) = 0.043.

- **U_m:** Mean annual windspeeds vary from between 2.8 and 6.3 m/s (EPA, 1985b). An assumption of 4.0 m/s in the absence of site-specific average wind speeds was made for the example scenarios of this assessment.

- **a, b, z, and x:** Simple assumptions can be made to assign values to the length terms above: a, b, z, and x. Assuming a square-shaped contaminated site, a equals b which equals the square root of the area of the site. A common assumption for z, the height of the exposed individual, is 2 m. The x term can be assumed equal to a side length (a or b), or can equal the side length plus the distance to the exposed individual if the contamination is not on-site and dispersion is modeled as "near field." For the residence and farm setting examples in Chapter 5, where the contamination was on-site, the x term was equal to a side length.

- **FREQ:** Where the wind blows from all directions equally, then it will blow from one compass sector about 15% of the time. On these bases, a FREQ of 0.15 was used in the example scenario demonstrating the soil contamination source category in Chapter 5. In most places, however, wind direction is much less variable, and the appropriate value is best determined with site specific information.

- **V:** Chapter 5 demonstrates “background” conditions for a "residence" and a "farm". In those settings, grass or crops are likely to substantially cover the soil, and the fraction of vegetative cover can range from 0.5 (minimal coverage) to 0.9 (more lush coverage). For the residence example setting in Chapter 5, V was set at 0.9 which assumes a continual grass cover over the contaminated soil. The V for the farm settings was instead 0.5. The area of contamination for the example farm settings was larger than the residence setting, 10 acres to 1 acre. The land where crops were grown was also contaminated; the 0.5 value for V assumes that the cropland is totally or partially bare at some times - perhaps during spring land preparation and fall harvest. For the demonstration of the soil contamination source category, the site of contamination is assumed to be bare, as in an active landfill or an industrial site. With this assumption, V is set equal to 0.0.

- **U_t:** As noted above, the average windspeed, U_m, is assumed to be 4.0 m/s. The threshold wind velocity, U_t, is the wind velocity at a height of 7 m above the ground needed to initiate soil erosion. It depends on nature of surface crust, moisture content, size distribution of

particles, and presence of non-erodible elements. It can be estimated on the basis of the following procedure (EPA, 1985b):

Step 1. Determine the Threshold Friction Velocity

This is the wind speed measured at the surface needed to initiate soil erosion. EPA (1985b) shows how it can be determined as a function of soil aggregate size distribution. However, for the "unlimited reservoir" approach for which Equation (4-25) was developed, soil particles are assumed to be fine at 1.5 mm or less as an average. This translates to a threshold friction velocity of 75 cm/s and less. A value of 50 cm/s might be reasonably assumed to be representative of these types of surfaces, and was assumed for this assessment.

Step 2. Estimate the "Roughness Height"

EPA (1985b) graphically shows the roughness height for a range of possible conditions. Included in this range are a roughness height of 0.1 cm for natural snow, 1.0 cm for a plowed field, 2.0-4.0 cm for grassland, 4.0 cm for a wheat field or for suburban residential dwellings, and up to 1000 cm for high rise buildings. The assumption made for the residence and farm example settings was 4.0 cm, following the information given for a wheat field or a suburban residence. The value assumed for the site of contamination in the demonstration of the soil contamination source category was 1.0 cm, which assumes that the plowed field value is the most analogous to the assumed bare soil site of contamination.

Step 3. Estimate Ratio of Threshold Wind Speed at 7 m to Friction Velocity

A chart provided by EPA (1985b) shows this ratio as a function of roughness height. For a roughness height of 4.0 cm, this ratio is seen to be 13. For a roughness height of 1.0 cm, this ratio is 16.5.

Step 4. Estimate Threshold Wind Speed

This is simply the product of the ratio given in step 3 above and the friction velocity. Using values given above, 50 cm/sec * 13 = 6.5 m/sec for the residential and farm settings, and 8.25 m/sec for the site of soil contamination.

- **F(x):** The model-specific function, F(x), is determined by first calculating the dimensionless ratio x, where $x = 0.886\ U_t/U_m$, and finding F(x) from a chart of F(x) versus x, as

provided in EPA (1985b). For $U_t = 6.5$ and $U_m = 4.0$, x = 1.44 and F(x) = 1.05. For $U_t = 8.25$ and $U_m = 4.0$, x = 1.83 and F(x) = 0.5.

4.3.4. Biota Concentrations

This section summarizes the algorithms to estimate contaminant concentrations in fish, vegetation (including vegetables for human consumption and pasture grass or fodder grown on contaminated soil for beef cattle consumption), beef, and milk. As will be shown, all algorithms are simple empirical equations which relate an environmental media concentration to a biota concentration, using a "biotransfer" or "bioaccumulation" factor.

4.3.4.1. *Fish Concentrations*

The procedure and supportive data for the algorithm to estimate fish tissue concentrations can be found in Cook, et al. (1991), in an assessment of risk of 2,3,7,8-TCDD to aquatic life and associated wildlife (EPA, 1993b) which EPA is conducting as part of its reassessment of dioxin-like compounds, and most recently in a technical support document for the Great Lakes Water Quality Initiative (EPA, 1995). Of those references, only EPA (1995) contains information on the suite of dioxin-like (and other) compounds.

Dioxin-like compounds share a high degree of hydrophobicity that increases as the degree of chlorination increases. Cook, et al. (1991) note that this corresponds in general to an increase in lipophilicity and an increase in ability to bind to organic carbon in sediments and to dissolved organic matter in water. However, these tendencies are not paralleled by an increase in bioaccumulation. Only the 2,3,7,8-chlorine-substituted congeners are substantially bioaccumulated by fish, although large quantities of other CDD/F congeners are found in sediments. This pattern of bioaccumulation results because of higher rates of metabolism of CDD/Fs in fish as compared to the 2,3,7,8-chlorine-substituted congeners (EPA, 1992a; Cook, et al., 1991, with references to Muir et al., 1986; Gobas, 1990). While the highly chlorinated 2,3,7,8-substituted congeners are very slowly accumulated, they have very slow elimination rates.

2,3,7,8-TCDD and other planar polyhalogenated aromatic hydrocarbons often have not been detected in water from aquatic ecosystems even when biota are highly contaminated. Because surface layers of bottom sediments are a good indicator of the relative amount of chemical in the system over the time scale involved for bioaccumulation of super-hydrophobic chemicals, a term known as the Biota to Sediment Accumulation Factor, or BSAF, has been offered as a measure of site-specific bioaccumulation potential. This term was proposed to

replace equivalent terms which were known as the Bioavailability Index, or BI (Kuehl, et al., 1987; Cook, et al., 1991; EPA, 1990b), the Accumulation Factor, AF (Lake, et al., 1990) and the Biota to Sediment Factor, or BSF (Parkerton, et al., 1993; Parkerton, 1991). BSAF is defined as:

$$BSAF = \frac{C_{lipid}}{C_{oc}} \quad (4\text{-}33)$$

where:

BSAF = biota to sediment accumulation factor, unitless
C_{lipid} = concentration of contaminant in lipid of fish, mg/kg,
C_{oc} = concentration of contaminant in bottom sediment organic carbon, mg/kg

The surface water algorithms estimate concentration of contaminant in bottom sediments (see Section 4.3.1 above). This concentration, C_{sed}, can be converted to an organic carbon basis as a function of OC_{sed}:

$$C_{oc} = \frac{C_{sed}}{OC_{sed}} \quad (4\text{-}34)$$

where:

C_{oc} = concentration of contaminant in bottom sediment organic carbon, mg/kg;
C_{sed} = concentration of contaminant in bottom sediment, mg/kg;
OC_{sed} = fraction organic carbon in bottom sediment, unitless

The organic carbon content of bottom sediments was assumed to 0.03; see Section 4.3.1. for the derivation of C_{sed}.

Since the accumulation of contaminant is assumed to occur only in fish lipid, a correction term to estimate the whole fish tissue concentrations is needed since fish consumption in g/day refers to whole fish consumption. The correction term is simply f_{lipid}, and so whole fish concentrations are simply $C_{lipid} * f_{lipid}$.

The BSAF was developed as a measure of bioaccumulation potential rather than as a predictor, as it is being used here. It is uncertain as to whether measured BSAFs are generally applicable to other water bodies. Efforts are underway to evaluate the general applicability of BSAFs (P. Cook, Duluth Environmental Research Laboratory, US EPA, 6201 Congdon Boulevard, Duluth, MN 55804, personal communication). Using the BSAF approach as a predictive tool greatly underplays the complexity of the processes transferring contaminants from aquatic ecosystems to aquatic organisms. EPA (1993b and 1995) provides a comprehensive discussion on aquatic impacts and processes for dioxin-like and related compounds. Following are some of the key issues to consider:

1) **Resident vs. Migratory Species:** Parkerton (1991) applied a bioenergetics-based bioaccumulation model in an attempt to duplicate BSAFs for 2,3,7,8-TCDD found for carp and blue crabs in the Passaic River, New Jersey. He showed nearly a ten-fold difference in 2,3,7,8-TCDD BSAF calculated from data for resident species as compared to migratory species in the Passaic River. This would be expected for fish which also reside part of the time in relatively clean water bodies; migration would enable depuration of residues from fish. The possibility that migration patterns might explain some of the results for fish concentrations of 2,3,7,8-TCDD in the Lake Ontario bioaccumulation study was also raised (EPA, 1990b). That assessment also discussed a related issue of concern - to consider lakewide average sediment concentrations or concentrations near where sampled fish were captured in calculating the BSAF. Even within a large lake, more sedentary populations of fish may be impacted by localized contamination.

2) **Past history of contamination:** If contamination of surface water bodies with hydrophobic compounds like the dioxin-like compounds has occurred principally in the past, then it can be expected that most of the contamination occurs in or near the bottom sediment layer and not within the water column. Furthermore, if inputs to water bodies are declining or low in comparison to past loadings, then sediments would be undergoing depuration - residue levels would be declining, and the system may not be equilibrium. EPA (1990b) noted that very low BAF*s (defined as a fish to sediment ratio not including the sediment organic carbon and fish lipid considerations of BSAFs) and BSAFs for 2,3,7,8-TCDD in Lake Ontario contrasts higher BAF*s for other hydrophobic compounds such as DDE or PCBs. An explanation offered is that loadings to the Lake may be declining, such that there is a substantial disequilibrium between sediments, water, fish, and their prey. One parameter required in the bioenergetics model Parkerton (1991) used (referred to in the above bullet) was a ratio of contaminant

concentration in bottom sediment to that in suspended sediment, rs/rw. In modeling exercises on the Passaic River, he found closer agreement between measured and predicted BSAFs with this ratio equal to 10 in contrast to 1, the only two values tested; a ratio of ten means that the concentration of contaminant in bottom sediment is ten times higher than it is in the suspended sediment. BSAFs predicted by the model were developed as the ratios in modeled fish lipid concentrations divided by modeled bottom sediment organic carbon normalized concentrations. Measured BSAFs used actual Passaic River fish lipid and bottom sediment concentrations of 2,3,7,8-TCDD. BSAFs predicted with this ratio equal to 1 were roughly 4 times as high as measured BSAFs, and BSAFs found with rs/rw equal to 10 were twice as high as measured. A related result of his modeling exercise was that, at best fit between modeled and measured BSAFs where the rs/rw was 10, dietary exposures explained over 50% of the BSAFs for carp and 85% in blue crabs, in contrast to water column exposures. He speculates that prey organisms consist of benthic animals which ingest contaminated bottom sediment. If the food chain begins near bottom sediments, and if food chain exposures are a principal explanation for fish tissue dioxin concentrations, than it follows that a model would perform better when bottom sediment concentrations drive fish tissue concentrations rather than water column concentrations, or equivalently, when rs/rw = 10. Finally, he notes that 2,3,7,8-TCDD contamination in Passaic river largely occurred as a result of historical loadings. The picture that emerges from Parkerton's modeling is as follows: sediments are serving as an internal source of contaminants due to past historical loadings, and the water column is in disequilibrium with bottom sediments and driven only by depuration of bottom sediment concentrations. The bioaccumulation of these compounds in carp and blue crabs appears to be mediated by trophic transfer via the benthic foodweb. In both the Lake Ontario and Passaic River studies, concentrations of 2,3,7,8-TCDD were higher in deeper bottom sediments as compared to surficial bottom sediments - this implies historical loadings and possibly depuration of surficial residues.

This issue is non-trivial for the methodology of this assessment, since an assumption for deriving suspended and bottom sediment concentrations is that the contamination is ongoing, and that the hypothetical water body may be closer to a state of equilibrium as compared to situations where contamination was principally in the past. The BSAF assumed for 2,3,7,8-TCDD in the demonstration scenarios of 0.09 is more in line with data from EPA (1990b) on Lake Ontario and from Parkerton (1991) from data in Passaic River, then with other data (presented later) where historical loadings are not as clear a principal source of bottom sediment contamination. The issue of ongoing versus historical contamination should be considered when assigning site-specific BSAFs.

3) **Variations among fish species, particularly column feeder vs. bottom feeder:** Feeding habits, age, migratory patterns, and lipid contents (including lipid content of edible vs. inedible fish tissues) are just a few of the interacting factors which determine a site-specific BSAF as a function of fish species. Bottom-feeders such as carp or catfish can have BSAF values that could be an order of magnitude higher as compared to column feeders. A calculated 2,3,7,8-TCDD BSAF for carp in Connecticut of 0.86 compares to the 2,3,7,8-TCDD BSAF of 0.03-0.07 calculated for trout by EPA (see Table 4-1). The demonstration of this approach in Chapter 5 assigns a single BSAF to each of the three example contaminants, and the assignment is expected to be more like BSAFs for column feeders. Although not unlike other simplifications of this assessment, such approaches are recognized as oversimplifications.

4) **Study designs to obtain BSAFs:** Although there is some evidence that BSAFs specific to a contaminant may be applicable to other aquatic settings, data to evaluate such a hypothesis is still sparse. Even data sets that do exist need to be carefully evaluated before deriving BSAFs. Such an evaluation should consider sediment as well as fish species data. Critical factors for sediment sampling include location, number, depth of sampling, variability, availability of organic carbon fraction information, and so on. Similar issues are pertinent for fish sampling and analysis.

Following now are guidance for the terms required for estimating fish tissue concentrations.

- **BSAF:** Table 4-1 summarizes literature from which biota sediment accumulation factors for dioxin and furan congeners could be developed. Only six sets of data were found in the literature. The data reported in EPA (1995) for Great Lakes Trout, from the Wisconsin River (Kuehl, et al. 1987), and that from 1 lake in Sweden (Kjeller, et al. 1990) both show decreasing BSAF with increasing chlorination. The BSAF of 2.94 for 2,3,7,8-TCDD determined from a lake in Sweden should be questioned since it is more than an order of magnitude different than any of the other data. Causes for this discrepancy could be manifold. Some observations from Kjeller, et al. (1990) might shed some light on this result. Although sediment data was from three water bodies, 8 of the 9 Pike samples (pike samples were composites of 2-5 fish from one location in the water body) were from one of the water bodies. This is why only data from the one water body was summarized in Table 4-1. This water body, Lake Vanern, was clearly the most contaminated of the three water bodies studied. A paper mill was located at the northern part of this lake and the authors concluded that discharges from this mill impacted the lake. The

average of 2,3,7,8-TCDD and 2,3,7,8-TCDF organic carbon normalized concentrations for five sediment samples from this lake was 297 pg/g; the analogous average concentration for 10 samples taken from another lake, Lake Vattern (6 samples), and a river, Dala (4 samples), was 65 pg/g. A similar disparity between Lake Vanern and the other water bodies is found with the penta-CDD/F concentrations: 205 pg/g vs. 108 pg/g, with similar comparisons for the hexa-, hepta, and octa-CDD/CDF. The sediment and corresponding pike sample nearest this mill had the highest concentrations reported - pike samples were given as 3000 and 833 pg/g lipid normalized 2,3,7,8-TCDF and 2,3,7,8-TCDF (a composite from 5 pike taken at this sampling station), respectively, and sediment was 1800 and 244 pg/g organic carbon normalized for 2,3,7,8-TCDF and 2,3,7,8-TCDD. Note the BSAF for 2,3,7,8-TCDD implied from this data point is 3.41. Another consideration for high BSAFs might be the source of contamination. Speculation from the Lake Ontario and Passaic River field data was that contamination principally occurred in the past, whereas in the Swedish data, contamination appears to have been ongoing at the time of sampling. This might be one indication that BSAFs for aquatic systems where contamination is ongoing might be greater than from systems where the contamination is primarily historical.

The Swedish data also illustrates some of the complexities of interpreting literature data. First, the sediment data was expressed concentrations normalized to "sediment contents of organic material" (sic). This was interpreted as organic matter normalized, not organic carbon normalized. Parkerton (1991) assumed that organic carbon was 45% of organic matter to derive BSAFs when organic carbon data was unavailable; following this lead, organic matter normalized concentrations in Kjeller, et al. (1990) were divided by 0.45 to arrive at organic carbon normalized concentrations. Also, there was not an exact match in "sites" between sediment samples and fish samples; these sites were physical locations within the large lake where samples were taken. There were five sites where sediment samples were taken, and five sites where composited pike samples were taken in Lake Vanern. However, one of the sediment and one of the pike samples were from unique sites; only four sites had both sediment and pike samples. The results in Table 4-1 were derived using average sediment and pike concentrations from only these four sites. Another way to have derived BSAFs would be to average all lake sediment and pike concentrations; since there may be some relationship between sediment and pike concentrations based on lake location, it was decided to include only the four sites with both fish and sediment samples. Finally, there were two sets of results listed for 1,2,3,4,6,7,8-HpCDF as though there were two unique sets of analyses for the same congener; this is why there are two entries for this congener in Table 4-1.

A complete discussion of the data generated by the Connecticut Department of Environmental Protection (CDEP, 1992) is included in Chapter 7. Generally, water bodies tested were mostly in rural/suburban settings rather than urban settings. Concentrations of 2,3,7,8-TCDD in surface soils and bottom sediments were in the low ppt level, indicating background impacts. BSAFs generated with that data ranged from 0.24 to 0.85 for TEQs, 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 2,3,4,7,8-PCDF.

EPA (1995) published BSAFs for lake trout for the 17 dioxin-like congeners based on a reanalysis of the Lake Ontario sediment and lake trout samples originally taken in 1987-88 and reported on first in EPA (1990). It is not clear how many of the samples were reanalyzed and why the 2378-TCDD lake trout BSAF was different in the 1995 report, 0.059, as compared to the 1990 report, 0.07. EPA (1995) also discussed the concept of the "bioequivalency factor", or BEF, which is defined as the ratio between the BSAF of each non 2378-TCDD dioxin-like congener to the BSAF of 2378-TCDD. These BEFs are listed in Table 4-1. They can be used to assign congener-specific BSAFs if all that is known for a specific site is the 2378-TCDD BSAF.

Excluding the Swedish data, there are 43 reported BSAFs for dioxin-like congeners in Table 4-1. These range from 0.00065 to 0.93, with lower BSAFs associated with higher chlorinated congeners. A BSAF of 0.09 will be assumed for 2,3,7,8-TCDD in the demonstration scenarios in Chapter 5. The BSAFs for the other dioxin-like congeners will be assigned based on the BEF for that congener. For example, the BSAF of 2,3,4,7,8-PCDF will be equal to 0.14, which is estimated as the BEF for 2,3,4,7,8-PCDF, 1.6, times the BSAF for 2,3,7,8-TCDD.

EPA (1990b) estimated BSAFs for PCBs and other selected chemicals (DDE, HCB, etc.) for Lake Ontario from several data sets. Later, EPA (1995) reported on BSAFs for subsets of the dioxin-like congeners from three data sets: Oliver and Niimi (1988), a reanalysis of their own sediment and late trout samples from the 1988 Lake Ontario study, and the EPA Green Bay/Fox River Mass Balance Study. Parkerton, et al. (1993) summarizes BSAFs for PCBs and other compounds from other water bodies using other data sets. A selected summary of BSAFs for PCBs taken from the two EPA references and the Parkerton, et al. (1993) reference is given in Table 4-2.

Two trends are apparent. First, the BSAFs for PCBs appear to exceed those of the dioxin and furan congeners by an order of magnitude and more. Second, and from limited data, it would appear that BSAFs increase from dichloro- through hexa- or perhaps hepta-chloro PCBs, and then decrease thereafter. An assignment of a BSAF for 2,3,3',4,4',5,5'-HPCB, which is abbreviated as PCB 189 in the IUPAC system, is not apparent from the data summary below. Two data points from EPA place the value for that congener at 0.71 and 3.45. The data point

from Siskiwit for the single heptachloro-PCB, which was 2,2',3,4',5,5',6-HPCB, was estimated by Parkerton, et al. (1993) as 12.5. The BSAF for the heptachloro-PCB congener group for flounder from New Bedford Harbor estimated by Parkerton, et al. (1993) was 0.84, with BSAFs for lobster and crab as 1.29 and 2.74, respectively. A value of 2.10 is assigned to 2,3,3',4,4',5,5'-HPCB for the example scenarios in Chapter 5, which is the midpoint of the two EPA data points specific to this congener

It should be noted that these assignments are based on data on vertebrate rather than invertebrate aquatic species. It is generally recognized that invertebrates do not possess the enzymatic capability to metabolize hydrophobic compounds as effectively as higher chordates. As a result, invertebrate species such as mussels, clams, oysters, shrimp, crabs and lobsters may have BSAF values much higher than those observed for fish. Parkerton (1991) and Parkerton, et al. (1993) reviewed the literature to estimate BSAFs of 1 to 5 for species including grass shrimp, sandworms, deposit feeding clams, and blue mussel for CDD/Fs and PCBs.

Finally, it should be noted that all bioconcentration or biotransfer parameters, such as the BSAF, are qualified as second order defaults for purposes of general use. Section 6.2. of Chapter 6 discusses the use of parameter values selected for the demonstration scenarios, including a categorization of parameters. Second order defaults are defined there as parameters which are theoretical and not site-specific, but whose values are uncertain in the published literature. The parameter values in this category should be considered carefully by users of the methodology.

- **f_{lipid}:** Lipid contents of edible fish species have been compiled in EPA (1995), and for the sake of brevity, this compilation will not be repeated here. Generally, lipid contents can range from 0.05 to greater than 0.20 (5% - 20%). BSAFs are typically developed on the basis of whole fish lipid content, so estimates of whole fish concentrations should be made with a whole fish lipid content. Parkerton, et al. (1993) cautions, however, that lipid contents of edible portions of fish may be lower than lipid contents of some of the fish portions that were sampled and used to develop BSAFs. Non-edible high lipid content portions include, for example, liver and hepatopancreas. Parkerton, et al. (1993) develops the parameter, β, which is defined as the ratio of the lipid content of the edible portion and the sampled tissue. To demonstrate the impact of this ratio, Parkerton used data from Niimi and Oliver (1989) which included PCB and other halocarbon compound concentration in whole fish and fillets of fish taken from the Great Lakes. The β (defined here as the ratio of lipid in fillet to lipid of whole fish) for these fish, which included brown trout, lake trout, rainbow trout, and coho salmon, ranged from 0.22 to 0.51. The ratio of fillet to contaminant concentrations ranged from 0.20 to 0.54.

In the context of the current model, concentrations in fish for estimating exposure are estimated as the product of: organic carbon normalized bottom sediment concentrations * BSAF * f_{lipid}. BSAFs (in theory) are independent of fish tissue being sampled - they are ratios of the organic carbon normalized concentration and fish lipid concentration. Users should be aware, however, that the f_{lipid} value assigned should correspond to the fish concentration of interest - that could be whole fish if the model is used in validation exercises or edible fish if the model is used for exposure assessment. Cook, et al. (1990) and EPA (1993b) assumed a lipid content of 0.07 for fish in discussions of BSAF and related methodologies for estimating bioaccumulation of 2,3,7,8-TCDD in aquatic ecosystems. This assessment will also assume a f_{lipid} of 0.07, and since its use in this context is in exposure assessment, this value could be thought of as a edible portion lipid fraction.

4.3.4.2. *Vegetation Concentrations*

Vegetation concentrations are required for the estimation of exposure to homegrown fruits and vegetables, and also for the beef and dairy food chain algorithms. Three principal assumptions are made to estimate vegetative concentrations:

- Outer surfaces of bulky below ground vegetation are impacted by soils which contain dioxin-like compounds. Inner portions are less impacted than outer portions, although data has shown some within plant translocation into below ground vegetables.
- Translocation of dioxin-like compounds from roots to above ground portions of plants are negligible compared to other mechanisms which impact above ground portions of plants. As such, translocation into above ground portions will be assumed to be zero.
- Unlike below ground vegetables, data has shown very little impact to inner portions of above ground bulky vegetation. Therefore, it will be assumed that outer and not inner portions of above ground bulky vegetation are impacted.

Concentration of contaminants in below ground vegetation is only required for vegetables (carrots, potatoes, e.g.) grown underground. The basis for the below ground algorithm is the experiments of Briggs, et al. (1982) on uptake of contaminants into barley roots from growth solution, and their elaboration of a Root Concentration Factor. The below ground concentration is given by:

$$C_{bgv} = \frac{C_s \quad RCF \quad VG_{bg}}{Kd_s} \qquad (4\text{-}35)$$

where:

C_{bgv}	=	fresh weight concentration of below ground vegetables, pg/g
C_s	=	contaminant concentration in soil, ppt or pg/g
Kd_s	=	soil-water partition coefficient, L/kg
	=	$Koc*OC_{sl}$
Koc	=	contaminant organic partition coefficient, L/kg
OC_{sl}	=	fraction organic carbon in soil, unitless.
RCF	=	root concentration factor equaling the ratio of the contaminant concentration in roots (fresh weight basis) and the concentration in soil water, unitless
VG_{bg}	=	empirical correction factor for below ground vegetation which accounts for the differences in the barley roots for which the RCF was derived and bulky below ground vegetables, unitless

Two processes, air-borne vapor phase absorption and air-borne particle deposition, are assumed to contribute to above ground vegetation concentrations:

$$C_{abv} = C_{vpa} + C_{ppa} \quad (4\text{-}36)$$

where:

C_{abv}	=	concentration in above-ground vegetation, expressed on a dry weight basis, pg/g or ppt
C_{vpa}	=	contribution of concentration due to vapor-phase absorption or airborne contaminants, pg/g or ppt
C_{ppa}	=	contribution of concentration due to wet plus dry deposition of contaminated particulates onto plant matter, pg/g or ppt

The basis for a vapor-phase transfer factor for various airborne contaminants, including 1,2,3,4-TCDD, from the atmosphere to vegetation was developed by Bacci, et al. (1990, 1992), with amendments suggested by McCrady and Maggard (1993), and McCrady (1994). The final values selected for the 17 dioxin-like CDD/Fs were developed by calibration (Lorber, 1995), and then field validated (Lorber and Pinsky, 1999), as described below. Bacci and coworkers conducted laboratory growth chamber experiments on the vapor-phase transfer of 14 organic

compounds from air to azalea leaves, and developed a generalized model to predict the vapor-phase bioconcentration factor based on a contaminant Henry's Constant, H, and octanol water partition coefficient, Kow. A similar experiment by McCrady and Maggard (1993) conducted for 2,3,7,8-TCDD vapor transfer to grass leaves suggested that the Bacci empirical algorithm to would greatly overestimate the transfer factor for 2,3,7,8-TCDD. The development of the biotransfer factor for vapor-phase dioxins, termed B_{vpa} in this assessment, was based on field data. Further details on these experiments are in the section below on this critical parameter. The algorithm estimating plant concentrations as a function of vapor-phase air concentrations is:

$$C_{vpa} = \frac{B_{vpa} \quad C_v \quad VG_{ag}}{d_a} \qquad (4\text{-}37)$$

where:

C_{vpa} = plant concentration due to vapor-phase absorption or airborne contaminants, pg/g or ppt, dry weight basis

B_{vpa} = mass-based air-to-leaf biotransfer factor, unitless [(pg contaminant/g plant dry)/(pg contaminant/g air)]

C_v = vapor-phase concentration of contaminant in air, pg/m^3

VG_{ag} = empirical correction factor which reduces vegetative concentrations considering that B_{vpa} was developed for transfer of air-borne contaminants into leaves rather than into bulky above ground vegetation

d_a = density of air, g/m^3, 1190

Several exposure efforts for 2,3,7,8-TCDD (Fries and Paustenbach, 1990; Stevens and Gerbec, 1988; Connett and Webster, 1987; Travis and Hattemer-Frey, 1991), have modeled the accumulation of residues in vegetative matter (grass, feed, vegetables) resulting from deposition of contaminated particulates. Key components of their approach, as well as the one for this assessment, include:

- Vegetative concentrations result from particulate deposition onto plant surfaces.
- Vegetative dry matter yield is the reservoir for depositing contaminants; this reservoir varies according to crop.

- Not all particulate deposition reaches the plant, some goes directly to the ground surface; the "interception fraction", less than 1.0, reduces the total deposition rate. This fraction can be related to the percent ground that is covered by the vegetation.
- Weathering processes, such as wind or rainfall, remove residues that have deposited onto plant surfaces via particle deposition, and this process is reasonably modeled as a first-order exponential loss with an associated weathering dissipation rate. All the above references have justified a dissipation rate derived from a half-life of 14 days (based principally on field measurements described in Baes, et al. (1984)); this is the value used for all dioxin-like compounds in this assessment as well. As well, a portion of particles depositing as wet deposition are not retained on the vegetation after the rainfall. A retention factor reduces total wet deposition considering this.
- Vegetative concentrations may not reach steady state because of harvesting or grazing, but a steady state algorithm is used.

The steady state solution for plant concentrations attributed to wet plus dry particle deposition is:

$$C_{ppa} = \frac{F_p}{1000 \; k_w \; Y_j} \qquad (4\text{-}38)$$

where:

C_{ppa}	=	plant concentration due to settling of contaminated particulates onto plant matter, pg/g or ppt, dry weight basis
F_p	=	unit contaminant wet plus dry deposition rate onto plant surfaces, pg/m^2-yr
k_w	=	first-order weathering dissipation constant, 1/yr
Y_j	=	dry matter yield of crop j, kg/m^2
1/1000	=	converts pg/kg to pg/g

The unit contaminant wet plus dry deposition rate, F, is given as:

$$F_p = C_p \; (V_d \; I_j + RN \; R_w \; W_p \; I_j) \qquad (4\text{-}39)$$

where:

F_p	=	unit contaminant wet plus dry deposition rate onto plant surfaces, pg/m^2-yr
C_p	=	air-borne particulate phase contaminant concentration, pg/m^3
V_d	=	deposition velocity, m/yr
I_j	=	fraction of particulates intercepted by crop j during deposition, unitless
RN	=	annual rainfall, m/yr
R_w	=	fraction of particles retained on vegetation after rainfall, unitless
W_p	=	volumetric washout factor for particulates, unitless

Following is brief guidance on assignment of values to the terms in Equations (4-35) to (4-39).

- **C_s and Kd_s:** This is the soil concentration and soil/water partition coefficient, respectively. The soil concentration is specified for the soil contamination source category. When the soil contamination is distinct from the site of exposure, the soil concentration at the site of exposure is modeled. As discussed in Section 4.3.2 above, two soil concentrations including one for a no-till and one for a tilled situation, are modeled in this situation. For modeling below ground vegetable concentration, the tilled concentration is required. The soil partition coefficient is a function of the contaminant organic carbon partition coefficient, Koc, and the soil organic carbon fraction, OC_{sl}, as discussed above in Section 4.3.1. Division of C_s by Kd_s results in the equilibrium soluble phase concentration of the contaminant, in mg/L.

- **RCF:** Briggs, et al. (1982) conducted experiments measuring the uptake of several compounds into barley roots from growth solution. He developed the following relationship for lipophilic compounds tested (lipophilic compounds were identified as those tested that had log Kow 2.0 and higher (n=7, r=0.981):

$$\log RCF = 0.77 \log (Kow) - 1.52 \qquad (4\text{-}40)$$

where:

RCF = root concentration factor equaling the ratio of the contaminant concentration in roots (fresh weight basis) and the concentration in soil water, unitless

Kow = contaminant octanol water partition coefficient, unitless

Since the highest log Kow of the seven for which this relationship was derived is 4.6, and the lowest log Kow for the dioxin-like compounds is above 6.0, this relationship may not hold for the dioxin-like compounds. However, a validation exercise described in Chapter 7 where predictions of dioxin-like compounds in carrots are compared with observations shows this factor to adequately perform for this class of compounds.

Briggs' experiments were conducted in growth solution. Therefore, the RCF is most appropriately applied to soil water in field settings. This is why the C_s was divided by Kd_s in Equation (4-35).

- **VG_{bg}:** This correction factor and the one used to correct for air-to-leaf transfer of contaminants, VG_{ag}, are based on a similar hypothesis. That hypothesis for VG_{bg} is that the uptake of lipophilic compounds into the roots of this experiments is due to sorption onto root solids. High root concentrations were not due to translocation to within portions of the root hairs. Direct use of the RCF for estimating concentrations in bulky below ground vegetation would overestimate concentrations since available data suggests some but little translocation to inner parts of below ground bulky vegetation for the dioxin-like compounds. The experiments of Muller, et al. (1994) showed that the outer portions (peel) of carrots had higher concentrations of dioxin congener groups as compared to inner portions (cortex and stele). However, they also found concentrations within the carrot, suggesting some within plant translocation. Their data is examined below and used to assign a value for VG_{bg} in this assessment.

One set of important soil-to-plant transfer experiments, however, did suggest that certain plants would sorb and translocate dioxins to a significant extent. Hulster, et al. (1994) found that dioxins were sorbed by the roots of vegetables of the cucumber family and made their weight into the above ground portions of these plants. They were unable to explain why this happened and noted that it was a distinctly different trend then they found in several of their other soil-to-plant transfer experiments. For this assessment, it will be assumed that the vegetables of the cucumber family are an anomaly and not typical of vegetation for human or animal consumption.

VG_{bg} converts an outer portion, or skin, concentration, into a whole plant concentration. If inner portions were entirely free of residue, the correction factor could be estimated as the ratio of the mass of the outer portion to mass of the entire vegetable:

$$VG_{bg} = \frac{MASS_{skin}}{MASS_{vegetable}} \quad (4\text{-}41)$$

where:

VG_{bg} = below ground vegetation correction factor, unitless
$MASS_{skin}$ = mass of a thin (skin) layer of below ground vegetables, kg/m^2
$MASS_{vegetable}$ = mass of the entire vegetable, kg/m^2

Simplifying assumptions are now made to demonstrate this ratio for a carrot and a potato. First, it will be assumed that the density of the skin and of the vegetable as a whole are the same, so the above can become a skin to whole vegetable volume ratio. The thickness of the skin will be assumed to be same as the thickness of the barley root for which the RCF was developed. Without the barley root thickness in Briggs, et al. (1982), what will instead be assumed is that the skin thickness is equal to 0.03 cm. This was the thickness of a leaf from broad-leaved trees assumed by Riederer (1990) in modeling the atmospheric transfer of contaminants to trees. The shape of a carrot can be assumed to be a cone. The volume of a cone is given as $(\pi/3)r^2l$, where r is a radius of the base and l is length. Assuming a carrot base radius of 1 cm and a length of 15 cm, the volume is 16 cm^3. The curved surface area of a cone is given as: $\pi r(r^2 + l^2)^{½}$, which equals 47 cm^2, given the r and l assumptions. The volume of the cone surface area is 47 cm^2 * 0.03 cm, or 1.41 cm^3. The skin to whole plant ratio for this carrot is 0.09 (1.41/16). A similar exercise is done for a potato, assuming a spherical shape with a radius of 3 cm. The volume is given as $4/3\pi r^3$, or 113 cm^3. The surface area of a sphere is $4\pi r^2$, or 113 cm^2, and the volume of this surface area is 3.39 cm^3. The skin to whole plant ratio for the potato is 0.03.

This exercise indicates lower bounds for such an empirical parameter. For exposure assessments, other factors which reduce vegetative concentrations should also be considered. Additional reductions in concentration result from peeling, cooking, or cleaning, for example. Wipf, et al. (1982) found that 67% of unwashed carrot residues of 2,3,7,8-TCDD came out in wash water, and 29% was in the peels. A peeled, washed carrot correction factor might instead be, 0.09*0.04, or 0.004 (0.09 from above; 0.04 = 100% - 67% - 29%). A 96% reduction in the estimated VG_{bg} for the potato (the potato is cleaned and the skin is not eaten; additional

reductions possibly when cooking the potato) would equal 0.001. In a site-specific application, the type of vegetation, preparation, and so on, should be considered.

As mentioned above, the Muller, et al. (1994) data did show concentrations in the inner parts of the carrot. They presented concentrations for the cortex and stele, as well as the carrot peel. One interesting trend with this data is that the cortex and stele concentrations are virtually the same with both the control and the contaminated soil. Also, the cortex and stele concentrations for the control carrots are slightly lower, but essentially similar to the peel concentrations for the control group. The authors of this research observed a lack of change in cortex and stele concentrations from the control to the contaminated soil, but offered no explanation. This suggests that the empirical parameter VG_{bg} should not be a constant but should vary, being higher at lower soil concentrations. With a lack of data to develop an algorithm for a varying VG_{bg}, it remains a constant for this assessment.

This data was examined to estimate the VG_{bg}. As noted above, a lower bound assignment of VG_{bg} for the hypothetical carrot was 0.09, and for the potato, was 0.03. This means that if there were absolutely no within plant translocation of dioxin residues - all residues were only in the skin of the carrot and potato - than the VG_{bg} would be 0.09 and 0.03. Muller, et al. (1994) did not include whole carrot concentrations or the necessary information to calculate whole carrot concentrations accurately. Therefore, simple assumptions will be made to do such. It will be assumed that the whole carrot concentration is estimated as 1 part peel concentration, 7 parts cortex concentration, and 2 parts stele concentration. The VG_{bg} is calculated as the whole carrot concentration divided by the peel concentration. Using this procedure, it is found that the VG_{bg} for the control soil varied between 0.38 and 1.00 for the 10 congener groups, with an average of 0.60, and that it varied between 0.14 and 0.39 for the contaminated soil, with an average of 0.24. These estimates are obviously higher than 0.09, indicating, as the data shows, that within plant translocation does occur for carrots. This would suggest a VG_{bg} of between 0.24 and 0.60, absent any consideration of washing or peeling (actually the full range of 0.14 and 1.00, considering differences among congener groups).

Data was sought to do a similar exercise for potatoes. Hulster and Marschner (1991) present concentrations found in potato tubers, both peeled and unpeeled; no data for concentration in peels alone is presented. Like the Muller, et al. (1994) data, simple assumptions need to be made to estimate the peel concentration in order to estimate the VG_{bg} for this data set. As derived above, it will be assumed that the peel is 3% of the entire potato volume. With this assumption, VG_{bg}s of between 0.03 and 0.05 are calculated for potatoes from the data of Hulster and Marschner (1991). This suggests that, unlike carrots, much of the concentration in the

potato, even at low soil concentrations, resides in the peel. Like the carrot, some within plant translocation is indicated for potates.

Another difference between the carrot data in Muller et al. (1994) and the potato data in Hulster and Marscher (1991) is the potential impact of peeling. A ratio of whole vegetable to peeled vegetable was estimated for both these sets of data. For the Muller data on carrots grown in control soils, where the inner carrot concentrations were not substantially different than outer carrot concentrations, the estimated ratio was 0.91, meaning that peeling would not effect the full concentration in these carrots. It should be pointed out that the control soil Toxic Equivalent concentration, 5 ppt, is typical of soils that are considered "background" or "typical". The impact of peeling was more pronounced for the contaminated soil, with an estimated ratio of 0.61. For the potatoes, peeling made a larger difference. The average peeled to unpeeled potato concentration ratio was about 0.20.

For the assessment in this document, "underground vegetables" are not any more defined than just that. Given the data examined in this section, a VG_{bg} of 0.25 will be assigned. This considers that a peeled carrot grown in typical soils could have a VG_{bg} of 0.60 according to the interpretation of the Muller, et al. (1994) data, whereas a peeled potato could have a VG_{bg} less than 0.01.

- **C_v, C_p:** The vapor (C_v) and particle (C_p) phase concentrations of contaminant in air, C_a, used in this algorithm is estimated using procedures described in Section 4.3.3 above.

- **B_{vpa}:** The first version of the air-to-leaf transfer factor used in the dioxin reassessment document (EPA, 1992b) used an empirical algorithm developed by Bacci and coworkers (Bacci, et al. 1990, 1992) who studied the vapor transfer of 14 organic chemicals, one of which was 1234-TCDD (not one of the 17 toxic congeners, but with similar fate properties to 2378-TCDD), to azalea leaves. These chamber experiments did not consider the effect of photodegradation on the transfer of the organic chemicals to the azalea leaves. The empirical relationship these researchers developed determined the volumetric transfer factor, B_{vol}, as a function of the contaminant Henry's Constant and log Kow:

$$\log B_{vol} = 1.065 \log Kow - \log \left(\frac{H}{R_i T}\right) - 1.654 \qquad (4\text{-}42)$$

where:

B_{vol} = Bacci volumetric air-to-leaf biotransfer factor, unitless [(µg contaminant/L of wet leaf)/(µg contaminant/L air)]
Kow = contaminant octanol water partition coefficient, unitless
H = contaminant Henry's Constant, atm-m^3/mol.
R_i = ideal gas constant, 8.205 x 10^{-5} atm-m^3/mol-K
T = temperature, 298.1 K
-1.654 = empirical constant

Then, McCrady and Maggard (1993) conducted chamber experiments on the transfer of 2378-TCDD vapors to grass leaves considering photodegradation. These experiments showed that the transfer of 2378-TCDD to grass leaves was about 40 times less than the transfer as calculated by the Bacci empirical algorithm. In addition to not considering photodegradation, McCrady and Maggard considered the difference in plant species between azalea leaves and grass leaves to be important in explaining the lower rate of transfer in their experiments as compared to Bacci's experiments. McCrady and Maggard's results were used in the next version of the air-to-plant model and the assignment of values to B_{vpa} (EPA, 1994). Specifically, the transfer factor for each dioxin congener was estimated using the Bacci algorithm, but this time all final results were divided by 40. Therefore, the B_{vpa} of the original model was reduced by a factor of 40 for all 17 dioxin and furan congeners for the second version of the air-to-leaf model.

Two key presumptions are inherent in using the Bacci algorithm divided by 40: 1) that the Bacci algorithm is generally appropriate for the dioxin congeners, despite the fact that the physical/chemical properties of the dioxin congeners are generally outside the range of the 14 organic chemicals used by Bacci, and 2) that the factor of 40 derived from one experiment on 2378-TCDD applies to all dioxin-like compounds.

The data of Welsh-Pausch, et al. (1995) will be used to develop an air-to-leaf transfer factor for the third version of the vapor phase air-to-leaf transfer factor described here, and also presented in Lorber (1995). Their data includes grass concentrations and air concentrations. Grass was grown in two flower boxes, with different agricultural soils in each box, beginning in May of 1991. The grass was cut back on July 17 in that year. On August 9, the grass was cut back again and the yield from the two boxes from the growth between July 17 and August 9 averaged 3900 g/m^2 fresh weight. This grass was analyzed for concentrations of dioxin congener groups, and these concentrations were provided on a fresh weight basis (i.e., pg/g fresh weight). On July 18, the first of two week long air samples were taken. These samples were taken very near the boxed grass. The samples were measured for the dioxin congener groups, not the

individual congeners. Representative congener group air concentrations were then determined as the average of the concentrations from the two samples. The concentration of dioxins in air remained relatively constant during the experimental period.

This data was used by McLachlan, et al. (1995) to verify an air-to-plant model based on fugacity concepts. Besides being a different model, McLachlan's modeling differed from the use of the data in this document in that it used to data to validate the model. Here, the data is used to calibrate a B_{vpa}. This was accomplished in the following 3-step procedure:

Step 1: Partition the total concentrations measured into a vapor and a particle phase. McLachlan, et al. (1995) had used the glass fiber filter/XAD trap 2-stage high volume air samplers to estimate vapor and particle fractions from the total reservoir. This apparatus will yield "operationally defined" vapor and particle fractions. The vapor fraction estimated this way will be larger than the vapor fraction estimated using the Junge model as applied and described by Bidleman (1988). The Bidleman model will be used to partition the total air concentration of the Welsh-Pausch, et al. (1995) experiments into a vapor and a particle phase. Whether the Bidleman model is more "correct" than the measurements of the 2-stage sampler is an ongoing technical issue. A full discussion of the issue for dioxins can be found in Chapter 3. Also, model comparisons of predicted and observed vapor/particle partitioning for other organic contaminants, including PCBs, PAHs, and organochlorine pesticides can be found in Chapter 7. Table 4-3 shows the vapor/particle partitioning as developed using the Bidleman model and used here compared against the measured vapor/particle partitioning from the air sampling apparatus. As an example of how the measured and the modeled vapor fractions are different, the air sampling apparatus measures 72% of the PCDD congener group to be in the vapor phase, whereas the Bidleman approach estimates that 13% of the PCDD congener group is in the vapor phase.

The vapor and particle fractions for the congener groups are modeled assuming an air temperature of 20 °C, and a particle density in air corresponding to a condition which Bidleman described as "background plus local sources". The average air temperature between July 17 and August 9 of 1991 was 18 °C (McLachlan et al., 1995), and the "background plus local sources" designation also appears most appropriate for the university city of Bayreuth, described as a typical background situation for this area of Europe by Welsh-Pausch, et al. (1995). Two alternate options instead of background plus local sources appear less relevant for Bayreuth: an "urban" condition (higher particle densities) and a "background" condition (lower particle densities).

Step 2: Model the deposition of particle-bound dioxins to the grass, and subtract out the resulting modeled grass concentration from the total concentration. Since an air-to-leaf vapor phase transfer factor is sought in this exercise, what is needed is the grass concentration due only to vapor transfers. The particle-bound impact to vegetation cannot be measured directly. Therefore, a model will be applied to estimate that part of total grass concentration of dioxin that was due to particle bound depositions. The model that will be applied was described earlier and is shown in Equation (4-38).

Step 3: What is now available after accomplishment of the above two steps is a concentration of vapor phase dioxins in air and a concentration of dioxins in grass due to vapor phase transfers. With appropriate conversions, the air-to-leaf transfer factor is now simply calculated as the vapor-impacted grass concentration divided by the vapor phase air concentration.

As noted, Equation (4-38) is used to estimate the particle deposition impact to the grass. The deposition F can be estimated as the particle bound fraction times a deposition velocity. The velocity of deposition will be assumed to be 0.002 m/sec, which was the velocity of dry deposition of dioxins as measured by Koester and Hites (1992). Wet deposition was not considered for this brief exercise; McLachlan, et al. (1995) indicates that only a small amount of rain fell during this time and that results implied that rain washed off the grass leaves. The interception fraction will be assumed to be 0.59, based on information provided in Baes, et al. (1984). A first-order weathering rate of 0.0495 day^{-1}, corresponding to a 14-day half-life, is used in this model. The experiment occurred between July 17 and August 9, so a time t of 24 days is assumed. Assuming 15% dry matter in grass, the fresh weight yield of 3900 g/m^2 translates to a yield of 0.585 kg/m^2 dry. The final fresh weight concentrations due to particle depositions and vapor transfers are shown in Table 4-3.

Also shown in Table 4-3 in the last column is the percent of total plant concentration that is estimated to be due to vapor transfers. Except for the octa congeners, it would appear that the grass is mostly impacted by vapor transfers. This, of course, is contingent on the validity of the particle impact model.

The volumetric air-to-leaf transfer factor, referred to as B_{vol}, is defined as the volumetric concentration of dioxins in grass due to vapor phase transfers divided by the volumetric concentration of dioxins in air. Appropriate units expressing this ratio are: [pg dioxin/m^3 grass]/[pg dioxin/m^3 air]. The air concentrations are already in the appropriate units. The grass concentrations as given in Table 4-3 are in units of ng dioxins per kg plant fresh weight; these concentrations need to be converted into a volumetric basis. To do the conversion, the denominator in this grass concentration needs to be converted to a volumetric basis. McCrady

and Maggard (1993) use a volumetric factor of 0.77 kg fresh leaf/L volume. Two other conversions necessary are a conversion from L to m^3 and a conversion from ng to pg. The final volumetric plant concentration in appropriate units is given as:

$$GC_{vol}\ \frac{pg\ dioxin}{m^3\ volume} = GC_{fr}\ \frac{ng\ dioxin}{kg\ plant\ fresh}\ \frac{0.77\ kg/L\ \ 1000\ pg/ng}{0.001\ m^3/L} \qquad (4\text{-}43)$$

where GC_{vol} is the volumetric grass concentration desired for calculation of B_{vol}, and GC_{fr} is the fresh grass concentration as reported in McLachlan, et al. (1995).

Table 4-4 now develops the final mass-based transfer factors, B_{vpa}. The volumetric transfer factor needs to be converted to the mass-based transfer factor, B_{vpa}:

$$B_{vpa} = \frac{1.19\ kg/m^3\ B_{vol}}{0.15\ \ 770\ kg/m^3} \qquad (4\text{-}44)$$

The B_{vpa} developed here for congener groups will be applied to all congeners in the congener group. The B_{vpa} for the congener groups calculated in this manner are compared against the B_{vpa} as developed in an earlier version of the Dioxin Exposure Document (EPA, 1994) which, as described above, were developed as function of the Bacci algorithms with an empirical correction factor based on the experiments of McCrady and Maggard (1993).

The B_{vpa} as calculated with the data of Welsh-Pausch, et al. (1995), are lower than the B_{vpa} as calculated in the earlier Dioxin Exposure Document (EPA, 1994). For 7 of the 10 congener groups, the difference is less than an order of magnitude. The exceptions are the two octa congeners and the hepta dioxin congener, where the B_{vpa} calculated from the Welsh-Pausch, et. al (1995) data are two or more orders of magnitude lower for the octa congeners and 1 order of magnitude lower for the hepta dioxin congener. In general, the trend of increasing B_{vpa} from the tetra through the octa congeners is consistent with both approaches.

It may be informative to speculate on why the transfer of vapor phase dioxins appears to be lower in the Welsh-Pausch, et. al (1995) data as compared to the McCrady and Maggard (1993) data. There may be a relevant species difference, such as the lipid content for example, in the grass species used by McCrady and Maggard (1993), Reed canary grass (*Phalaris*

arundinacea L.), and the grass in the Welsh-Pausch, et al. (1995) experiments, Welsh Ray Grass (*Lolium multiflorum*). The climate might have different in Bayreuth, leading to more photodegradative loss in the Welsh-Pausch data. Certainly the experimental designs were different. McCrady and Maggard (1993) used a 2-stage chamber experimental design, including an uptake phase in which the grass was not exposed to sunlight, and a release phase where the grass was kept in sunlight. Uptake and release were occurring simultaneously and in sunlight in the Welsh-Pausch, et al. (1995) experiments. Certainly it seems possible that the net transfer rates might have been lower in the McCrady and Maggard (1993) experiments had the uptake and release phases both occurred in sunlight.

It should be noted that all bioconcentration or biotransfer parameters, such as the B_{vpa}, are qualified as second order defaults for purposes of general use. Section 6.2. of Chapter 6 discusses the use of parameter values selected for the demonstration scenarios, including a categorization of parameters. Second order defaults are defined there as parameters which are theoretical and not site specific, but whose values are uncertain in the published literature. The parameter values in this category should be considered carefully by users of the methodology. However, a model testing exercise published in Lorber and Pinsky (1999) and described in Chapter 7 lends credibility to the use of these CDD/F B_{vpa} for general purposes.

- **VG_{ag}:** The same discussion for this correction factor for below ground vegetation applies here. Fruits such as apples, pears, plums, figs, peaches, and so on, can be approximated by spheres, and upper bound estimates of correction factors would be less than 0.05. Peeling, cooking, and cleaning further reduces residues. The VG_{ag} for unspecified above ground fruits and vegetables in this assessment is assumed to be 0.01. Like VG_{bg}, this value is assigned considering that it should be less than estimated just based on surface volume to whole fruit volume ratios.

Two other VG_{ag} values are required for this assessment. One is for pasture grass and the other for other vegetation consumed by cattle. Both are required to estimate concentrations in these vegetation consumed by cattle in order to estimate beef and milk concentrations. A VG_{ag} value of 1.0 was used to estimate pasture grass concentrations since there is a direct analogy between the grass in the Welsch-Pausch, et al. (1995) experiments for which the B_{vpa} was developed and pasture grass of the cattle diet. However, VG should be less than the other general category of cattle vegetation defined in this assessment, "hay/silage/grain". Pasture grass is considered as a separate diet category because it is a principal component of the cattle diet and most subject to impact by dioxin-like compounds because it is leafy, whereas other cattle

vegetation are lumped together in this second category. As described below, this second general category of non-grass cattle vegetation include some thin leafy (hay) as well as bulky (corn silage and other grains) vegetation to consider. A volume ratio of outer surface to whole surface area to volume vegetation could be used to assign a value to VG, if specific assumptions concerning proportions of each type of vegetative cattle intake were made. An appropriate assumption for a fully protected vegetation such as grain would be zero. Silage can be considered part protected and part leafy. Since specific assumptions concerning hay/silage/grain intake are not being made for this exercise, a simple assumption that VG equals 0.50 for hay/silage/grain is instead made, without rigorous justification.

The only experimental evidence that a VG_{ag} for vapor transfers of dioxin-like compounds is justified came in a study by McCrady (1994). McCrady experimentally determined uptake rate constants, termed k_1, for vapor phase 2,3,7,8-TCDD uptake into several vegetation including kale, grass, pepper, spruce needles, apple, tomato, and azalea leaves. Recall that the similar experimental design of both McCrady and Maggard (1993), and Bacci, et al. (1990; 1992), included an initial phase where vegetation in experimental chambers were exposed to the vapor-phase organic chemicals. The uptake which occurs during this initial phase is described with the rate constant, k_1. A second "elimination" phase then occurs where organic vapors are removed from the chambers and the chemicals allowed to volatilize or otherwise dissipate from the vegetation. The rate constant for this phase is termed k_2. A steady state bioconcentration factor (i.e., B_{vpa}), is then estimated as k_1/k_2. The uptake rate constants from air to the whole vegetation estimated in the McCrady (1994) experiments demonstrate the concept behind the VG parameter. The uptake rate for an apple divided by the uptake rate for the grass leaf was 0.02 (where uptake rates were from air to whole vegetation on a dry weight basis). For the tomato and pepper, the same ratios were 0.03 and 0.08. The VG_{ag} is 0.01 for fruits and vegetables in this assessment, but note above that the simple exercise with a conical carrot and spherical potato estimated a surface volume to whole fruit volume ratio of 0.09 (carrot) to 0.03 (potato); a value of 0.01 for fruits and vegetable empirically considers factors such as washing or peeling which would reduce exposures. McCrady (1994) then went on to normalize his uptake rates on a surface area basis instead of a mass basis; i.e., air to vegetative surface area instead of air to vegetative mass. Then, the uptake rates were substantially more similar, with the ratio of the apple uptake rate to the grass being 1.6 instead of 0.02; i.e., the apple uptake rate was 1.6 times higher than that of grass, instead of 1/50 as much when estimated on an air to dry weight mass basis. The ratios for tomato and pepper were 1.2 and 2.2, respectively. McCrady (1994) concludes, "The results of our experiments have demonstrated that the exposed surface area of plant tissue is an important

consideration when estimating the uptake of 2,3,7,8-TCDD from airborne sources of vapor-phase 2,3,7,8-TCDD. The surface area to volume ratio (or surface area to fresh weight ratio) of different plant species can be used to normalize uptake rate constants for different plant species." McCrady cautions, however, that uptake rates are only part of the bioconcentration factor estimation, and he is unsure of the impact of surface area and volume differences on the elimination phase constant, k_2 (personal communication, J. McCrady, US EPA, ERL-Corvallis, Corvallis, OR 97333). Still, his experiments do appear to justify the use of a VG parameter since the B_{vpa} were developed on an air to whole plant mass basis, and his results are consistent with a VGag of 0.01 for fruits and vegetables.

- **kw:** Fries and Paustenbach (1990) note that this approach may overestimate concentrations because crops can be harvested or pastures grazed before the plant concentrations reach steady state, and that a kw based on a weathering half-life of 14 days may be too long given experimental results of Baes, et al. (1984) which showed a range of 2-34 days, and a median value of 10 days. On the other hand, Umlauf and McLachlan (1994) discuss the phenomena of the transfer of semivolatile organic compounds (SOCs) from depositing particles onto the leaf - the particles themselves may weather off the leaves with a half-life of 14 days, but the SOCs would transfer from the particle and not weather off the leaves. Umlauf and McLachlan (1994) could not find information on the transfer of SOCs from particles to leaves, but they speculated that the lipid covering of the cuticle would facilitate a rapid particle to leaf transfer. In their modeling of several SOCs to spruce leaves, they assumed that the SOCs completely transferred from the particles to the leaves in both wet and dry particle-bound deposition with no subsequent loss of contaminant via weathering or degradation. This is equivalent to assuming an infinite half-life rather than a 14-day half-life. Umlauf and McLachlan (1994) found reasonable model performance when comparing their modeling results with measurements of several SOCs including some PCBs on spruce leaves. Stevens and Gerbec (1988) used a 14-day half-life but did not assume a steady-state concentration is necessarily reached in vegetation. They considered harvest intervals by including the exponential term, $(1-e^{-kt})$, and assigning values of t based on harvest intervals of different crops. This assessment uses a kw of 18.02 yr^{-1}, which is equivalent to a half-life of 14 days. However, based on the discussions of Umlauf and McLachlan (1994), this is recognized as an important area of uncertainty. If their consideration of the transfer of SOCs from particles to leaves is valid, than an assignment of a kw of 18.02 yr^{-1} will significantly underestimate the impact of dry and wet deposition to vegetation.

- **I_j and Y_j:** Interception values and crop yields were determined in the afore-mentioned assessments based on geographic-specific crop yield data provided in Baes, et al., (1984) and the following types of crop-specific relationships estimating interception fraction based on yield (Y), also presented in Baes, et al., (1984):

corn silage: $I = 1 - e^{-0.768Y}$
hay/grasses: $I = 1 - e^{-2.88Y}$
lettuce: $I = 1 - e^{-0.068Y}$

Judgments by Fries and Paustenbach (1990) on high, medium, and low yields of silage, hay, and pasture grass, and the use of the first two interception equations above (the first for silage, and the second for hay and grass), can give some guidance on interception fractions and yields for these crops:

	Yield (kg/m^2)	Intercept Fraction
corn silage	0.30 (low)	0.20
	0.90 (med)	0.50
	1.35 (high)	0.64
hay	0.25 (low)	0.51
	0.45 (med)	0.73
	1.30 (high)	0.98
grass	0.05 (low)	0.13
	0.15 (med)	0.35
	0.35 (high)	0.64

This information can be used for cattle intake of vegetation, and the resulting beef and milk concentrations. The medium values for grass, 0.15 kg/m^2 yield and 0.35 interception, were used for the example setting in Chapter 5. An average of the medium values for hay and silage, 0.63 kg/m^3 yield and 0.62 interception, were used for the second category of cattle vegetation for Chapter 5, the hay/silage/grain category.

Stevens and Gerbec (1988), using yields obtained from the Minnesota State Agricultural Office, derived the following yield and interception estimates, respectively, for vegetables for human consumption in their assessment: lettuce - 8.6,0.72; tomatoes - 12.0,0.55; and beans - 2.7,0.18. Average yields and interception fractions from their exercise: 7.8 kg/m^2 and 0.48, were used in the example setting in Chapter 5. These vegetable yields are fresh weight, so they need

to be converted to a dry weight basis in order to estimate a C_{ppa} appropriate for use in Equation (4-38). Since vegetables are generally 80 ->90% water, a fresh to dry weight conversion factor of 0.15 was used, resulting in an average vegetable dry matter yield of 1.17 (7.8 * 0.15). This was used in the example settings in Chapter 5.

- **V_d:** Particles settle to the ground surface and plant surfaces due to the forces of gravity. Gravitational settling velocity is a function of particle size, with more rapid settling occurring with larger particles. The algorithm used to estimate the concentration of contaminated particulates in air estimates the suspension of particles less than and equal to 10 μm, which is commonly referred to as inhalable size particles. Seinfeld (1986) listed a gravitational deposition velocity of 1 cm/sec for 10 μm size particles. This deposition velocity will be used in this assessment, and in units of m/yr, this equals 315,360 m/y.

- **RN:** Geraghty, et al. (1973) provides a map showing isolines average annual rainfall throughout the United States. This map shows low rates of 5 to 20 inches/year in the desert Southwest, moderate rates of 25 to 40 in/yr in the Midwest cornbelt, 40 to 60 in/yr in the South, and so on. The example scenarios of Chapter 5 were described as rural, with land in agricultural and non-agricultural settings. A rate of 1 m/yr (39 in/yr) will be used in the example scenarios.

- **R_w:** It is assumed that dry depositions fully adhere to plant surfaces; the weathering constant, k_w, models the loss of the vegetative reservoir of particle bound contaminants due to wind, rain, or other weathering process. However, it is not clear that wet deposition should also be assumed to fully adhere during a wet deposition event. Hence, the R_w parameter, or fraction of wet deposition adhering, was introduced. Prior modeling efforts of the impact of depositions of dioxin-like compounds to vegetation are unclear with regard to wet deposition. Stevens and Gerbec (1988), Fries and Paustenbach (1990), Webster and Connett (1990), and Travis and Hattemer-Frey (1991) all model particle deposition impacts of 2,3,7,8-TCDD to vegetation in air-to-beef/milk modeling. None of them discuss the distinction in wet and dry deposition, and model "total deposition" impacts, describing total as wet and dry deposition, total deposition, or simply as deposition. On the other hand, McKone and Ryan (1989) reduce the wet deposition portion of total deposition. They promote use of a "b", which they define as the fraction of material retained on vegetation from wet deposition. They recommend a value between 0.1 and 0.3.

The clearest indication of the fate of wet deposition of particles can be found in Hoffman, et al. (1992). In that field study, simulated rain containing soluble radionuclides and insoluble particles labeled with radionuclides was applied to pasture-type vegetation under conditions similar to those found during convective storms. The fraction of the labeled particles found to remain on the vegetation after the rainfall varied from 0.24 to 0.37. Nine values comprised this range, including particle sizes of 3, 9, and 25 μm, and cover described as clover, fescue, and mixed (a site with old field vegetation including fescue, grasses, weeds, and wild flowers). Based on this work, the R_w will be assumed to be 0.30 for all vegetation and dioxin congeners of this assessment.

- **W_p:** Washout ratios are generally defined as the concentration of contaminant in rain to the concentration of contaminant in air. Concentrations of contaminants in air and rain water can be derived as a mass of contaminant divided by a mass of air/water or a volume of air/water. Mackay, et al. (1986) shows that volume-based washout ratios (mass of contaminant mixing in m^3 air or water, e.g.) exceed mass-based washout ratios (mass of contaminant mixing in kg of air or water) by a factor of 815, which is the ratio of water and air densities. The washout ratio used in this assessment is a volumetric ratio based on methodologies described by Bidleman (1988). Using a volumetric ratio then allows for direct use of contaminant concentrations estimated in this methodology since they are already on a $\mu g/m^3$ volume basis.

  Bidleman (1988) defines the overall washout ratio as: (mass contaminant/volume rain) ÷ (mass contaminant)/(volume air). Bidleman (1988) also discusses that fact that overall washout includes both wet deposition of particulates and scouring of contaminants in the vapor phase. He includes methodologies for estimating the vapor/particulate ratios for semi-volatile organic compounds (abbreviated SOCs) and also for estimating the washout ratios for vapors. However, he claims that if H is sufficiently high, vapor dissolution in droplets is negligible and only the particulate fraction is removed by wet deposition. He claims this to be the situation for n-alkanes, PCBs, chlordane, DDT, and 2,3,7,8-TCDD. Developing overall washout ratios for these and several other SOCs, he estimates that vapor scouring accounts for 1% of the overall washout ratio for 2,3,7,8-TCDD. For PCBs, he estimates similar percentages of 2, 4, and 28% for Aroclors 1260, 1254, and 1248, respectively. Based on this work, it will be assumed that vapor scouring of the dioxin-like compounds is small in comparison to wet deposition and the washout ratio for this assessment will only be applied to the air-borne particulate concentration of dioxin-like compounds.

Bidleman (1988) does not provide a chemical or site-specific equation which estimates the particle-phase washout ratio (which he does for the vapor-phase washout ratio). Rather, he summarizes available data and concludes that there is a wide range of the particle-phase washout ratio, W_p, for SOC: between $2x10^3$ and $1x10^6$. He claims that a typical range is 10^5 to 10^6, and uses a W_p of 2×10^5 in his exercises to estimate the overall washout ratio for several SOCs.

Koester and Hites (1992) list vapor and particle scavenging ratios for congener groups of dioxin-like compounds. To derive these ratios, they used air concentrations for congener groups that were taken at one time period in Bloomington and Indianapolis, Indiana, and rainfall depositions of these compounds at these sites measured during a second period of time. Using the Bidleman vapor/particle partitioning model used in this assessment, they estimate the vapor/split for the air concentrations. With these observations and models, they conclude that the overall washout ratio (sum of vapor and particle ratios) ranges from 10^4 to 10^5, which contrasts the typical range of 10^5 to 10^6 noted above from Bidleman (1988). Also, their calculations indicate that vapor scavenging of dioxin-like compounds is comparable to particle scavenging, also in contrast to the Bidleman analysis summarized above. However, they did not state whether their washout ratios were volume or mass-based. If they were mass-based, then a conversion to volume based would put them in the 10^7 to 10^8 range, which seems improbable given the Bidleman summary above. Therefore, it will be assumed that they are volume-based, and they are appropriate to use for this assessment. Since no clear trend for particle washout ratios with regard to the degree of chlorination increased appears in Koester and Hites' data, the midpoint of their calculated range, $5 * 10^4$, will be used for all example compounds in this assessment.

As a final note, the multiplication of the above terms, $W_p * C_{pa} * RN * R_w$, does result in wet deposition in appropriate units of $\mu g/m^2$-yr, although that is not immediately obvious. First, multiplication of W_p, in (μg contaminant/m^3 rain)÷($\mu g/m^3$ air), and C_{pa}, in μg contaminant/m^3 air, leaves a partial term in units of μg contaminant/m^3 rain. Then, multiplication of this partial term times annual rainfall rate, thought of as m^3/m^2-yr instead of m/yr, gives the final quantity in the appropriate units.

When calculating concentrations in below ground fruit and vegetables using Equation (4-35), C_{bgv} is on a fresh weight basis since the RCF developed by Briggs, et al. (1982) is on a fresh weight basis, and no correction for estimating exposures is necessary. However, C_{abv} as estimated in Equation (4-36) is on a dry weight basis, and should be multiplied by a dry weight to fresh weight conversion factor when applied to above ground fruits and vegetables. A reasonable estimate for this parameter for fruits and vegetables is 0.15 (which assumes 85% water), which

was used in this assessment. When using Equation (4-36) to estimate C_{abv} for the beef and milk food chain algorithm, a conversion to fresh weight is not required, however, since the algorithms were developed assuming dry weight concentrations.

4.3.4.3. *Beef and Milk Concentrations*

The algorithm to estimate the concentration of contaminant in beef and/or milk was based on methods developed by Fries and Paustenbach (1990). They developed the beef bioconcentration factor for 2,3,7,8-TCDD, which is defined as the ratio of the concentration of the contaminant in beef fat to the concentration in the dry matter dietary intake of the beef cattle. They discussed bioavailability, which, as they define it, is the fraction of ingested contaminant which is absorbed into the body. It depends on the vehicle of ingestion - dioxin in corn oil has a bioavailability in the range of 0.7 to 0.8, in rodent feed it has an estimate of 0.5, while in soil it has a range of 0.3 to 0.4. They emphasized the importance of the differences in diet between cattle raised for beef and those which are lactating in explaining different food product concentrations. Although there is likely to be some difference in the bioconcentration tendencies for lactating and non-lactating cattle, Fries and Paustenbach in fact used the same bioconcentration for beef fat and milk fat, and the same will be done here.

The concentration in the fat of cattle products is given as:

$$C_{fat} = BCF\ FF\ (DF_s\ B_s\ AC_s + DF_g\ AC_g + DF_f\ AC_f) \quad (4\text{-}45)$$

where:

C_{fat} = concentration in beef fat or milk fat, pg/g

BCF = bioconcentration ratio of contaminant as determined from cattle vegetative intake (pasture grass or feed), unitless

FF = feedlot factor for beef fat calculation, ≤ 1 for beef fat and =1 for milk fat, unitless

DF_s = fraction of cattle diet that is soil, unitless

B_s = bioavailability of contaminant on the soil vehicle relative to the vegetative vehicle, unitless

AC_s = average contaminant soil concentration, pg/g

DF_g = fraction of cattle diet that is pasture grass, unitless

AC_g = average concentration of contaminant on pasture grass, pg/g

DF_f = fraction of cattle diet that is feed, unitless

AC_f = average concentration of contaminant in feed, pg/g

The following is offered as brief guidance to these terms and also the justification for the values selected in the example Scenarios in Chapter 5.

- **Beef/milk bioconcentration factor, BCF:** Fries and Paustenbach (1990) developed the concept of a beef/milk bioconcentration ratio and applied it to 2,3,7,8-TCDD. BCF is defined as the concentration of contaminant in fat of cattle products (i.e., dairy and beef) divided by the concentration in dry matter intake. One key difference in the dietary intake of cattle raised for beef versus cattle raised for dairy is that cattle raised for beef tend to be pastured more than dairy cattle and be more exposed to contaminated soil, whereas lactating cattle are more often fed high quality feed, including grains which are expected to be substantially residue free since they are a protected vegetation. Another key difference is that the dioxins in lactating cows generally will reach a steady state in the fat of the animal (muscle fat and milk fat) much more rapidly than in non-lactating cattle because the excretion of milk will result in a large excretion of dioxins. For non-lactating cattle, excretion only occurs in feces and urine. Based on modeling, McLachlan (1994) speculates that it would take approximately 6 years for dioxins to reach steady state in non-lactating cattle because of the slow excretion rate through feces and urine, and that at steady state, concentrations in the muscle fat of non-lactating cattle would be much higher than in milk. However, dioxin concentrations in beef fat are generally found to be similar to that in milk fat. McLachlan (1994) explains it this way: "...it will take 6 yr to approach this steady state, much longer than the 1.5 yr that beef cattle typically live. During this time, the animal is also growing, continuously diluting its contaminant reservoir. As a result, the contaminant levels in commercial beef fat are generally not much higher than in milk fat." For this reason, the BCFs that are developed below based mostly on milk fat will be applied to both milk and beef fat.

Based on literature studies of cattle consuming feed contaminated with dioxin-like compounds, Fries and Paustenbach (1990) calculated a BCF of between 4 and 6, and assumed a value of 5.0 for 2,3,7,8-TCDD. Being developed directly from data of cattle ingesting contaminated feed, this BCF value of 5.0 already considers the bioavailability of the experimental contaminated feed. It will be assumed that the bioavailability of the cattle vegetation in this assessment equals that of the experimental feed. Therefore, a value of 5.0 can go directly into Equation (4-45) when applied to concentrations in grass and pasture. However,

this value should not be applied to soil, since it has been shown that TCDD on soil is less bioavailable than TCDD on other vehicles. This is why a B_s appears in Equation (4-45) - it adjusts BCF when applied to a soil concentration. The value of B_s is described below. The Fries and Paustenbach (1990) literature review is reproduced in Table 4-5, which additionally shows results generated based on information in McLachlan, et al. (1990) and Fries, et al. (1999).

Although the BCF of 5 determined by Fries and Paustenbach (1990) for 2,3,7,8-TCDD appears high based on the literature for this compound, Fries and Paustenbach (1990) discuss how short duration feeding trials (the 21 days of Jensen and Hummel (1982) and the 28 days of Jensen, et al. (1981)) do not result in steady state bioconcentration ratios. Extrapolating the data to a point where steady state is speculated to be reached, Fries and Paustenbach (1990) developed the arguments for the range of 4 to 6 for 2,3,7,8-TCDD. The second example compound in Chapter 5 was 2,3,4,7,8-PCDF. Fries and Paustenbach (1990) observed that bioconcentration ratios for PCDDs and PCDFs decreased significantly as chlorination increased, although their literature seems to imply that this effect is most pronounced for hepta- and octa- PCDDs and PCDFs. They could not locate data in the literature for penta-PCDDs or PCDFs.

McLachlan, et al. (1990) was the first study where BCFs for cow milk could be generated for furan congeners. They conducted a mass balance of dioxin and furan congeners in a lactating cow. They carefully accounted for 16 of the 17 dioxin and furan congeners of toxicity equivalency to 2,3,7,8-TCDD in the intake of a lactating cow in food, air, and water, and measured amounts in feces, urine, and milk, while attributing the rest of the intake to a compartment they termed, storage/degradation/experimental error. They obtained data well into steady state, and provided information necessary to estimate milk BCFs including: information appropriate to estimate the dry matter intake by the cattle; ng/day congeners in feed, water, and air; L/day milk production (density assumed to be 0.9 g/cm^3); and percent fat in milk. The data for estimating the dry matter intake of the cattle was expressed in two ways. One, the wet weight of feed materials was given, and assuming a dry weight fraction (the actual dry weight fraction was not given), one could estimate a dry matter intake. Two, it was stated that the feces flux of 5 kg/day was 30% of the dry weight intake. Therefore, the dry matter intake is calculated at 16.7 kg/day. However, in a later report on this same data set (McLachlan, 1993), it was stated that the feces flux from this experimental animal of 7 kg/day was 33% of dry matter intake. In a personal communication (letter, M. McLachlan to M. Lorber dated 4/2/95), the author confirmed that the correct total dry matter intake was 21 kg/day, and this value was used in the generation of BCFs shown in Table 4-5.

Fries, et al. (1999) conducted a feeding experiment where four cows were fed PCP-contaminated wood. Specifically, a 3 g/day dose of ground PCP-treated wood as administered to each cow for 58 days. The mixed feed was sampled, and a sample of each cow's milk was obtained on days 28, 42, and 56. Feed amounts were carefully controlled to not only these cows but to other cows at the USDA agricultural research facility. Bulk milk was obtained from cows who were not treated, and the concentrations from these samples served not only as controls for the laboratory, but also were used to calculate a limited set of BCFs for background settings. BCFs were calculated when both feed and milk were higher than background. The results for the cows fed the wood as well as for background cows are shown in Table 4-5. As seen, there is reasonable agreement between the cows fed the contaminated wood and the background cows, with the exception, perhaps, of two of the furan congeners, and there is also good agreement between these BCFs and those developed from the data of McLachlan, et al. (1990). Also, the BCF for 2,3,7,8-TCDD was highest in this experiment at 7.1 as compared to other BCFs calculated for 2,3,7,8-TCDD

The McLachlan data will be used to assign BCFs for the demonstrations in Chapter 5. The BCF value for 2,3,7,8-TCDD value is 5.73 and the BCF for 2,3,4,7,8-PCDF is 4.13, in the demonstration scenarios which include a dioxin, a furan, and a PCB. For the demonstration of the incinerator, the suite of dioxin-like compounds are demonstrated, and the full BCF set developed by McLachlan and coworkers will be used.

A review of the literature for PCBs is given in Table 4-6. McLachlan and coworkers measured a suite of PCBs in his lactating cow mass balance experiments and reported the results in McLachlan (1993). However, unlike the dioxin results which showed a favorable mass balance result (i.e., most of the mass of the dioxin intake by the cow could be accounted for in the feces, urine, and milk - the remainder attributed to storage, metabolism, or experimental error), the PCBs results showed that up to 40% more PCBs were being excreted through urine, feces, and milk, than was taken up by the cattle. McLachlan (1993) discounted the possibility that the cow was losing body fat which could explain the result, and instead speculated that there was secondary contamination of the feed through binder twine that had been treated with recycled oil (i.e., the amount of PCB intake by the cow was underestimated). In any case, this data could not be used to generate BCFs for PCBs.

Although PCBs, dioxins, and furans are related compounds in terms of environmental fate characteristics, a difference in bioaccumulation potential is noted with higher degrees of chlorination, based on the study of Tuinstra, et al. (1981). Their work implies increasing bioaccumulation potential as the degree of chlorination increases. They developed BCF values

(defined in the same manner as in this assessment) for a suite of congeners identified to occur in Aroclor 1260 administered to lactating cows. Therefore, their data allowed for a partial examination on congener bioaccumulation patterns. The results given in Table 4-6 are interpreted from the data supplied in Tuinstra, et al. (1981). Tuinstra determined the identity and percentage of specific congeners which comprise Aroclor 1260. He was able to identify 36 congeners, but could only quantify 27 of them (because of the unavailability of standards for 9 congeners). These 27 comprised 81%, by mass, of the Aroclor 1260. Tuinstra was able to estimate BCF values for most, but not all, of the identified congeners - for 23 of the 27 congeners they identified (which equaled 77% of the congeners, by mass, of Aroclor 1260). As seen in Table 4-6, the average congener-group BCF value increases from about 2 to 4 going from hexa- to nanochloro-PCBs. However, there was a wide range of measured BCF values for specific congeners. In the heptagroup, for example, Tuinstra estimated BCF values between 0.4 and 5.2. Fries, et al. (1973) showed increasing BCF values in milk fat at 20, 40, and 60 days for Aroclor 1254 up to a value of 4.8 at day 60. The body fat BCF value at 60 days, the only time such a measurement was taken, was 3.4. The trend of having a higher BCF value for milk fat as compared to body fat for lactating cows was also noted by Willett, et al. (1987). They fed lactating cattle Aroclor 1254 sorbed to ground corn. In three sequential periods of 60 days, they fed the cattle 10, 100, and then 1000 mg/day of Aroclor 1254. Given their average daily dry matter intake of 19.5 kg during the experiment, the concentration during each of those 3 periods was 0.51, 5.13, and 51.28 mg/kg (ppm). However, milk and body fat concentrations of PCBs were given after 60, 120, and 180 days, so that for estimation of the BCF value, what is needed is average concentration of Aroclor intake after these periods. These averages are 0.51, 2.82, and 18.97 mg/kg. Given the reported concentrations of PCBs in milk and body fat after these experimental periods, BCF values were estimated and given in Table 4-6. Two studies, that of Willett and Liu (1982) and Perry, et al. (1981), contained data from which estimates of BCF could be made, except that these studies did not report daily dry matter intake. An estimate of 19.5 kg/day was assumed for lactating cattle for these studies, which was the experimental dry matter intake noted by Willett, et al. (1987). Willett and Liu (1982) dosed cattle for only 20 days, and arrived at the lowest noted BCF value for Aroclor 1254, 1.2. The trend of increasing BCF value over time of dosing was noted by Fries, et al. (1973). Willett, et al. (1990) conclude that steady state is reached after about 60 days, so that estimates of BCF made from experiments less than 60 days may not reflect steady state conditions. Perry, et al. (1981) had a high BCF value, 4.2, despite the dosing period being only 32 days. This would appear to be the result of having a high concentration in the diet. Similarly high BCF values with corresponding high

concentration in dosed intake were noted in Fries, et al. (1973) and Willett, et al. (1987). It should be noted that the concentrations in body fat in the studies of Willett and Liu (1982) and Perry, et al. (1981) were corrected as recommended by Willett, et al. (1990) in estimating BCF values.

Five trends for PCBs were discussed above: 1) that steady state is reached after approximately 60 days, 2) that higher BCF values appear to result with higher concentrations in feed, 3) that BCF values for milk fat may exceed those of body fat for lactating cows (this also seems true for dioxins/furans; see Table 4-5), 4) that the BCF values tend to increase with increasing chlorination of PCB congener groups, and 5) that this fourth trend is based on a limited set of data and much variability exists within specific congener groups.

Generally there is a sparsity and inconsistency in the data which would allow for definitive estimation of BCF values for the example heptachloro-PCB example compound in Chapter 5, 2,3,3',4,4',5,5'-PCB. Most of the data noted is for Aroclor 1254, and this data implies BCF values between 1.2 and 4.8. Based on the results from Tuinstra, et al. (1981) for the average of eight heptachloro-PCBs, a BCF value of 2.3 will be assigned to 2,3,3',4,4',5,5'-PCB.

It should be noted that all bioconcentration or biotransfer parameters, such as the BCF, are qualified as second order defaults for purposes of general use. Section 6.2. of Chapter 6 discusses the use of parameter values selected for the demonstration scenarios, including a categorization of parameters. Second order defaults are defined there as parameters which are theoretical and not site specific, but whose values are uncertain in the published literature. The parameter values in this category should be considered carefully by users of the methodology.

● **FF:** Fries and Paustenbach (1990) summarize pertinent literature to conclude that cattle raised for beef are not slaughtered without an intervening period of high-level grain feeding. Agricultural statistics (USDA, 1992) show that 32.9 million cattle were slaughtered in 1991. Of this number, 6.1 million were cows and bulls that likely did not go through a feedlot prior to slaughter. Quarterly statistics from 1991 show that at any time, cattle and calves on feed for slaughter range from 10 to 12 million. Fries uses these statistics to conclude that 75 to 80% of the total beef supply is from animals that went through a feedlot finishing process, and that the portion of beef that did not go through a feedlot process are (generally speaking) those 6.1 million cows and bulls (personal communication, G. Fries, USDA Agricultural Research Service, Beltsville, Maryland, 20705). He suggests that a representative feedlot finishing process would include a length of 120 days and diet consisting of 20% corn silage and 80% grain. The grains can be assumed to be residue-free, since grains are protected and, as discussed above, little

within plant translocation of outer contamination can be assumed. Also, the ears of the corn silage are in the same category, leaving only the stalks and leaves of the corn silage impacted by atmospheric transfers of dioxin-like compounds.

A feedlot finishing process is important to consider if assessing beef impacts in a site-specific assessment. However, data could not be found in the literature which measured the impact of this process to beef concentrations. Such impacts could occur as the result of increased weight gain from substantially residue-free feeds. Fries and Paustenbach (1990) and Stevens and Gerbec (1988) modeled the impact of a residue-free grain-only diet for four months prior to slaughter. Based on within-cow dilution and depuration considerations, both efforts estimated that the feedlot process would reduce beef concentrations by about one-half. This translates to an assignment of 0.5 for FF. This was the assumption used in the air-to-beef food chain validation exercise described in Chapter 7.

The demonstration scenarios of Chapter 5 assume that farming families slaughter a portion of their cattle for home consumption, and that they do not put their cattle through any special diet before slaughter. Therefore, an FF = 1 is assumed for the demonstration scenarios in Chapter 5.

With the use of an FF, it is noted that the quantity in the parenthetical of Equation (4-45) above describes the cattle diet prior to slaughter.

- **Soil bioavailability, B_s**: This parameter reduces the bioconcentration ratio, F, considering that soil is a less efficient vehicle of transfer compared to feed. Remember that the values of BCF appropriate for Equation (4-45) already consider bioavailability and were developed from experimental data placing the BCF of 2,3,7,8-TCDD in the 4 to 6 range. Fries and Paustenbach (1990) reviewed several studies on the oral bioavailability of TCDD in soil in the diet of rats, and concluded that soil is a less efficient vehicle of transfer as compared to rat feed. If the same is true for cattle - that soil is less efficient than their feed - than the BCF value must be reduced when applied to soil ingestion. Most studies reviewed by Fries and Paustenbach used corn oil as the positive control, since there is a high absorption of TCDD in rats when corn oil is used as the vehicle, with 70-83% of the administered TCDD dose absorbed. Their literature review on rat data showed that the bioavailability of TCDD in soil was between 0.4 and 0.5 that in corn oil, or 0.3 to 0.4 overall. The literature implied a range of 0.5 to 0.6 of TCDD in standard rat feed is absorbed, and although few studies were available, a similar 50% absorption rate of TCDD in cattle feed was noted. They concluded, therefore, that the rat data was a reasonable surrogate for cattle. The B_s can be thought of as the ratio of BCF values between soil

and feed, or, $(BCF_{soil})/(BCF_{feed})$. If the difference in BCF_{soil} and BCF_{feed} is explained solely by bioavailability differences, then the ratio of overall bioavailability of soil to feed should equal this ratio. As described above for rat data, the overall bioavailability of soil was 0.3-0.4, and the overall bioavailability of feed was 0.5-0.6. The ratio of overall bioavailabilities is, therefore, (0.3-0.4)/(0.5-0.6). If the argument that this ratio equals the ratio of BCFs is valid, than this would lead to a B_s of 0.5 to 0.8. This implies that absorption of TCDD when soil is the vehicle is 50 to 80% of what it would be if feed were the vehicle. These assumptions and implications are made for this assessment, and the soil bioavailability term, B_s, used for all example compounds in Chapter 5 is 0.65.

- **Soil diet fraction, DF_s:** Fries and Paustenbach (1990) report that soil intake by cattle feeding on pasture varies between 2 and 18% of total dry matter intake, depending on whether the grazing area is lush or not. The soil diet fraction would be lower for cattle which are barn-fed with minimal opportunity for contaminated soil intake. Cattle raised for milk are rarely pastured, so one possible assumption for estimating milk fat concentrations would be a DF_s of 0.0. Fries and Paustenbach (1990) assumed between 0 and 2% of the dry matter intake by lactating cattle was soil in various sensitivity tests. Since cattle raised for beef are commonly pastured, a conservative assumption would be a high DF_s of 0.15 (15%), although a more reasonable assumption which would consider grazing in lush conditions and/or a portion of diet in feed or supplemental feed leads to DF_s less than 0.10. Fries and Paustenbach (1990) assumed DF_s of between 0 and 0.08 for beef cattle in various sensitivity tests. The example settings in Chapter 5 assume 0.02 (2%) for lactating cattle, and 0.04 (4%) for beef cattle.

- **Feed and grass diet fractions, DF_f and DF_g:** The sum of the three diet fractions, $DF_s + DF_f + DF_g$ must equal 1.0. Setting DF_s equal to 0.02 (2%) for lactating cattle assumed that they are pastured to some extent or could be taking in residues of soil sticking to home grown feed. Assuming lactating cattle graze a small amount of time, the DF_g for lactating cattle will be 0.08 (8%). This assessment simplifies the definitions of dairy and beef cattle diets by defining non-pasture grass vegetation simply as "feed". Feeds include hay, silage, grain, or other supplements. While dairy cattle are lactating, 90% of their dietary intake is assumed to be in this general category. Beef cattle spend a significant amount of time pasturing. However, their diet is supplemented with hays, silages, and grains, and particularly so in colder climates where they need to be housed during the winter. In this assessment, the simple assumption that

they ingest equal proportions of pasture grass and feeds is made. Therefore, with 4% soil ingestion, DF_f and DF_g are both 48% for beef cattle.

- **Average contaminant soil concentration, AC_s:** The simplest assumption for AC_s would be that it equals the initial level of contamination, C_s. However, this would be too high if the cattle also graze in uncontaminated areas. Where cattle have random access to all portions of a grazing area with contaminated and uncontaminated portions, a ratio of the spatial average of the contaminated area to the total area should be multiplied by C_s to estimate AC_s. If cattle spend more time in certain areas, these areas should be weighted proportionally higher. Different assumptions for determining AC_s might also be in order when using Equation (4-45) to estimate milk fat as compared to beef fat concentrations. Lactating cattle, if pastured, might graze on different areas than beef cattle. After determining a spatial average based on current conditions, a second consideration might be given to temporal changes. If soil levels are expected to change over time (due to changes in source strength or other factors) then the concentrations should be averaged over the exposure duration as well. The example scenarios in Chapter 5 where beef and milk exposures were estimated were termed "farms". The methodologies in this chapter were used to estimate the average soil concentration over the entire farm property. Assuming the cattle are raised on the farm property, than 100% of their intake of soil comes from the farm. This means that the average soil concentration, AC_s in Equation (4-45), is equal to the level of contamination given as the initial level, or determined as average for the farm based on fate and transport algorithms.

- **Average feed and pasture grass concentration, AC_f and AC_g:** The concentration of contaminant in pasture grass or feed is equal to C_{abv} as calculated in Equation (4-36). As described earlier, pasture grass or feed grown on-site can be impacted by air-to-plant vapor phase transfer and particulate deposition. Refinements noted above include the empirical parameter VG_{ag} equals 1.00 when applying the air-to-leaf transfer algorithm to pasture grass and 0.50 when applied to cattle feed. A refinement noted here, and like AC_s above, is that an assumption needs to be made about the fraction of feed or fraction of pasture grass that is impacted by contamination. Part of the feed diet could come from outside sources and not be contaminated, and part of the grazing area could be far from a localized area of soil contamination, making it less impacted by contaminated particulates or vapors. The simplest assumption is that the entire vegetative diet of the cattle includes pasture grass and feed impacted by the contaminated soil, in which case AC_f and AC_g would equal C_{abv}. For the sake of

simplicity and consistency, the assumption made for AC_s was also made for AC_f and AC_g in the example Scenarios in Chapter 5. That is, the grass and feed intakes of beef and dairy cattle originate within the farm property and concentrations in grass and feed are a function of the soil concentrations within the farm property; AC_f and AC_g are equal to C_{abv} as calculated in Equation (4-36). For site-specific situations, AC_f and AC_g should be estimated as C_{abv} reduced according to assumptions on quality of cattle feed, and impacts of air-borne contaminants on grazing land and cattle feed grown at the site where cattle are raised.

There is one final but critical note on solving for beef and milk concentrations given a solution for C_{fat} as in Equation (4-45). Human daily ingestion amounts are typically expressed in whole product rather than the fat portion of product. Whole milk is 4% fat, meaning that the C_{fat} needs to be multiplied by 0.04 to get whole milk concentration. Similarly, beef is generally 18-22% fat, meaning that the C_{fat} needs to be multiplied by 0.18-0.22 to get whole beef concentration. However, the ingestion rates in this assessment for beef and milk were developed on a fat basis, so no adjustment is necessary.

4.3.4.4. *Chicken and Egg Concentrations*

The algorithm to estimate the concentration of contaminant in chicken and/or eggs is the same algorithm as in beef/milk above. The experiments used to develop the chicken and egg bioconcentration factors were conducted by the Hazardous Materials Laboratory at the California EPA (Stephens, et al. 1995), and they will be described below. To review, the equation used to calculate the concentration of dioxin-like compounds in chicken and egg fat is:

$$C_{fat} = (BCF\ DF_s\ B_s\ AC_s) + (BCF\ DF_g\ AC_g) + (BCF\ DF_f\ AC \quad (4\text{-}46)$$

where:

C_{fat} = concentration in chicken fat or egg fat, pg/g

BCF = bioconcentration ratio of contaminant developed for chicken vegetative intake, unitless

DF_s = fraction of chicken diet that is soil, unitless

B_s = bioavailability of contaminant on the soil vehicle relative to the vegetative vehicle, unitless

AC_s = average contaminant soil concentration, pg/g
DF_g = fraction of chicken diet that is incidental vegetation while free ranging, unitless
AC_g = average concentration of contaminant on free range vegetation, pg/g
DF_f = fraction of chicken diet that is feed, unitless
AC_f = average concentration of contaminant in feed, pg/g.

The scenario of principal concern for chicken and egg contamination is the free range chicken scenario. This is the scenario where chickens are allowed to graze during all, or a portion, of their lives. The feed they consume could be spread out on the ground or in troughs. When they are free ranging but not eating their formulated feed from troughs, they still may forage for vegetation or earthworms which would give them considerable exposure to soil and vegetation, not to mention the earthworms which could be a source of dioxin-like compounds (earthworm exposure is not considered in this model). The percentage of all chickens raised for meat or eggs in this manner is a very small percentage of the total; most chickens are raised in commercial settings where their cages are raised and they have little exposure to soil or vegetation. When raised this way, their exposure to dioxins is only through the feed, and measurements of dioxin in chicken feed have shown little or no dioxin residues (Chang, et al, 1989; Stephens, et al, 1995). Chang, et al. (1989) sampled eggs from three sources: from foraging chickens that were raised near a contaminated PCP site in Oroville, CA (see the discussion of BCF below for a discussion of this site), from foraging chickens that were raised 4.5 km away in the neighboring town of Palermo, and from a grocery store, which were considered the control eggs. They found that the eggs from the foraging chickens near the site contained the highest concentrations of dioxin and furan congener groups (individual congeners were not reported in Chang, et al., 1989), with eggs from Palermo containing concentrations of dioxins and furans about 3 to 5 times less, and the commercial eggs being one to two orders of magnitude less than the eggs from near the PCP site.

The demonstration of this pathway in Chapter 5 is a free range scenario. The following is offered as brief guidance to the parameters in Equation (4-46) above and also the justification for the values selected in the example Scenarios in Chapter 5.

- **Chicken/egg bioconcentration factor, BCF:** In 1987, an explosion and resulting fire occurred at the Koppers Wood Preservative Treatment plant in Oroville, CA. Subsequent environmental studies found soil concentrations of the tetra through octa congener groups up to the ppm level adjacent to the fire site, and impacts to foraging chickens were also found, as was

discussed above (Chang, et al, 1989). The concern over this site led Stephens, Petreas, Hayward, and colleagues at the Hazardous Materials Laboratory (HML) of the California Environmental Protection Agency (Cal-EPA) to begin an investigation to test the hypothesis that grazing chickens would bioaccumulate dioxins. The first phase of their study, the laboratory phase, involved dosing chickens with feed mixed with soils of varying known levels of dioxins and furans. The completed results of this study have been published (Stephens, et al. 1995), with earlier publications available on the design and some interim results (Stephens, et al., 1992; Petreas, et al., 1991). Briefly, the study design was as follows. White Leghorn (Babcock D 300) chickens were randomly assigned to three groups with 22 individual chickens per group. The control group was fed a formulated laying-bird diet containing 10% uncontaminated soil - i.e., soil from a rural background setting with low levels of dioxins and furans. The TEQ concentration on this uncontaminated soil was less than 0.5 ppt. The "low" group was fed the same formulated diet to which they mixed soil to obtain a 9 (feed):1 (soil) ratio. The decision to have soil be 10% of the diet was based on discussions they had with agricultural experts on the amount of soil a free range chicken would take in. The soil had a CDD/F concentration of 42 ppt I-TEQ. It was taken from the backyard of a residence near the Koppers site, and had a similar sandy loam texture as the uncontaminated soil. The "high" group was fed the same formulated diet containing 10% of the same backyard soil but this time with several of congeners spiked in the soil to much higher levels. The concentration on this spiked soil rose to 459 ppt I-TEQ. Analysis by Stephens, et al. (1995) suggested that this spiking did not affect the bioavailability of the spiked congeners in the soil. Analysis of the feed before the introduction of any soils showed non-detects (with detection limits near or below 1 ppt, mostly at 0.1 ppt) for all congeners. Once the soils and feed were mixed, the I-TEQ concentrations in the feed/soil mixture for the "control", "low", and "high" groups were 0.6, 3.2, and 35.8 ppt, respectively (counting non-detects at half-detection). Eggs were collected every 5 days during the first month and every 10 days thereafter. Chickens were culled on days 10, 20, 41, 80, 164, 188, 210 and 278. Samples were taken of blood, feces, liver, adipose, and thigh muscle. Stephens, et al. (1995) reported on the analysis of liver, adipose, thigh muscle and egg for the suite of 17 dioxin-like compounds at various time intervals.

They also developed bioconcentration factors for these four tissues and for both feeding regimes, "low" and "high". To calculate the BCF, they averaged the tissue concentrations for days 80 and 164 when the animals had apparently reached a steady state, and for eggs at days 80, 160, and 178. The same will be done for the calculation of BCFs in this assessment. However, the BCFs for this assessment will be different than those published by Stephens, et al. (1995).

Their BCFs were defined as the concentration in the whole tissue on a wet weight basis divided by the concentration in the feed/soil mixture. Furthermore, although the concentration in the soil/feed mixture was determined and reported, Stephens, et al. (1995) surmised that the concentrations in the soil alone were more reliable than the concentrations measured in the feed/soil mixture. Therefore, the concentrations to which the chickens were exposed was calculated as the soil concentration divided by 10. The difference for this assessment is that the BCFs will be defined as the concentration in the tissue on a lipid basis divided by the concentration in soil, rather than the feed/soil mixture. The calculation for BCFs will also involve the use of the soil bioavailability term, B_s, as shown above in Equation (4-46). The procedure to calculate BCFs from the data is now explained.

Assuming that the chickens were not exposed to vegetation and that the feed concentrations were equal to 0.0 in the Cal-EPA experiments, Equation (4-46) reduces to the following:

$$C_{fat} = BCF\ DF_s\ B_s\ AC_s \qquad (4\text{-}47)$$

The congener-specific BCFs were then easily calculated assuming that the DF_s is equal to 0.10 and, the B_s is equal to 0.65, as it was above for the beef/milk bioconcentration algorithm, and directly using the soil concentrations as reported in Stephens, et al. (1995). Table 4-7 shows the final BCFs calculated in this manner from the Cal-EPA data. Stephens, et al. (1995) made the following three pertinent observations regarding this data and the development of the BCFs: 1) the highest concentrations were found in the liver, implying that mechanisms other than lipid solubility operate in that organ, 2) the soil had a high organic matter content, which the authors suggested would result in a lower observed bioavailability of the dioxins in the chickens than could have been observed had the soil organic matter content been lower and perhaps more typical of agricultural soils, and 3) the BCFs were higher in the "high" exposure group as compared to the "low" exposure group.

With regard to the first observation, the higher BCFs for the liver as compared to the other three tissues is apparent from Table 4-7 for both the low and high group. This is not relevant for exposure unless, of course, one were predicting concentrations in chicken livers for human consumption. In that case, one could use the liver-specific BCFs in Table 4-7. With regard to the second observation, this is important in that it provides some justification for the B_s of Equation (4-47) which was assigned a value of 0.65. The BCFs in Table 4-7 should, therefore,

be interpreted as BCFs specific to non-soil chicken intakes which are assumed to include chicken feeds and incidental vegetation in the model used in this assessment. This makes the chicken/egg BCFs analogous to the beef/milk BCFs. With regard to the third observation, Stephens, et al. (1995) tested the observation statistically and found that the BCFs of 3 congeners - 12378-PCDD, 234678-HxCDF, and 1234678-HpCDF - were significantly different at the $p < 0.05$ level and that the BCFs of 2 congeners - 2378-TCDF and 1234789-HpCDF - were significantly different at the $p < 0.025$ level. Even without statistical significance, it does appear that the trend of higher BCFs for the high exposure regime holds up for the other congeners as well.

Other interesting trends to observe in this data qualitatively (without statistical rigor) are related to the bioconcentration differences between adipose, thigh, and egg within the low group alone and/or compared against the high group. One important observation is that, in the low group, the dioxins concentrate more in the adipose lipid as compared to the thigh lipid, but this difference is much smaller in the high group. This might suggest that the dioxins deposit first, or preferentially, in adipose tissue rather than muscle tissue at low doses. Another trend is that, at the low dose, the dioxins concentrate in the lipid of the thigh and the egg about equally, but in the high group, the dioxins concentrate more in the thigh lipid as compared to the egg lipid.

In real world settings, soil concentrations to which chickens are exposed are expected to be more like the “low” exposure as compared the “high” exposure. Because of this, the BCFs for the low exposure group will be used in this assessment. For site-specific assessments where the soils are highly contaminated, and the assessor has justification for assuming that chickens are grazing on the highly contaminated soil, it would be appropriate to use the BCFs for the “high” group. The BCFs developed for the thigh and egg will be used for the calculation of concentrations in chicken meat and eggs, respectively. This is a different strategy than for the calculation of dioxin concentrations in beef or milk. There, a single set of BCFs were used to calculate concentrations in the fat of beef or milk. Here, the data appears robust enough to support separate BCFs. BCFs for two congeners in the low group could not be reliably calculated because one or both of the measurements (i.e., the soil/feed measurement and/or the tissue measurement) were below the quantification limit. These congeners are 2378-TCDD and 234678-HxCDF. For 2378-TCDD, it is noted that for the high exposure group, the 2378-TCDD BCF is about 1.3 times that of the 12378-PCDD BCF for both the thigh and egg. Based on this observation, the BCF for 2378-TCDD for thigh and egg will be 8.8 (i.e., 6.8*1.3) and 7.8 (6.0*1.3), respectively. The BCFs for the three HxCDFs for which a BCF could be estimated appear to be within a factor of 2-3 of each other. Based on this observation, the BCF for 234789-HxCDF for the thigh and egg will be estimated as an average for the three HxCDFs for these

tissues for which the BCF was derived. This calculation results in a 234789-HxCDF BCF of 4.1 for thigh and 6.2 for egg.

The only data that could be found for developing PCB BCFs was from a study by Fries, et al. (1977), and this data was only pertinent for Aroclor mixtures. Fries, et al. (1977) fed caged White Leghorn hens, 41 weeks of age, various PCB Aroclor mixtures at either 2 or 20 ppm in their standard breeder diet. Data was taken at nine weeks, after establishment of steady state, for body fat and egg concentrations of the 6 different Aroclor mixtures. In order to calculate concentrations, Fries et al. (1977) assumed that the eggs weighed 50 grams and that the body fat was 10% of the full weight of body tissue. BCFs for these Aroclors were calculated in this assessment as the ratio of the egg fat concentration to the feed concentration, for egg BCFs, and the body fat concentration to the feed concentration. Fries, et al. (1977) had provided full egg concentrations, and these were converted to egg fat concentrations by assuming that lipid is 10% of the full egg weight. The assumption of Fries, et al. (1977) that the fat content of his tested tissues was 10% will be retained here. The BCFs for the Aroclors are shown in Table 4-8.

A noteworthy trend for this data, as observed by Fries, et al. (1977), is that the PCBs appear to be retained at greater amounts as the degree of chlorination continues but then drops off at the higher chlorinated congeners. This is apparent in Table 4-8, as the BCFs increase through Aroclor 1248, but then drop off for Aroclor 1254 for the low dose and at 1268 for the high dose. The BCFs for the eggs continue to increase suggesting that excretion through eggs continues to be a mechanism for removal through the high chlorinated congeners. It is unclear that the BCFs from this study are pertinent to the modeling of this assessment, not only because they are on Aroclors and not on the dioxin-like PCB congeners, but also because soil concentrations are unlikely to reach the 2-20 ppm level for individual dioxin-like PCBs. Still, it is the only data that could be found. Without rigorous justification, it will be assumed that the BCFs for the low dose of Aroclor 1254, 6.5 for egg fat and 7.4 for body far, are appropriate for the dioxin-like PCB demonstrated in Chapter 5, 2,3,3',4,4',5,5'-PCB.

It should be noted that all bioconcentration or biotransfer parameters, such as the BCF, are qualified as second order defaults for purposes of general use. Section 6.2. of Chapter 6 discusses the use of parameter values selected for the demonstration scenarios, including a categorization of parameters. Second order defaults are defined there as parameters which are theoretical and not site specific, but whose values are uncertain in the published literature. The parameter values in this category should be considered carefully by users of the methodology.

- **Soil bioavailability B_s; Feed, grass, and soil diet fractions, DF_f, DF_g, and DF_s; and average feed, grass, and soil concentrations, AC_f, AC_g, AC_s:** The soil bioavailability is assumed to be 0.65, as it was for the beef/milk algorithm. It is important for users to understand that the BCFs were developed with this assumption. If other users believe it is more appropriate to assume that the BCFs as directly derived from the Stephens, et al. (1995) experiments are equally appropriate for soils, incidental vegetation, and feeds, than the BCFs need to be adjusted downward by multiplying them by 0.65. If doing this, users should then not apply a B_s in the calculation of chicken and egg concentrations for a free range or other scenario which has the chickens exposed to soil. Following on the lead of the Cal-EPA experiments, it will be assumed that soil is 10% of a free range chicken diet, and DF_s will be equal to 0.10. Since the chickens are free ranging, it also seems reasonable that they should exposed to some incidental vegetation. No guidance could be found on the assignment of DF_g, but it does seem reasonable that the chicken would ingest less incidental vegetation than soil, particularly if their exposure to soil occurs when the chickens are feeding and their feed is spread out on a certain patch of ground worn bare to soil. On that basis, DF_g will be assigned a value of 0.05, and DF_f will be 0.85. The soil concentration, AC_s, could be modeled as in the case of erosion from a site of contamination to a site of exposure, or as in the case of stack emission deposition. For the latter case, the soil concentration assumed will be the untilled soil concentration. The soil concentration could also be specified, as in the case of soil contamination which is on-site. The incidental vegetation will be assumed to be leafy, as in grass, and the concentration in the grass will be modeled as grass would be modeled in the context of the source category. Based on the measurements of Chang, et al. (1989) and Stephens, et al, (1995), it will be assumed that the concentration on chicken feed will be zero.

4.3.5. Specific Cases of Soil Contamination

This section provides background information on specific sites of soil contamination which have been studied for the presence and impact of dioxin-like compounds. These include landfills used for disposal of ash from municipal waste combustion facilities, the disposal of sludge from pulp and paper mills, and sites of soil contamination typified by the sites monitored in the National Dioxin Study (in many cases, Superfund sites or sites that were in some stage of being considered for inclusion on the NPL list at the time of the study; EPA, 1987). Discussion of these particular sites does not imply that they represent the bulk of such sites nationally, or that they are discussed here based on any critical environmental or exposure rational. They are discussed because they present unique issues for emissions and fate and transport of dioxin-like

compounds from sites of soil contamination, and because they have been studied. Issues discussed below are pertinent for other types of off-site soil contamination sites.

4.3.5.1. *Landfills Receiving Ash from Municipal Waste Incinerators*

Particular issues regarding landfills receiving ash include: the impact of soil cover on releases, the ash concentrations, the size of such landfills, the quantity of ash generated by incinerators, and the fugitive emissions that result from ash management. Key sources providing information for this section include a methodology document describing approaches to estimating environmental releases and exposures to ash (EPA, 1991), and a contractor report applying these types of methodologies using site-specific data from several ash landfills (MRI, 1990). Each of the identified topics will be discussed in turn.

- **Landfill Cover:** Whether or not ash is covered once it is disposed of at the landfill is critical in determining releases and subsequent exposures. Currently, practices at operating landfills vary from no coverage after disposal on active portions of the landfill to daily coverage of disposed ash. MRI (1990) visited six facilities disposing ash, including ash monofills and municipal solid waste landfills. In one of the facilities, an ash monofill located at the site of the combustor, the disposal area encompassed 15 acres and did not use daily cover until final elevation was reached. At that time, a clean cover of 2 feet of soil would be applied. At a second facility, located at the site of the combustor but landfilling municipal solid waste as well as ash, ash was used for different purposes, including a subbase roadbed material, as soil substitute for earth work, and as a daily cover for MSW receipts. An assumption of bare surfaces (i.e., no vegetation) during the period of landfilling activity, with concentrations of dioxin-like compounds equal to concentrations in the ash would appear to be appropriate assumptions for practices at these two landfills.

Where daily cover is employed, however, appropriate assumptions are not straightforward. Of the remaining four sites studied by MRI, two employed daily covers ("clean cover material" in one case and a "HDPE liner" in the other, sic), and daily coverage practices were not discussed for two sites. Approaches described for airborne emissions and erosion losses would have to be modified when daily cover is applied. First, losses of contaminants via overland soil or wind erosion could not be expected to occur when cover (soil cover or otherwise) is in place, although the active part of the landfill would be subject to erosion during an operating day. Even in that case, however, site-specific practices might include little or no ash disposal during periods of soil-erosion-producing storms. Depending on site-specific practices,

one might estimate annual erosion losses using methodologies described in this assessment, and then empirically reduce erosions losses based on these practices and scientific judgement.

Air emissions from active portions of the landfill, as in wind erosion and volatilization, also are obviously impacted by cover practices. These emissions would occur during the actual disposal. Wind erosion and volatilization fluxes could be estimated as given in earlier sections, and then reduced by two-thirds, which might correspond to an assumption of disposal during 1/3 of a day or a year, etc. When covered by soil or a synthetic cover, wind erosion losses would not occur. However, buried residues may diffuse through layers of clean soil and be released via volatilization.

Estimates of volatilization release via diffusion through clean cover have been made. A rigorous approach for such estimates is detailed in Hwang, et al. (1986). Use of this approach requires a computer to iteratively solve a partial differential equation, expressed in terms of a Fourier series. It can be shown, with these equations, that the vapor emission rate through such a cover will not reach steady state for hundreds of years. Hwang's approach was applied to an earlier assessment for 2,3,7,8-TCDD (EPA, 1988b). Calculations were performed for 2,3,7,8-TCDD contamination with a thickness of contamination of 8 ft, and clean caps ranging from 10 to 25 cm. The results of this exercise suggest that the average emission rate of a 70-year period are 1/4 to 1/5 of what they would be without the cap. Based on this exercise, a simple assumption might be made that a clean cap will reduce the average emission rate calculated without a clean cap by 80%. However, these results are not consistent with those described in Jury, et al. (1990). The analytical solution developed by Jury was demonstrated on 35 organic compounds. One exercise conducted by Jury was to estimate the cover thickness required to restrict volatilization to less than 0.7% of the mass incorporated in soil. For 2,3,7,8-TCDD, the thickness was estimated at 0.7 cm for a sandy soil and 0.2 cm for a clayey soil. This appears to contradict the work of Hwang since it shows an essentially insignificant loss for a cap much less thick than the 10-25 cm cap in the exercises using Hwang's approach. However, Jury's approach allows for assumptions on degradation of the buried compound. For that exercise, Jury assumed that the half-life for 2,3,7,8-TCDD was 1 year. This is a very rapid degradation rate, given information that the dioxin-like compounds resist degradation, particularly when not exposed to sunlight. On the other hand, the Hwang model assumes no degradation loss, and as such, the generalization from his exercise might be an overestimate. Hwang's exercise might also have overestimated since it assumed a rather thick 8-ft layer of subsoil contamination. From these arguments, it would appear that neither exercise appropriately evaluated the difference in volatilization in a no cover versus a cover situation.

The above discussions concerned flux calculations when cover practices are used. One set of adjustments discussed reduced a total potential flux of volatilized or wind eroded losses based on a portion of the time that the ash would be uncovered. A second discussion indicated that some loss via volatilization might be modeled with a clean cap. In any case, it is clear that cover practices will reduce losses. Cover practices must be considered when evaluating the exposure to ash disposed of in landfills.

- **Ash Concentrations:** A key consideration, of course, in modeling transport of dioxin-like compounds from an ash landfill is the concentration on the ash. Ash concentrations of dioxin-like compounds have been found to vary widely, from non-detect (generally less than 0.1 ppb) to the hundreds and thousands of part per billion. Table 4-9 appears in EPA (1991) and summarizes concentrations of dioxin-like compounds and PCBs found in fly, bottom, and combined ash. These data are a summary of 19 references, ranging in publication date from 1974 to 1990. It should be noted that, except for 2,3,7,8-TCDD and 2,3,7,8-TCDF, results listed are for congener groupings defined by degree chlorination.

- **Size of Landfill and Amount of Ash Landfilled:** The size of the landfill and the amount of ash applied daily or over time are both required for estimating exposures nearby. These can both be obtained from site-specific observations. Amounts of daily disposed ash are required to estimate fugitive particulate emissions, as will be discussed shortly. Amounts of daily or ultimate disposal are also tied to landfill size, or the portion of a landfill that is active on a daily basis. One common practice is to fill cells of a landfill one at a time, and once filled, to cover with a 2-ft (or so) layer of clean soil. The appropriate size in this case is the average size of a landfill cell. If daily coverage is applied, than the size for modeling purposes corresponds to the area over which daily coverage occurs. This can also vary depending on the depth of disposal during a day. A six-inch daily coverage, for example, would take twice as much space as a 1-ft depth of daily disposal. If the intent of a day's disposal is to cover over the entire area of an active cell, then depth of coverage need not be considered in determining landfill size.

Determination of landfill size (or the size of the active portion of the landfill) may be required in the absence of site-specific information, such as in the planning stages for a new incinerator. This is where details on landfill management need to be determined. One important detail, as already noted, is the amount of ash generated for daily disposal. Cook (1991) assumes that bottom and fly ash combined comprise about 11% of total receipts on a volume basis. However, a relationship between ash generated and solid waste received by an incinerator on a

mass basis is more useful for estimating daily disposal amounts. In an EPA (1990f) report on ash characterization, ash mass was estimated as an average of 29.5% of municipal solid waste received in five facilities studies, with a narrow range of 25-35%. This mass was estimated on a wet weight basis. Ash is wetted when exiting the incinerator, and water comprises 20-30% of the total weight at that point. If the ash is immediately trucked for landfill disposal, its total weight includes the weight of this quench water. Often ash is stored at the incinerator site in piles prior to disposal, that storage ranging from hours to days. In this circumstance, much of the quench water would have drained off or evaporated, and then the total weight hauled would be closer to a dry weight estimate. In summary, the amount of ash generated to be disposed of a daily basis can be estimated as: the daily receipt of municipal solid waste (tons) * a wet weight ash fraction (0.25-0.35) * a wet to dry weight conversion if appropriate (wet weight * 0.80, e.g.).

- **Fugitive Particulate Emissions:** Fugitive emissions can occur from the time ash exits the incinerator for temporary storage at the facility site (or immediate loading onto trucks for disposal) until ultimate disposal. Approaches to estimate fugitive releases from incinerator ash management are described in EPA (1991), and will be summarized here.

As noted, ash can be wet when exiting the quench tank. If stored at the facility site prior to disposal in a landfill, leaching from piles can occur. Because dioxin-like compounds are strongly hydrophobic, however, the impact of leaching is unlikely to occur much beyond the soil beneath and near the storage piles. If loaded onto trucks when very wet, leaking onto roadways may also occur. If these storage piles are left uncovered, they would of course be subject to erosion losses, which might move residues further from the piles than just leaching of water from the piles.

Of more concern than water-borne losses due to ash management are fugitive emissions of dry ash. Wind erosion, which can occur from open storage piles or uncovered portions of the landfill, is a fugitive emission that has been discussed for soil contamination. Specific practices in the management of ash can also result in fugitive emissions. Such practices include: 1) loading onto and dumping out of trucks, 2) truck transport from the incinerator facility to the landfill site, 3) truck or other traffic over paved or unpaved roadways at the incinerator site, at the landfill site, or other roadways containing contaminated dust, and 4) spreading and compacting of ash at the landfill site. A set of empirical emission factor equations for estimating fugitive particulate emissions, called "AP-42" equations, have been developed by EPA's Office of Air Quality Planning and Standards (EPA, 1985a; EPA, 1988a). Specifics on applying these equations for ash management are described in EPA (1991). An example of their application

using site-specific information for ash management is detailed in MRI (1990). An abbreviated listing of emission factor equations that have been used in these two publications are:

- Vehicular traffic over unpaved roadways. Dust on the surfaces of roads, both unpaved and paved, can become suspended due to vehicular traffic. When these roadways are near ash storage piles or within the landfill, that dust can become contaminated. The emission factor equation for emissions from unpaved roadways is:

$$E_{up} = 1.7\ k_{unp} \left(\frac{scu}{12}\right) \left(\frac{Vs}{48}\right) \left(\frac{W}{2.7}\right)^{0.7} \left(\frac{nw}{4}\right)^{0.5} \left(\frac{365 - NP}{365}\right) \quad (4\text{-}48)$$

where:

E_{up}	=	emission flux for unpaved surfaces, kg/VKt (VKt equals vehicle kilometer traveled)
k_{unp}	=	particle size multiplier specific to the unpaved road emission flux equation, unitless
scu	=	silt content of unpaved roadway, %
Vs	=	vehicle speed, km/hr
W	=	vehicle weight, kg
nw	=	number of wheels per vehicle, unitless
NP	=	number of days with >0.25 mm precipitation per year, unitless

- Emissions off trucks in transit. Although no emission factor equations have specifically been developed for trucks while in transit from the incinerator facility to the landfill, such emissions can occur if the ash is dry, and partially or completely uncovered. The following equation for estimating emissions from open storage piles has been suggested for use in estimating fugitive emissions from trucks in transit (EPA, 1991; the emission factor equation from EPA, 1985a). Note that use of this equation will require specific management assumptions in order to estimate the number of uncovered hectares per day: the number of trucks in use per day, the surface area of trucks, the percent of uncovered area if a tarpaulin is used, the moisture content of ash, and so on.

$$E_t = 1.9 \left(\frac{sca}{1.5}\right) \left(\frac{f}{15}\right) \left(\frac{365 - NP}{365}\right) \quad (4\text{-}49)$$

where:

E_t = particulates emitted from trucks in transit, kg/day/hectare
sca = silt content material of ash, %
NP = number of days with >0.25 mm precipitation per year
f = percentage of time that the unobstructed wind speed exceeds 5.4 m/s.

- Loading and unloading. The unloading operations at the disposal site may result in the release of fugitive dust. The following emission factor equation provides emission factors for kilograms of particulate emitted per megagram (metric ton, or 1000 kg) of soil loaded and unloaded:

$$E_{lu} = 0.0016\ k_{unl} \left(\frac{U_m}{2.2}\right)^{1.3} \left(\frac{MC}{2}\right)^{-1.4} \quad (4\text{-}50)$$

where:

E_{lu} = emission factor for loading and unloading, kg dust/MT ash
k_{unl} = particle size multiplier, unitless
U_m = wind speed, m/s
MC = material moisture content, %.

- Spreading and compacting of ash at the landfill. An emission factor specifically for ash spreading and compacting has not been developed. However, emission factor equations for similar applications have been applied for estimating fugitive emissions due to spreading and compacting. MRI (1990) used an AP-42 emission factor developed for dozer moving of overburden in western surface coal mines. Kellermeyer and Ziemer (1989) assumed that the spreading and compaction of ash was analogous to vehicular transport on unpaved surfaces, and used the emission factor for that process. A third possible assumption is that the processes of spreading and compacting are analogous to agricultural tillage. That emission factor equation for agricultural tillage is:

$$E_{at} = 5.38 \; k_{at} \; scs^{0.6} \qquad (4\text{-}51)$$

where:

E_{at} = emission factor for agricultural tillage, kg/ha
k_{at} = particle size multiplier, unitless
scs = silt content of soil, %.

When applying such equations, there are further key issues to consider. These include:

- Concentrations on fugitive ash emissions: When such an emission occurs from ash surfaces, such as from storage piles, off trucks in transit, in spreading and compacting, and so on, than there is a good argument to assume that such concentrations on such emissions are "enriched" in comparison to an ash average. The argument here is similar to the argument for enrichment assumed for eroded soils: processes resulting in fugitive air emissions favor lighter particles with more surface area and hence more sites for binding. No data could be found to assign a value to an ash enrichment ratio. MRI (1990) did, however, take data on municipal waste combustor facility roadway dust, and based on that data and statistical evaluations, speculated that fly ash constituted the principal source of lead and cadmium found on paved surfaces. Since fly ash is finer than bottom or combined ash, one hypothesis for this finding is that fugitive emissions from ash management at the combustor site transported these finer particles to roadway surfaces. This is not to imply, however, that concentrations in dust suspended from roadways due to traffic should be higher in concentration than concentrations in ash - this enrichment concept only applies to ash surfaces themselves. Rather, the concentration on roadway suspended dust should be lower than on the ash. This is because contaminated dust on roadways mixes with clean dust from other sources. As noted, MRI (1990) did take roadway dust samples, and their data appears to place such a dilution factor (concentration on roadway dust divided by concentration on ash) in the range of 0.1 to 0.3. Specifically, they took particulate samples from landfill haul routes while at the same time taking samples of incinerator ash being delivered for disposal the same day. Each paired sample (roadway particulate and ash), were measured for four metals: As, Cd, Cr, and Pb. Several paired samples were taken on both paved and unpaved haul routes. Ratios were then generated for roadway particulate metal concentrations over ash metal concentrations. Results were: As - paved and unpaved ratios were similar and consistently near 0.1 (roadside particulate concentrations of As were 10% of ash

concentrations of As), Cd - paved and unpaved ratios were similar and ranged between 0.0 and 0.4, Cr - paved ratios ranged from 0.3 to 0.6, while unpaved had a wide range of 0.3 to 2.0, Pb - paved and unpaved ratios were similar between 0.0 and 0.2. For analogous situations - daily deliveries of contaminated ash - one might assume a dilution factor in the 0.1-0.2 range.

- Selection of values for emission factor equations: As noted, all these equations are empirical equations. They were developed from data on sites where such emissions occur, such as strip mining sites. EPA (1988a) describes the range of conditions over which such equations were developed. What is meant by "conditions" are such factors as the range of vehicle weights in the data set, the range in number of wheels on such vehicles, and so on. Application of these equations for situations not included within these ranges should be done cautiously. Very critical also is the selection of the particle size multiplier variable, k. These values range from about 0.10 to no higher than 1.0. Lower k values are used to estimate emissions of the smallest sized particles; generally particles less than 5 μm in diameter. Higher k values are used to estimate emissions of all sized particles less than a higher diameter, usually either 15 or 30 μm. If these equations are used to only estimate particulate inhalation exposures, than the k value corresponding to 10 μm sized particles, or inhalable sized particles, should be used. When used to estimate total emissions, than the highest k value listed should be used. Such estimations are appropriate when also evaluating impacts to off-site soils or vegetation.
- Controls for fugitive emissions: All these equations were developed when no fugitive emission controls were in place. Common controls for roadway dust suppression include wetting or use of a chemical dust suppressant. Ash transported in trucks is commonly wetted and/or a tarpaulin is used to control emissions off trucks. There is no guidance or data on the effectiveness of such controls, but they must be considered. In demonstrating these procedures, EPA (1991) assumed that controls on emissions resulted in 90% reductions in potential emissions. If a control is known to be in place and used on a regular basis, than this percent reduction is probably a reasonable starting assumption.

4.3.5.2. *Land Application of Sludge from Pulp and Paper Mills*

This discussion focuses on an assessment on the land application of sludge from bleached kraft and sulfite pulp and paper mills (EPA, 1990e). Focusing on this source of sludge does not imply that pulp and paper mills produce more sludge than other industries, or that sludge from pulp and paper mills contains more dioxin-like compounds than other sludges. However, it is known that dioxin-like compounds are found in pulp and paper mill sludges. Also, because of the 104-mill study in 1988, much information is available on the content and disposal of this

sludge (further information on the 104-mill study can be found in EPA (1990c,d)). Some of the issues briefly discussed below for pulp and paper mill sludges would also pertain to sludges containing dioxin-like compounds from other sources.

EPA (1990e) described frequency distributions of concentrations of 2,3,7,8-TCDD and 2,3,7,8-TCDF for 79 mills reporting this information and also broke out the data based on disposal option. Although EPA (1990e) used the disposal option breakout of concentrations in their assessment of the impacts of the various options, it is not felt that the disposal option of choice is based on concentration. Over all options, the median (50% percentile as given in EPA (1990e)) and maximum 2,3,7,8-TCDD concentrations found in sludges were 51 and 3800 ng/kg (ppt), respectively. The median and maximum 2,3,7,8-TCDF concentrations found were 158 and 17100 ppt.

Fate and transport for contaminants is sludge is dependent on disposal means. Of the approximate 2.5 million metric tons of pulp and paper mill sludge generated annually (as estimated in the 1988 104-mill study), five principal options for disposal were noted: landfilling (44% of all sludge disposed), surface impoundments (24%), land application (12%), incineration (12%), and distribution and marketing (8%). Impacts by incineration were not discussed in EPA (1990e) and are not discussed in this section. Key issues pertaining to each disposal issue are now discussed.

- **Landfilling:** The issue of coverage as discussed above for ash landfills is relevant for any landfill. However, fugitive particulate emissions during sludge handling and disposal is not an issue as it was for disposal of ash from incinerators due to the differences in moisture content. Sludge is much higher in moisture at the time it is disposed of in comparison to ash - with moisture contents as high as 90%.

- **Surface Impoundments:** It was assumed in EPA (1990e) that sludge disposed of in surface impoundments have a higher moisture content as compared to sludge disposed of in landfills. Surface impoundments were located at the mill site, explaining the assumption for a higher moisture content. A surface impoundment in the EPA (1990e) assessment was defined as a facility in which the sludges are stored or disposed on land without a cover layer of soil. For this type of management, soil cover would not be an issue. Concentrations would be those measured in the sludge. Also, vegetative cover would be expected to be minimal, which would influence parameters associated with soil erosion.

- **Land Application:** Twelve percent of all sludge produced annually was land applied. Four of the 104 mills applied the sludge to forest land, two mills land applied the sludge to agricultural land, and two mills used the sludge for abandoned mine reclamation. The high organic matter content (EPA (1990e) assumed a 25% organic carbon fraction in sludge) and high fraction of clay-sized particles make sludge an attractive soil amender. Sludge is either applied to the land surface with or without incorporation. When not incorporated, sludge can be assumed to replace surface soils and concentrations would be those in the sludge. When incorporated, soil concentrations can be estimated simply as (in mg/kg): (mass of contaminant added, mg)/(mass of sludge added, kg + mass of soil in mixing zone, kg). One key issue when incorporated is the number of years of such treatments. Most of the land application uses of paper and pulp mill sludges reported in EPA (1990e) made applications in only one year. As easily seen in the above suggested equation, higher concentrations result with more years of incorporation. The other key issue with incorporation, of course, is the depth of incorporation. For agricultural applications, the depth of incorporation assumed in EPA (1990e) was 15 cm, similar to the 20 cm incorporation assumed for home vegetable gardening in this assessment. For silvicultural uses, the assumption in EPA (1990e) was 2.5 cm, which corresponds to some but minimal mixing. For abandoned mine reclamation, the assumption was 0 cm incorporation. Routes of exposure might also vary from focuses in this document depending on land application choice. When applied to agricultural land, impacts to food crops would demand particular attention (the procedures in this assessment were demonstrated with home grown vegetables, although of course impacts to food crops are critical when agricultural field soils are impacted by dioxin-like compounds). When applied to forest land, ecological impacts might warrant particular attention, as was discussed and demonstrated in EPA (1990e). A final issue to consider when land applying sludge to land is a rate of dissipation/degradation of dioxin-like compounds. Landfills and surface impoundments have ongoing surface applications and over time, the total depth of applications in the range of meters, so an assumption of a constant source strength over a period of exposure, as was assumed in this assessment for soil contamination sources, is reasonable. However, if only a few centimeters of surface soil are impacted, which might be the case for single applications to land and/or surface applications with no incorporation, an assumption of dissipation may be warranted. EPA (1990e) assumed no degradation of 2,3,7,8-TCDD in their assessment of impacts from land applications.

- **Distribution and Marketing Uses:** The volume of sludge distributed and marketed was approximately 8% of the total amount of sludge generated for the 104-mill study. For this

use, sludge was composted and then sold as a soil amendment in residential, agricultural, and commercial settings. More attention to the dermal contact pathway appears appropriate for this usage. Site-specific factors, and the values for these factors used in EPA (1990e), include: 1) depth of incorporation - 0, 15 and 25 cm in assumptions characterized as high, best, and low estimates, 2) garden size - 0.016 and 0.022 hectares characterized as low/best estimate and high, and referencing a national gardening survey, 3) rate of application - between 5 and 20 dry metric tons per hectare references a USDA publication on use of sewage sludge compost for soil improvement and plant growth, and 4) years of using such compost - 20 without specific reference. The years of application is needed for estimating soil concentrations during and after the period of exposure, using a simple ratio as discussed above in land application.

4.3.5.3. *Sites Studied in the National Dioxin Study*

The National Dioxin Study (EPA, 1987) focused on sites of known or suspected contamination of soil by 2,3,7,8-TCDD. There were 7 "Tiers" of investigation, with roughly decreasing expectations of finding 2,3,7,8-TCDD. Tiers 1 and 2 included 2,4,5-TCP production and associated disposal sites (Tier 1) and sites where 2,4,5-TCP was used as a precursor in the manufacture of pesticidal products and associated disposal sites (Tier 2). These tiers had the highest expectation for finding 2,3,7,8-TCDD. There were originally thought to be 450 sites that would fall in Tiers 1 and 2, but after investigation, only 100 sites were included for study. Some were downgraded into Tier 3. Of the 100 sites studied, 20 were on or were proposed for inclusion in the Superfund National Priorities List. Tiers 3 and 5 were associated with 2,4,5-TCP formulation (Tier 3) and use (Tier 5). Tier 6 were organic chemical or pesticide manufacturing facilities were 2,3,7,8-TCDD was suspected of being present. Tier 4 included combustion sources and are not discussed further in this section. Tier 7, basically an examination of background areas, are also not discussed here.

Issues that are identified as important in fate and transport modeling for this subcategory of off-site sources include concentrations, the possibility of ground water contamination, and site-specific characterization. These are discussed in turn.

- **Concentrations:** Only 11 of the 100 Tier 1 and Tier 2 sites were eventually classified as requiring "no further action" because 2,3,7,8-TCDD soil concentrations were very low, < 1 ppb, or not detected (with detection limits generally at 1.00 ppb). Where it was detected, a general trend was to find very high concentrations where 2,4,5-TCP production wastes were stored or disposed of, with much lower concentrations at soils near these particular

areas. At hot spots, concentrations were as high as 2,000 parts per million, but generally soil concentrations were in the parts per billion. It was this parts per billion generalization that led to the assignment of a 1 ppb soil concentration for the demonstration of the off-site source category in Chapter 5. There were findings in the low ppb range for Tiers 3, 5, and 6, but at much lower frequency and no findings higher than the tens of ppb range. For exposure assessments, the characterization of soil concentrations in a site containing hot spots has to be carefully considered. For site evaluations and proposed options for remediation, an areally weighted average might be considered, although this could dilute loss estimates depending on the area chosen - choosing a large area corresponding to property lines might, for example, lead to an "average" concentration orders of magnitude lower than concentrations found in hot spots. One approach which should be considered is a "hot spot" impact compared to an areally averaged impact. It should also be remembered that removal of highly contaminated soils is a common practice and another option for evaluation would be a concentration assuming hot spots are removed.

- **Potential for Ground Water Contamination:** PCBs have been found in ground water in sites associated with dielectric fluids of transformers. Oils can migrate through soils as a separate immiscible phase and reach ground water, which has been the common explanation for PCB impacts to ground water. Ground water contamination by 2,3,7,8-TCDD has very rarely been found in ground water, although it has been released to the environment in an oil matrix. The Times Beach area of Missouri is the principal example of this release, where waste oils containing 2,3,7,8-TCDD were used for dust control. Ground water sampling did occur in many of the Tier 1 and 2 National Dioxin Study sites, but the results were mostly non-detects. One occurrence at 0.18 ppt was noted for the Hyde Park site of Hooker Chemical in Niagara, NY, and a high of 1.8 ppb was found in an on-site monitoring well at National Industrial Environmental Services in Furley, KS. There were, however, numerous high occurrences in sub-soil samples in hot spot areas, in bottom sediments of evaporation lagoons, and so on, in the hundreds of ppb range.

There have been some limited experimentation showing different patterns of 2,3,7,8-TCDD migration in soils in the presence of solvents or in an oily matrix. Palusky, et al. (1986) studied the mobility of 2,3,7,8-TCDD in soils associated with each of 6 solvents. Migration was found to be higher with aromatic solvents and chloroform in comparison to saturated hydrocarbons and methanol. They speculated that the extent of migration related to the solubility of 2,3,7,8-TCDD in the solvent. Puri, et al. (1989) studied the migration potential of 2,3,7,8-

TCDD in soil, water, and waste oil mixtures. Over time, they observed a reversible sorption pattern of TCDD, and concluded that a carrier medium with a significant amount of waste oil would play a dominant role in the movement of TCDD through soils.

- **Site-specific Characterization:** In the case of landfills or sludge land application sites, the assignment of a soil concentration and an area can be made with some reasonableness. Such is not the case with the industrial contamination sites such as those studied in the National Dioxin Study, as briefly discussed above in the concentration bullet. Most of the sites studied in the National Dioxin Study were in the order of tens of hectares to below ten hectares. On the other hand, the Dow Chemical site in Midland, Michigan is described as a site 607 ha in size (Nestrick, et al, 1986). That area corresponds to the size of the property, and the many soil sampling sites within that area were described as "background". Several of the pesticide formulator sites studied in Tier 3 were 2 hectares or less in size. Many of the them were extensively or partially paved with buildings, which complicate fate and transport modeling. Some of the Tier 5 sites of 2,4,5-TCP use were agricultural fields, which are less complicated to describe. However, two sites were described as 2500 acres in size, which again is very large and makes assignment of an average soil concentration non-trivial. Other use sites were described as railyards and railroad rights of way. While estimates of loss into air could be made in complicated sites such as these, use of soil erosion modeling becomes very complicated if not undoable with paved areas, buildings, drainage ditches, roads, and the like.

4.4. ALGORITHMS FOR THE STACK EMISSION SOURCE CATEGORY

Contaminants emitted from incinerator stacks are transported in air and deposit on the exposure site, water bodies that may be used for drinking or fishing purposes, and on surrounding land. Chapter 3 describes the application of the ISCST3 model to obtain vapor-phase air concentrations and deposition rates of particles at a specified distance from an example stack emission source. These quantities are assumed to be given for purposes of discussion in this section; further discussion of the air transport modeling is given in Chapter 3.

Estimating soil concentrations based on particulate depositions follows a similar approach as estimating exposure site soil concentrations resulting from erosion of contaminated soil from off-site areas of contamination. Section 4.4.1. describes how soil concentrations are estimated given total (wet plus dry) deposition rates. Surface water impacts are assumed to result from direct deposition onto surface water bodies as well as erosion from the impacted effective drainage area. This solution is an extension of the solution given in Section 4.3.1. for the soil

contamination source category, and is given in Section 4.5.2. Following now are bullet summaries for similarities and small refinements to algorithms previously discussed:

- **Air impacts:** The atmospheric transport modeling described in Chapter 3 was comprised of two computer simulations: one which considered that emissions were in a vapor form and were transported as such, and one which considered that emissions were in particle form and likewise were transported as such. The result of the vapor-phase runs was a unitized ambient air concentration at various distances up to 50 km in all directions from the stack. Only the results in the predominant wind direction were used in this demonstration. The result of the particle-phase runs were an ambient reservoir of air-borne contaminants sorbed to particulates (used only for inhalation exposures), and wet and dry deposition unit rates also at various distances up to 50 km. By "unitized", what is meant is that emissions for the vapor or particle runs can be thought of as "1" mass/time (g/sec) emissions. Results for all distances are linear with respect to this emission rate; that is, if the rate of vapor contaminant determined to be emitted is "5", than ambient air concentrations at any location are 5 times what they are when "1" is assumed to be emitted. The same holds true for emissions in the particle phase. Chapter 3 developed a framework for assigning a vapor and a particle fraction for specific dioxin congeners. For example, 2,3,7,8-TCDD was assumed to have a vapor fraction of 0.51 (51% was in vapor form) and a particle fraction of 0.49. The final model results for air concentrations, and dry and wet deposition rates for all congeners, starting from these unit model runs and then incorporating congener-specific emission rates and vapor/particle splits, are given in Tables 3-12 to 3-17. The vapor-phase air concentrations were used to model vapor phase transfers in the vegetative bioconcentration algorithms. They were also used, summed with the simulated reservoir of particle-bound contaminants, to estimate the total reservoir of contaminant available for inhalation exposures.
- **Vegetative impacts:** The rates of wet and dry deposition modeled by ISCST3 were used to determine vegetative impacts. The model for particle deposition impacts to vegetation is described in Section 4.3.4.2 above. Of course, this above section solves for dry deposition as a reservoir times a dry deposition velocity (for dry deposition), and as a reservoir times rainfall and a washout factor (for wet deposition); such a solution is not required for the stack emission source category

since the deposition totals are estimated by the ISCST3 model. Other parameters for the vegetative model - the B_{vpa} (air-to-leaf vapor transfer factor), the R_w (fraction of wet deposition retained on vegetation surfaces), crop yields and interceptions, and the vegetative washout factor, k_w, are used for the stack emission source category.

- **Biota concentrations:** The algorithm estimating concentration in fish tissue based on bottom sediment concentrations is the same as in previous source categories. Modeled rates of contaminant deposition on particles onto the exposure site are used to estimate a "tilled" and an "untilled" soil concentration, as described below in Section 4.4.1. Underground vegetable concentrations are a function of tilled soil concentrations. The soil concentration used for cattle soil ingestion is untilled. Beef and milk concentrations are again a function of vegetative and soil concentrations, diet fractions, and bioconcentration and bioavailability factors as described in Section 4.3.4.3.

4.4.1. Steady-State Soil Concentrations

Chapter 3 describes the use of the ISCST3 Model to estimate the particulate phase deposition rates at the exposure site. This total deposition rate, F, includes both dry and wet deposition, and is used to estimate the soil concentrations. The deposition of contaminated particulates from the air is assumed to be somewhat analogous to the process of eroding contaminated soil from an off-site source depositing on an exposure site. Specifically, the following assumptions are also made: 1) only a thin layer of soil becomes contaminated, 2) this layer is either "untilled" or "tilled", depending on surface activities, and 3) surface residues are assumed to dissipate with a half-life of 25 years corresponding to a first order decay rate of 0.0277 yr^{-1}. Considerations of upgradient erosion and exposure site soil removal are not made. Depositions occur over the exposure site and surrounding land area on an on-going basis. It might be said that upgradient soil concentrations are similar to exposure site concentrations at all times. Like the soil source categories, a tilled mixing depth of 20 cm, and an untilled mixing depth of 2 cm is assumed for this source category. The qualitative mass balance statement (similar to the one made above in Section 4.3.2, with ΔC equaling change in exposure site soil concentrations over time) can now be made as:

(the incremental addition to C resulting from the change in deposition of stack emitted particulates) -

ΔC = (the incremental substraction of C resulting from degradation of residues at the exposure site)

This is mathematically stated as:

$$\frac{dC}{dt} = \frac{F}{M} - kC \quad (4\text{-}52)$$

where:

C = the exposure site soil concentration, mg/kg
F = deposition rate of contaminant on particles, mg/yr
M = mass of soil at exposure site into which contaminant mixes, kg
k = first order dissipation rate constant, 1/yr.

The solution to this equation is:

$$C = \frac{F}{kM} \left(1 - e^{-kt} \right) \quad (4\text{-}53)$$

which computes C as function of time, t. Similar to the assumption made above in Section 4.3.2, the steady state solution for C is simply F/kM. The deposition rates supplied by the ISCST3 model are in units of g/m^2-yr, so a conversion to mg/yr requires a multiplication by the land area of the exposure site and a multiplication of 1000 mg/g. Procedures to estimate M are given above in Section 4.3.2.

4.4.2 Surface Water Impacts

The solution for stack emission impacts to surface water bodies is an extension of the solution for the soil contamination source category described in Section 4.3.1. Stack emissions deposit onto soils within the effective drainage area to result in an average basin-wide soil concentration. Soil erosion then delivers contaminants to surface waters as in Section 4.3.1. Stack emissions also directly deposit onto and impact the surface water body as well. All the assumptions laid out at the beginning of Section 4.3.1 apply here as well. New quantities needed for this solution include: a rate of contaminant deposition onto soils of the effective drainage area used to estimate average soil concentrations (such concentrations are estimated using the

approach given in Section 4.4.1. above), a rate of contaminant deposition onto the water body, and a rate of particulate matter deposition onto the water body.

Equations (4-1) through (4-8) are now displayed again with these additions.

$$C_{swb}\ ER_w + DEP_c = C_{wat}\ V_{wat} + C_{ssed}\ M_{ssed} + C_{sed}\ M_{sed} \quad (4\text{-}54)$$

where:

C_{swb} = concentration on soil entering water body, mg/kg
ER_w = total watershed annual soil erosion, kg/yr
DEP_c = total annual direct deposition of contaminant, mg/yr
C_{wat} = dissolved-phase concentration in water column, mg/L
V_{wat} = water body annual volume, L/yr
C_{ssed} = concentration on suspended sediment, mg/kg
M_{ssed} = mass of suspended sediment introduced per year, kg/yr
C_{sed} = concentration on sediment settling to bottom, mg/kg
M_{sed} = mass of bottom sediment introduced per year, kg/yr

Mass balance and equilibrium equations continue:

$$ER_w + DEP_p = M_{ssed} + M_{sed} \quad (4\text{-}55)$$

$$M_{ssed} = f_s\ ER_w + f_{sd}\ DEP_p \quad (4\text{-}56)$$

$$M_{sed} = (1 - f_s)\ ER_w + (1 - f_{sd})\ DEP_p \quad (4\text{-}57)$$

$$C_{wat} = \frac{C_{ssed}}{KD_{ssed}} \quad (4\text{-}58)$$

$$C_{sed} = C_{ssed} \frac{OC_{sed}}{OC_{ssed}} \quad (4\text{-}59)$$

where:

DEP_p = total annual direct deposition of particulate matter, kg/yr
f_s = fraction of annual erosion remaining as suspended materials, unitless
f_{sd} = fraction of annual deposition remaining as suspended material, unitless
Kd_{ssed} = soil-water partition coefficient for contaminant in suspended sediment, L/kg
OC_{ssed} = fraction organic carbon in suspended sediment, unitless
OC_{sed} = fraction organic carbon in bottom sediment, unitless

Substituting again as in Equation (4-7):

$$C_{swb}\ ER_w + DEP_c = C_{ssed} \left[\frac{V_{wat}}{Kd_{ssed}} + f_s\ ER_w + f_{sd}\ DEP_p + \frac{OC_{sed}}{OC_{ssed}} \right.$$

$$\left. \left[(1 - f_s)\ ER_w + (1 - f_{sd})\ DEP_p \right] \right] \quad (4\text{-}60)$$

As before, the bracketed quantity in the right hand side of Equation (4-60) can be termed ϕ, so that C_{ssed} can be solved as $(C_{swb}\ ER_w + DEP_c)/\phi$. The numerator in this term can be expanded to describe contaminant contributions by the effective drainage area which has received depositions, the first quantity in the numerator, and to describe direct depositions, the second quantity:

$$C_{swb}\ ER_w + DEP_c = C_w\ SL_w\ A_w\ E\ SD_w + RDEP_c\ A_{wat}\ 1000 \quad (4\text{-}61)$$

where:

C_{swb} = concentration on soil entering water body, mg/kg
ER_w = total watershed erosion, kg/yr
DEP_c = annual deposition of contaminant on water body, mg/yr

E	=	enrichment ratio, unitless
C_w	=	average soil concentration of dioxin-like compound in effective area of watershed, mg/kg
SL_w	=	average unit soil loss for land area within watershed, kg/ha-yr
A_w	=	effective drainage area of watershed, ha
SD_w	=	sediment delivery ratio for watershed, unitless
$RDEP_c$	=	rate of contaminant deposition, g/m^2-yr
A_{wat}	=	area of water body, m^2
1000	=	converts g to mg

Again as before, the right hand side of Equation (4-61) can be termed, ρ, and the concentration in suspended sediment, C_{ssed}, is equal to ρ/ϕ. Other water body concentration terms, C_{wat} and C_{sed}, can now be solved using Equations (4-58) and (4-59). Guidance on these terms and assignment of values for the demonstration scenarios in Chapter 5 is now given.

- **C_{swb} and ER_w:** Equation (4-61) shows all the terms necessary to arrive at an estimate of the annual contaminant entry into the water body via erosion, the C_{swb} * ER_w term. Section 4.4.1 describes the algorithm to estimate soil concentrations given a deposition rate of contaminant. One deposition rate will be chosen to represent average deposition rates over the effective drainage area of the watershed (the effective drainage area is termed A_w). This rate will be the rate given in ISCST3 modeling at 5.0 kilometers. Tables 3-15 and 3-16 (Chapter 3) display wet and dry deposition rates for this distance. These rates are added to arrive at total deposition, shown in Table 3-17. Second, a representative mixing depth to characterize average watershed soil concentrations needs to be selected. Previous algorithms used a mixing depth of 20 cm for tillage activities, specifically home gardening, and 2 cm for non-tilled soil concentrations. For the sake of demonstration, it will be assumed that a representative watershed depth will equal 10 cm, which might be interpreted as an average of tilled and untilled lands within the effective drainage area. The values for SL_w (6455 kg/ha-yr), A_w (100,000 ha), ER (3), and SD_w (0.06) were all given and discussed in Section 4.3.1. and will not be repeated here.

- **DEP_c:** The second quantity of Equation (4-61) describes the annual input to the surface water body that comes from direct deposition. This term is $RDEP_c$ * A_{wat} * 1000, where $RDEP_c$ is the rate of contaminant deposition onto the water body (g/m^2-yr) , A_{wat} is the area of the water body (m^2) , and 1000 converts g to mg. The rate of contaminant deposition at 5 km will

also be used to describe direct deposition impact to the surface water body. Depositions nearer to the emission source will be greater and depositions further from the emission source will be less. The area of the water body has not been required for any other reason, and one will now be given. First, the effective drainage area of 100,000 ha is reasonably large and has resulted in a river with an annual flow volume of $4.8*10^{11}$ L/yr ($4.8*10^{8}$ m^3/yr). This volume is also equal to the average cross sectional area of the river (m^2) times stream velocity (m/yr). Assuming a stream velocity of $4.73 * 10^{6}$ m/yr (15 cm/sec; ½ ft/sec), which is reasonable for a river, the cross sectional area is solved as 100 m^2. An average 5 m depth and 20 m width appear reasonable. This width times the stream length would give stream surface area, A_{wat}. Assuming a rectangular shaped watershed, dimensions of 500 ha wide by 2,000 ha long (to arrive at the 100,000 ha effective drainage) seem reasonable. This length of 2,000 ha translates to 200,000 meters, and the full surface area of the stream is $4*10^{6}$ m^2. This will be the value assumed for A_{wat}.

- **DEP_p:** The rate of particulate deposition onto the lake is required to achieve a mass balance of all annual soil erosion + particle deposition contributions to water body solids. The rate of particulate matter emitting from the stack and arriving at downwind locations was not supplied in Chapter 3. Goeden and Smith (1989) modeled the impacts of a resource recovery facility to a local water body. In their analysis, they assumed that the stack emitted 4.63 g/s particulate matter and that the annual deposition of stack-emitted particulate matter to the nearby impacted water body was 0.03 g/m^2-yr. This deposition rate will be adopted for this assessment. Now, with the surface area as solved for above at $2*10^{6}$ m^2, the total particle deposition, $DEP_{p,}$ is 60 kg/yr.

- **f_s and f_{sd}:** These are the fractions of total erosion and depositing particles remaining as suspended materials within a year. As discussed in the solution for the contaminated soil source category in Section 4.3.1, f_s was solved for as: a value for total suspended solid, TSS of 10 mg/L, multiplied by a total flow volume V_{wat} of 4.8×10^{11} L/yr, divided by the total erosion into the water body, $1.29*10^{7}$ kg/yr. This resulted in an f_s of 0.36. Note that this implies a total suspended load of 480,000 kg/yr. It could be assumed that the minuscule 60 kg/yr of particles directly depositing onto the stream remain in suspension during the year, on the basis of being smaller in size than eroded soil. This assumption will, in fact, be made, but it will be supported as follows.

In a quiescent water body, settling occurs through gravity and can be expressed in terms of Stokes Law:

$$V_s = (g / 18\mu) (\rho_s - \rho) d^2 \quad (4\text{-}62)$$

where:

V_s	=	Stokes settling velocity, cm/sec
g	=	acceleration of gravity, 980 cm/sec^2
μ	=	absolute viscosity of water, g/cm-sec (poise)
	=	0.089 g/cm-sec @ 25 C
ρ_s	=	particle density, g/cm^3
ρ	=	density of water, 1 g/cm^3
d	=	particle diameter, cm

For purposes of this discussion, a reasonable assignment of particle density of is 2.5 g/cm^3 for depositing particles or eroding soil. Therefore, making substitutions, the right hand side of Equation (4-62) reduces to 918 d^2.

Now, assumptions for the particle sizes of eroding soil and depositing particles can be made to arrive at a ratio of settling velocities, V_{ssoil}/V_{spart}. The basis for assigning an enrichment ratio for delivery of contaminants via soil erosion was that fine-sized particles were the ones eventually reaching the water body via erosion. Lick (1982) states that a major fraction of the sediments (suspended and bottom) in the Great Lakes are fine grained, silts and clays, and that data from Lake Erie indicates that 90% of the sediments are of this category. Brady (1984) shows USDA's classification of soils according to particle size, and gives a range of 0.0002 to 0.005 cm for silt sized particles and less than 0.0002 for clay size particles. The following assumptions are made to arrive at a representative diameter for particles in eroded soil: eroded soil is comprised of a 50/50 split of these two sized particles, silt-sized particles are, on the average 0.0026 cm in diameter, and clay size particles are 0.0001 cm in diameter. With these assumptions, the average particle size for eroding soil is 0.0014 cm. The settling velocity for a 0.0014 cm particle is 1.8 x 10^{-3} cm/sec. In Section 3.4.3, Chapter 3, the argument was developed that 87.5% of the total emission rate of dioxin-like congeners would be associated with particles less than 2 μm. The basis of this argument was a surface area to volume ratio, with smaller particle sizes having significantly larger ratios. This does not mean that 87.5% of the 1 kg/yr depositing particles are of this size. However, for this discussion, the size of depositing particles will be assumed to be 2 μm (2 x 10^{-4} cm), since these size particles deliver most of the dioxin-like compounds to the water body (and the ultimate purpose of this exercise is to determine a

value for the fraction of depositing particles which remain suspended and impact suspended sediment concentrations). The settling velocity, V_{spart}, is estimated as 3.7×10^{-5} cm/sec.

The ratio V_{ssoil}/V_{spart} is about 50. Said another way and with all the assumptions and simplifications made above, depositing particles will remain in suspension 50 times longer than eroding soil in a quiescent water body.

Given this high a difference in settling velocities, it seems reasonable to assume f_{sb} equals 1.0. The fraction of soil erosion remaining in suspension, f_s, will be estimated given TSS, V_{wat}, etc., as before (see Section 4.3.1), only DEP_p (the total amount of depositing particles, in kg/yr) will comprise a given increment of suspended materials when solving for f_s.

- **V_{wat}, OC_{ssed}, OC_{sed}, and Kd_{ssed}:** These have all been discussed in Section 4.3.1. The values for these parameters in the demonstration scenarios in Chapter 5 are: $V_{wat} = 4.8 \times 10^{11}$ L/yr, $OC_{ssed} = 0.05$, $OC_{sed} = 0.03$, and $Kd_{ssed} = OC_{sed} * Koc$, where Koc is the organic partition coefficient of the contaminant.

4.5. ALGORITHMS FOR THE EFFLUENT DISCHARGE SOURCE CATEGORY

Dioxin-like compounds can be released to waterways via various types of effluent discharges such as discharges from municipal waste water treatment facilities and pulp and paper mills using chlorine bleaching. These emissions have declined substantially in recent years, especially from pulp and paper mills. Since the procedures for considering point source discharges to waterways are somewhat different than those associated with the nonpoint source procedures for soil contamination and stack emissions, they are covered separately in this section. This source category is also different from others in that effluent discharges into surface water bodies are assumed only to impact fish and water.

The approach used in this report is an extension of the "simple dilution" model described in the Superfund Exposure Assessment Manual (EPA, 1988c). Other models are available which offer more spatial and temporal resolution than the model described here. One such model is the EXposure Analysis Modeling System, or EXAMS (Burns, et al., 1982, and Burns and Cline, 1985). The EXAMS and a simple dilution model were both applied in an assessment of effluent discharges from pulp and paper mills (EPA, 1990d). In this assessment, 98 of the 104 pulp and paper mills were modeled with both models using site-specific information (water body flow rates from STORET for all but 6 of the mills, effluent flow rates and contaminant discharges, etc.). Three key quantities - one model result and two model parameters - led to a range of exposure conditions for humans consuming fish impacted by discharges from these pulp and

paper mills: a water column concentration, a bioconcentration factor (BCF) applied to the water column concentration to get fish tissue concentration, and a fish ingestion rate. The simple dilution model was used to estimate total water concentrations - i.e., mg TCDD total/L water. The EXAMS model was used to estimate dissolved phase water column concentration - i.e., mg TCDD dissolved in water column/L water. Then, with each set of water concentrations, two sets of exposure estimates (a low and a high estimate, in one sense) were generated - one with a BCF of 5,000 and a fish ingestion rate of 6.5 g/day, and one with a BCF of 50,000 and a fish ingestion rate of 30 g/day. Note that in deriving the range of results in that exercise, the BCF was applied to both a total and a dissolved phase water concentrations. EPA (1993b) and EPA (1995) discuss several bioconcentration/bioaccumulation empirical parameters for 2,3,7,8-TCDD, and makes the clear distinction for those which are to be applied to a total water concentration versus those applied to a concentration in the dissolved phase. The dilution and EXAMS model study indicated that the simple dilution model generally estimated higher water column contaminant concentrations compared to the EXAMS model, although this trend was not consistent among all water bodies modeled. The results from both models were comparable when the receiving water body had relatively low suspended solids concentration.

One key limitation of the EXAMS and the simple dilution model for use with dioxin-like compounds in aquatic systems is that they do not account for sediment transport processes. The EXAMS model was designed to determine the fate of transport of contaminants in the dissolved phase. Another spatially and temporally resolved model for this source category is the Water Analysis Simulation Package, the most up-to-date version termed WASP4 (Ambrose, et al., 1988). This model does include sediment processes and has been applied in a comprehensive evaluation of 2,3,7,8-TCDD bioaccumulation in Lake Ontario (EPA, 1990b). It requires extensive site-specific parameterization, but should be considered for more detailed site-specific evaluations of strongly hydrophobic and bioaccumulating contaminants such as the dioxin-like compounds.

The dilution model described below will be demonstrated in Chapter 5 with a set of data developed using site-specific data from the 104 pulp and paper mills of the 104-mill study. As will be discussed below, a hypothetical effluent discharge will have characteristics developed as the average of key characteristics from the 104 mill study. These key data include: flow rates of the receiving water bodies, suspended solids concentration in these receiving water bodies, effluent discharge flow rates, suspended solids in the effluent discharges, organic carbon content of solids in the effluent stream, and discharges of 2,3,7,8-TCDD.

4.5.1. The Simple Dilution Model

The principal assumption for the simple dilution model is that contaminants released into a water body uniformly mix and equilibrate with the surrounding water in an area near the effluent discharge point. This area is commonly referred to as a "mixing zone". For application of this model with dioxin-like compounds, what is desired is a concentration on the suspended solids in this mixing zone. Multiplication of the organic carbon normalized concentration on suspended solids and a Biota Suspended Solids Accumulation Factor, or BSSAF, will result in a concentration of contaminant in fish lipids. This is defined similarly to the BSAF used for other source categories of this assessment, except that the organic carbon normalized concentration is that of suspended solids rather than of bottom sediments.

The BSSAF is one of several empirical factors discussed for estimating the impact to fish in water bodies impacted by 2,3,7,8-TCDD (EPA, 1993b). Others include the BSAF, total and dissolved phase bioconcentration factors (BCFs), and total and dissolved phase bioaccumulation factors (BAFs). BAFs and similar to BSAFs and BSSAFs in that all three reflect total exposure of fish to contaminant, including water column, sediment, and food chain exposures. The BCFs reflect water column exposures only. EPA (1993b) states that there is currently no data available on organic carbon normalized concentrations of dioxin-like compounds on suspended solids, hence no basis to compare BSAF and BSSAF. This assessment assumes a similar numerical assignment of BSSAFs and BSAFs.

The total water concentration in a simple dilution model is:

$$C_{tot} = \frac{MASS_c}{Q_e + Q_u} \qquad (4\text{-}63)$$

where:

C_{tot} = total water concentration, mg/L
$MASS_c$ = mass of contaminant in discharge, mg/hr
Q_u = harmonic mean flow at a point just upstream of effluent discharge, L/hr
Q_e = effluent flow, L/hr

Dissolved phase and suspended sediment concentrations are then estimated using an approach developed by Mills, et al. (1985) and others:

$$C_{wat} = \frac{C_{tot}}{1 + (Kd_{mix} \; TSS_{mix} \; 10^{-6})} \quad (4\text{-}64)$$

$$C_{ssed} = Kd_{mix} \; C_{wat} \quad (4\text{-}65)$$

where:

C_{wat}	=	dissolved-phase water concentration of contaminant, mg/L
C_{tot}	=	total water column concentration, sorbed + dissolved, mg/kg (note: mg/kg is essentially equal to mg/L since 1 L ≈ 1 kg)
Kd_{mix}	=	suspended sediment-water partition coefficient for contaminant in mixing zone, L/kg
TSS_{mix}	=	total suspended solids in water column in mixing zone, mg/L
C_{ssed}	=	concentration of dioxin-like compounds on suspended sediments, mg/kg
10^{-6}	=	converts mg/L to kg/L

The total suspended solids concentration in the mixing zone is a function of the suspended solids just upstream of the discharge point and the suspended solids introduced in the effluent stream:

$$TSS_{mix} = \frac{TSS_u \; Q_u + TSS_e \; Q_e}{Q_u + Q_e} \quad (4\text{-}66)$$

where:

TSS_{mix}	=	adjusted total suspended solids concentration, mg/L
TSS_u	=	total suspended solids concentration at a point just upstream of effluent discharge, mg/L
TSS_e	=	total suspended solids concentration in effluent discharge, mg/L
Q_u,Q_e	=	upstream harmonic mean flow and effluent discharge flow rates, L/hr

The suspended solids partition coefficient in the mixing zone is a function of the organic carbon partition coefficient of the contaminant and the organic carbon fraction of suspended solids:

$$Kd_{mix} = Koc\ OC_{mix} \quad (4\text{-}67)$$

where:

Kd_{mix} = suspended sediment-water partition coefficient in the mixing zone, L/kg
Koc = compound specific organic carbon partition coefficient, L/kg
OC_{mix} = organic carbon content of suspended sediments in the mixing zone, unitless

This organic carbon content can be solved as the weighted average concentrations of the organic carbon contents of the suspended solids in the effluent discharge and the suspended solids of the receiving water body:

$$OC_{mix} = \frac{TSS_u\ Q_u\ OC_u + TSS_e\ Q_e\ OC_e}{TSS_u\ Q_u + TSS_e\ Q_e} \quad (4\text{-}68)$$

where:

OC_{mix} = organic carbon content of suspended solids in mixing zone, unitless
TSS_u = total suspended solids concentration at a point just upstream of effluent discharge, mg/L
TSS_e = total suspended solids concentration in effluent discharge, mg/L
Q_u,Q_e = upstream harmonic mean flow and effluent discharge flow rates, L/hr
OC_u, OC_e = organic carbon contents of suspended solids upstream of the discharge point and within effluent discharge stream

Fish lipid concentrations for this solution are then given as:

$$C_{lipid} = BSSAF \frac{C_{ssed}}{OC_{mix}} \quad (4\text{-}69)$$

where:

C_{lipid}	=	fish lipid concentration, mg/kg
BSSAF	=	biota suspended solids accumulation factor, unitless
C_{ssed}	=	concentration of dioxin-like compounds on suspended sediments, mg/kg
OC_{mix}	=	organic carbon content of suspended sediments, unitless

Finally, whole fish concentrations are simply this lipid concentrations times a fraction of fish lipid, or $C_{lipid} * f_{lipid}$.

The harmonic mean flow, Q_e, is distinct from the long term average flow. To understand the difference, the following discussion is offered. Assume, for this discussion, that the effluent flow, Q_e, is much lower than the receiving water body flow, Q_i, and therefore it can be neglected. The daily average total water concentration to which a fish is exposed, C_i, is then a function of the daily mass of chemical released, $MASS_i$, divided by the average flow for that day, Q_i:

$$C_i = \frac{MASS_i}{Q_i} \quad (4\text{-}70)$$

Bioconcentration factors are multiplied by an average concentration, C_{avg}, over n days. Assuming the loading is constant, $MASS_i$ = MASS, then the average concentration is given as:

$$C_{avg} = \frac{1}{n} \Sigma \frac{MASS}{Q_i} \quad (4\text{-}71)$$

This is equivalent to:

$$C_{avg} = \frac{MASS}{Q_H} \quad (4\text{-}72)$$

where Q_H is the harmonic mean flow defined by:

$$\frac{1}{Q_H} = \frac{1}{n} \Sigma \frac{1}{Q_i} \quad (4\text{-}73)$$

This is different from the arithmetic average flow, Q_{avg} (i.e., mean flow):

$$Q_{avg} = \frac{1}{n} \Sigma Q_i \quad (4\text{-}74)$$

To see how these numbers would differ, consider 10 daily average flows of 1, 1, 1, 1, 2, 2, 3, 4, 7, 10. The Q_H is calculated as 1.72, whereas the Q_{avg} is calculated as 3.20. The difference is further illustrated by considering the effect on the calculation of the concentration to which one would apply the bioconcentration factor. If the daily load were 10.0, then the sequence of water concentrations would be 10, 10, 10, 10, 5, 5, 3.3, 2, 1.4, and 1. The average concentration is 5.77, and this is the appropriate concentration to use with a bioconcentration factor. If the daily load of ten were divided by the Q_H of 1.72, one would arrive at this correct concentration, but if the daily load were divided by the average flow of 3.2, the incorrectly calculated average concentration would be 3.1.

The key model parameter for the effluent discharge model is the BSSAF. A value of 0.09 for 2,3,7,8-TCDD was assumed for BSAF based on data from Lake Ontario. One important difference between the Lake Ontario ecosystem and the effluent discharge source category is that the impact to Lake Ontario is thought to be principally historical (EPA, 1990b), while for the effluent source category, the impact is, by definition, ongoing. This difference may translate to differences in assignment of BSSAF as compared to BSAF. Consider two aquatic settings where bottom sediments are found to have equal concentrations of dioxin-like compounds - one in

which contamination is ongoing and one in which contamination is primarily in the past. For the aquatic setting where contamination occurred in the past, water column and suspended sediment concentrations would be lower as compared to the aquatic setting where contamination is ongoing, because water column impacts are only a function of depuration of bottom sediments for the historically impacted water body. It is certainly arguable that exposure of aquatic organisms is greater in the ecosystem where impacts are ongoing, as compared to a system where impacts are historical, when bottom sediment concentrations are equal in the two systems. Now recall the assumption made for the soil contamination and stack emission source categories (in both cases the water body impact is ongoing) concerning the relationship between suspended and bottom sediments - that the organic carbon normalized concentrations are equal. If this is a valid assumption for a system with ongoing impacts, and if in fact fish are relatively more exposed when impacts are ongoing rather than historical, then this argues that a BSSAF for an ongoing contamination setting should be greater in numerical value than a BSAF for a setting where contamination was historical.

However, no data could be found to support such a hypothesis, and there would be no numerical basis for an assumed difference between BSAF and BSSAF. For this reason, the values assumed for BSSAF and BSAF are equal for this assessment. It should be noted that all bioconcentration or biotransfer parameters, such as the BSSAF, are qualified as second order defaults for purposes of general use. Section 6.2. of Chapter 6 discusses the use of parameter values selected for the demonstration scenarios, including a categorization of parameters. Second order defaults are defined there as parameters which are theoretical and not site specific, but whose values are uncertain in the published literature. The parameter values in this category should be considered carefully by users of the methodology.

The effluent discharge solution algorithm was evaluated using data and information from the 104 pulp and paper mill study (EPA, 1990c), which measured discharges of 2,3,7,8-TCDD from 104 mills in 1988, and from the National Study of Chemical Residues in Fish (NSCRF; EPA, 1992a), which measured fish tissue concentrations of 2,3,7,8-TCDD at points downstream from several of these mils. A third modeling study (EPA, 1990d) collected critical data for this modeling evaluation, such as harmonic mean flows downstream of the mills. Finally, the National Council for Air and Stream Improvement (NCASI) provided details on their assessment of this data, which was used here. Importantly, this information included linking specific fish samples to specific mills. A full description of this modeling evaluation is in Chapter 7, Section 7.2.3.6.

There was a dichotomy of model performance as a function of the size of the receiving water body. For most of the mills, the receiving water bodies had harmonic mean flows around 10^8 L/hr, with a range of 10^7 to 10^9 L/hr. A small number of mills, however, discharged into more substantial receiving water bodies which had an average flow of 5×10^{10} L/hr. Comparing model predictions of fish tissue concentrations for mills discharging into the smaller water bodies, it was found that the model tended to underpredict fish tissue concentrations - the average predicted whole fish concentration was near 7 ppt, whereas the average observed whole fish concentration was near 15 ppt. The same was not true for the large receiving water bodies. In that case, the average whole fish tissue concentration observed was an order of magnitude or more higher than predicted whole fish concentration. No precise explanation could be given for this result. The most likely explanation is that, for these large water bodies, there were other sources of dioxin releases. This comparative exercise did assume inherently that the effluent discharge was the sole source of fish tissue concentrations of 2,3,7,8-TCDD.

It was noted that, for the smaller receiving water bodies, an increase in the assumed BSSAF of 0.09 (which was the value of BSAF assumed otherwise in this assessment) to 0.20 resulted in an average model prediction of fish tissue concentration of near 15 ppt, essentially the same as the observed fish concentration. This could be some empirical evidence for the argument developed above - that the BSSAF for a system with ongoing impacts should be greater in numerical value than a BSAF developed from data on an ecosystem where impacts were primarily historical.

In any case, parameters for the demonstration scenario in Chapter 5 for this source category were derived from 104-mill data. Data from only 77 of the mills was used for the following parameter developments. Mills not included are: 1) the ten mills discharging into the largest water bodies, 2) 9 mills for which EPA (1990d) was unable to derive harmonic mean flows from STORET data, and 3) 8 mills for which data on total suspended solids content in the effluent stream was unavailable from EPA (1990c; actually 11 mills did not suspended solids data, but three were in other categories deleted).

Values of model parameters for the demonstration are now summarized:

- **TSS_u, TSS_e:** The average upstream total suspended solids term from the 77 mills, TSS_u, was 9.5 mg/L. The average suspended solids concentration within the effluent streams from the 77 mills was 70 mg/L.

- **OC_u, OC_e:** No information was available on the organic carbon content of the suspended solids upstream of the effluent discharge point. A value of 0.05 was assigned, which was the value assigned for other source categories. No data as well could be found for the

organic carbon content of the effluent solids. However, such solids are essentially biosolids from biological treatments of mill sludges. The organic carbon content of such solids is expected to be much higher than 0.05. The value recommended for OC_e was 0.36 (Steven Hinton, PhD., P.E., National Council of the Paper Industry for Air and Stream Improvement, Inc.; Department of Civil Engineering, Tufts University, Medford, MA 02155). This was based on an average proportion of carbon in algal biomass of 0.36 given in Morel (1983).

- **Q_u, Q_e:** Flow values for the receiving water and effluent stream were summarized in EPA (1990d). The average effluent flow rate, Q_e, for the 77 mills was $4.10 * 10^6$ L/hr, and the average harmonic mean flow for the receiving water body, Q_u, was $4.65 * 10^8$ L/hr.

- **Koc, BSSAF, f_{lipid}:** Values of Koc and f_{lipid} are the same ones which have been used for the other source categories. As discussed in the introduction to this section, the Biota Suspended Solids Accumulation Factor, BSSAF, will be assumed to be the same as the Biota Sediment Accumulation, BSAF. This value is 0.09 for 2,3,7,8-TCDD.

- **$MASS_c$:** The mass of 2,3,7,8-TCDD exiting from the 77 mills averaged 0.197 mg/hr. However, this data was pertinent for 1988. Since then, pulp and paper mills have reduced the discharge of dioxin-like compounds in their effluents by altering the pulp bleaching processes. Gillespie (1992) reports that data on effluent quality from all 104 mills demonstrate reductions in discharges of 2,3,7,8-TCDD of 84%. On this basis, the value of $MASS_c$ for all three example compounds will be 0.0315 mg/hr (16% of 0.197 mg/hr).

Using these parameters in the simple dilution model for 2,3,7,8-TCDD results in the following:

1) If the mass loadings of 2,3,7,8-TCDD are assumed to be fully sorbed to solids in the effluent discharge, and not to exist in the soluble phase in the discharge, than the concentration of 2,3,7,8-TCDD on discharging effluent solids is $1.1*10^{-4}$ mg/kg, or 110 ppt.

2) The total suspended solids concentration in the mixing zone, TSS_{mix}, equals 10.0 mg/L. The organic carbon content of suspended solids in the mixing zone, OC_{mix}, is estimated as 0.069. It is seen how the effluent discharge influences these two key quantities: the unadjusted TSS_u was given as 9.5 mg/L, and the unadjusted OC_u was 0.05.

3) The overall suspended solids concentration of 2,3,7,8-TCDD in the mixing zone after mixing and equilibrating with surrounding water, C_{ssed}, was 4.5 ppt. This compares to the concentration that might be on the effluent solids of 110 ppt, indicating more than an order of magnitude reduction in concentration by mixing with solids of the receiving water body, and partitioning into the water column.

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Table 4-1. Available Biota to Sediment Accumulation Factors, BSAF, for dioxin-like compounds.

Reference/Congener	Fish Species	Water Body	# Sed. Samples # Fish Samples	BSAF	Comments
Kuehl, et al., 1987	Carp	Wisconsin River	1/1		Laboratory flow through experiment using Wisconsin River sediment and Lake Superior water; BSAFs determined from one "representative" sediment sample and one "composited" fish sample; sediment organic carbon and fish lipid contents given in article; no other details provided.
2378-TCDD				0.27	
2378-TCDF				0.06	
12378-PCDD				0.06	
1234/678-HxCDD				0.035	
123678-HxCDF				0.037	
1234678-HpCDD				0.0048	
1234678-HpCDF				0.0033	
US EPA, 1990b		Lake Ontario			Comprehensive field study on bioaccumulation of 2378-TCDD in Lake Ontario; BSAFs are estimated given 55 sediment samples and specific number of fish samples as noted; report evaluates matching fish with sediment data from sites where fish were caught
2378-TCDD	Brown Trout		55/81	0.03	
2378-TCDD	Lake Trout		55/81	0.07	
2378-TCDD	Smallmouth Bass		55/14	0.05	
2378-TCDD	White Perch		55/38	0.20	
2378-TCDD	Yellow Perch		55/77	0.03	
Parkerton, 1991		Passaic River			7 "resident" fish species were best represented by carp; "migratory" species were eel and striped bass; TCDD contamination attributed to historical industrial input, particularly a 2,4,5-T plant operation from 1940s to 60s.
2378-TCDD	Resident Fish		61/11	0.081	
2378-TCDD	Migratory fish		61/15	0.009	
2378-TCDD	Blue Crab		61/14	0.055	

Table 4-1. (Cont'd)

Reference/Congener	Fish Species	Water Body	# Sed. Samples # Fish Samples	BSAF	Comments
Kjeller, et al, 1990	Pike	Lake Vanern			Results presented at right derived from data in Kjeller, et al (1990); data includes sediment samples from four sites in Lake Vanern and 6 composited (2-5 fish in composite) pike associated with the four sites; pike concentrations reported in article on a lipid basis; Lake Vanern is near a paper mill.
2378-TCDD			4/6	2.94	
12378-PCDD			4/6	1.03	
123478-HxCDD			4/6	0.17	
123678-HxCDD			4/6	0.086	
123789-HxCDD			4/6	0.018	
OCDD			4/6	0.002	
2378-TCDF			4/6	1.40	
1234/78-PCDF			4/6	0.25	
23478-HxCDF			4/6	0.71	
123478/9-HxCDF			4/6	0.036	
123678-HxCDF			4/6	0.065	
123789-HxCDF			4/6	0.27	
234678-HxCDF			4/6	0.047	
1234678-HpCDF			4/6	0.0009	
1234789-HpCDF			4/6	0.023	
1234678-HpCDF			4/6	0.006	
OCDF			4/6	0.0001	

Table 4-1. (Cont'd)

Reference/Congener	Fish Species	Water Body	# Sed. Samples # Fish Samples	BSAF	Comments
US EPA, 1993b		different bodies	NA		Results compiled in EPA (1993) for 2378-TCDD; details found in these studies:
2378-TCDD	Smelt			0.04	Batterman, et al. (1989)
2378-TCDD	Sculpin			0.12	Batterman, et al. (1989)
2378-TCDD	Herring Gull			0.43	EPA (1990b) and Braune, Norstrom (1989)
2378-TCDD	Bullhead			0.05	Cook (unpublished) as listed in EPA (1993b)
2378-TCDD	Sandworm			0.48	Rubinstein, et al. (1983)
2378-TCDD	Clam			0.93	Rubinstein, et al. (1983)
2378-TCDD	Shrimp			0.73	Rubinstein, et al. (1983)
CDEP, 1992	See "Comment"	23 different bodies			Data supplied by Connecticut DEP; complete data description in Chapter 7 of this assessment; study designed to evaluate newly operating resource recover facilities. BSAFs are calculated based on 521 fish samples including the species: carp, channel catfish, white catfish, white sucker, brown bullhead, yellow perch
2378-TCDD			346/521	0.86	
2378-TCDF			346/521	0.25	
23478-PCDF			346/521	0.47	
I- TEQ			346/521	0.24	

Table 4-1. (Cont'd)

Reference/Congener	Fish Species	Water Body	# Sed. Samples # Fish Samples	BSAF	BEF	Comments
US EPA, 1995	Lake Trout	Lake Ontario	NA			EPA (1995) claims that the Lake Ontario data from EPA (1990b) was reanalyzed for the suite of dioxin-like congeners. It is not clear why the 2378-TCDD for lake trout was 0.059 in this study but listed as 0.07 for lake trout in EPA (1990b). It is also not clear how many samples of fish and sediment were reanalyzed for the data on the right. Also listed to the left are the "bioequivalency factors", or BEFs, as listed in EPA (1995) and as developed from this data set. See text for more detail.
2378-TCDD				0.059	1.00	
12378-PCDD				0.054	0.92	
123478-HxCDD				0.018	0.31	
123678-HxCDD				0.0073	0.12	
123489-HxCDD				0.0081	0.14	
1234678-HpCDD				0.0031	0.051	
OCDD				.00074	0.012	
2378-TCDF				0.047	0.80	
12378-PCDF				0.013	0.22	
23478-PCDF				0.095	1.6	
123478-HxCDF				0.0045	0.076	
123678-HxCDF				0.011	0.19	
123789-HxCDF				0.037	0.67	
234678-HxCDF				0.04	0.63	
1234678-HpCDF				.00065	0.011	
1234789-HpCDF				0.023	0.39	
OCDF				.00099	0.016	

Table 4-2. Available Biota to Sediment Accumulation Factors, BSAF, for PCBs.

Reference/Congener	Fish Species	Water Body	BSAF	Comments
EPA (1990b) PCB	trout, salmon, perch, bass	Lake Ontario	1.40, 0.77, 0.52, 0.86, 3.35, 1.42	These BSAF were compiled in EPA (1990b) from several data sources, years of study, and fish species. The summary provided was not specific in terms of BSAFs associated with specific fish species. It is assumed that "PCBs" described in EPA (1990b) meant "total PCBs". There was one BSAF of 0.58 derived in EPA (1990b) for Aroclor 1254
EPA (1995) Total PCBs PCB 105 PCB 118 PCB 156 PCB 180	Trout	Lake Ontario	 1.85 2.70 4.09 3.97 3.78	EPA (1995) used the data of Oliver and Niimi (1988) to derive the BSAFs listed for total PCBs and the PCB congeners. EPA (1995) also lists BSAFs for numerous other non-dioxin-like PCB congeners.
EPA (1995) PCB 77 PCB 105 PCB 118 PCB 126 PCB 167 PCB 180 PCB 189	Trout	Lake Ontario	 0.29 4.49 1.72 3.21 0.69 3.26 0.71	EPA (1995) derived these BSAFs based on their reanalysis of sediment and trout data from the original Lake Ontario study (1990b). EPA (1995) also lists BSAFs for numerous other non-dioxin-like PCB congeners.

Table 4-2. (cont'd)

Reference/Congener	Fish Species	Water Body	BSAF	Comments
EPA (1995) PCB 77 PCB 105 PCB 118 PCB 167 PCB 180 PCB 189	Brown Trout	Green Bay, WI	 4.12 5.35 4.96 16.0 10.96 3.45	EPA (1995) derived these BSAFs from data on lake trout from the Green Bay. The study from which these data came from was described as EPA's Green Bay/Fox River Mass Balance Study which involved extensive sampling of water, sediment and fish in 1989. No further citation was provided in EPA (1995) for this study.
Parkerton, et al (1993) trichloro-PCB tetrachloro-PCB pentachloro-PCB hexachloro-PCB heptachloro-PCB octachloro-PCB	lake trout, whitefish	Siskiwit Lake	 0.45-2.6 0.71-1.3 3.4-9.4 2.9-20.8 12.5 2.2-12.7	Compiled by Parkerton, et al. (1993) from data in Swackhammer, et al. (1988) and Swackhammer and Hites (1988); Parkerton presents data for individual congeners - summary at left aggregates by chlorination and includes both fish species; only one data point presented by heptachloro-PCB.
Parkerton, et al (1993) Total PCBs	Three species of marine fish	Rio de La Plata, Argentina	 4.40	Determined by Parkerton, et al (1993) from Columbo, et al (1990) on total PCBs. Columbo reference has data on PCBs 5-8, 14, 19, 28-31, 52, 101, 110, 138, 153, 180.

Table 4-2. (cont'd)

Reference/Congener	Fish Species	Water Body	BSAF	Comments
Parkerton, et al (1993)	flounder, lobster, crab	New Bedford Harbor		Compiled by Parkerton, et al. (1993) from data in BOS (1990); summary at left is the range of values for PCB congener groups, and averaged across the noted species.
dichloro-PCB			0.11-0.59	
trichloro-PCB			0.26-0.65	
tetrachloro-PCB			0.65-1.02	
pentachloro-PCB			1.05-2.08	
hexachloro-PCB			1.29-4.00	
heptachloro-PCB			0.84-2.74	
octachloro-PCB			0.23-1.17	
nonachloro-PCB			0.02-0.38	

Table 4-3. Data and parameters used to determine the part of the plant concentration which was due to the deposition of particle bound dioxins (see below table for definition of columns).

#1	#2	#3	#4	#5	#6	#7	#8
Cl_4DD	0.51/0.49 (0.90/0.10)	0.029	0.0141	0.007	0.13	0.123	94
Cl_5DD	0.13/0.87 (0.72/0.28)	0.029	0.0251	0.013	0.13	0.117	90
Cl_6DD	0.03/0.97 (0.55/0.45)	0.053	0.0513	0.027	0.14	0.113	81
Cl_7DD	0.01/0.99 (0.23/0.77)	0.088	0.0873	0.046	0.13	0.085	65
OCDD	0.002/0.998 (0.07/0.93)	0.163	0.1629	0.084	0.19	0.106	56
Cl_4DF	0.53/0.47 (0.91/0.09)	0.190	0.0887	0.046	0.63	0.584	93
Cl_5DF	0.20/0.80 (0.78/0.22)	0.104	0.0827	0.043	0.25	0.208	83
Cl_6DF	0.06/0.94 (0.52/0.48)	0.082	0.0766	0.040	0.15	0.110	74
Cl_7DF	0.02/0.98 (0.23/0.77)	0.057	0.0559	0.029	0.14	0.111	79
OCDF	0.002/0.998 (0.11/0.89)	0.026	0.0259	0.014	0.029	0.016	54

Column Definition:
#1 - Congener Group
#2 - Vapor/Particle Fractions. Ratios in parenthesis were the fractions measured in the 2-stage air sampling equipment. See text for more detail.
#3 - Total air concentration, pg/m^3
#4 - Particle bound air concentration, pg/m^3
#5 - Plant concentration calculated to be due to particle deposition, ng/kg fresh
#6 - Total plant concentration, ng/kg fresh
#7 - Plant concentration calculated to be due to vapor transfer, estimated as Column 6 - Column 5, ng/kg fresh
#8 - Percent of plant concentration due to vapor transfers.

Table 4-4. Development of the B_{vpa} using data of Welsch-Pausch, et al (1995) compared against the B_{vpa} as developed in EPA (1994) (see below table for column definitions).

# 1	# 2	# 3	# 4	# 5	# 6
Cl_4DD	94400	0.0149	$6.35*10^6$	$6.55*10^4$	$1.0*10^5$
Cl_5DD	90100	0.0039	$2.32*10^7$	$2.39*10^5$	$6.3*10^5$
Cl_6DD	87300	0.0017	$5.05*10^7$	$5.20*10^5$	$6.9*10^5$ - $2.3*10^6$
Cl_7DD	65200	0.00074	$8.83*10^8$	$9.10*10^6$	$1.0*10^7$
OCDD	81300	0.00036	$2.25*10^8$	$2.36*10^6$	$2.4*10^9$
Cl_4DF	450000	0.101	$4.44*10^6$	$4.57*10^4$	$1.5*10^5$
Cl_5DF	159000	0.0168	$9.47*10^6$	$9.75*10^4$	$3.8*10^5$ - $5.3*10^5$
Cl_6DF	84900	0.0054	$1.57*10^7$	$1.62*10^5$	$5.9*10^5$ - $1.4*10^6$
Cl_7DF	85400	0.00106	$8.05*10^8$	$8.30*10^6$	$6.8*10^5$
OCDF	12000	0.000054	$2.21*10^8$	$2.28*10^6$	$1.7*10^8$

Column Definitions:

#1 - Congener
#2 - Vapor phase volumetric grass concentration, pg/m^3
#3 - Vapor phase volumetric air concentration, pg/m^3
#4 - B_{vol} calculated from the data of Welsh-Pausch, et al (1995)
#5 - B_{vpa} calculated from the data of Welsh-Pausch, et al (1995)
#6 - B_{vpa} as developed in EPA (1994). These B_{vpa} were calculated for the individual dioxin-like congeners. Where a range is presented, such as for Cl_6DF, this was the range for the dioxin-like congeners in the congener group.

Table 4-5. Ratios of dioxins and furans in milk fat (MF) and body fat (BF) to concentrations in diets of farm animals.

Animal	Days	Compound	BF:Diet	MF:Diet	Reference
Goats	56	2378-TCDD	-	2.8	Arstilla et al. (1981)
Cows	21	2378-TCDD	-	4.4	Jensen & Hummel (1982)
Cows	70	123678-HxCDD 1234678-HpCDD OCDD	3.9 0.4 0.1	5.7 0.6 0.1	Firestone, et al (1979)
Steers	28	2378-TCDD	3.5	-	Jensen, et al (1981)
Heifers	160	123678-HxCDD 1234678-HpCDD OCDD 1234678-HpCDD OCDF	2.1 0.2 0.05 0.3 0.1	- - - - -	Parker, et al (1980)
Cow	92	2378-TCDD 12378-PCDD 123478-HxCDD 123678-HxCDD 123789-HxCDD 1234679-HpCDD 1234678-HpCDD OCDD 234/78-TCDF 1234/78-PCDF 23478-PCDF 123478/9-HxCDF 123678-HxCDF 234678-HxCDF 1234678-HpCDF 1234789-HpCDF OCDF I-TEQ	- - - - - - - - - - - - - - - - - -	5.76 5.55 2.69 2.32 2.99 0.27 0.48 0.69 1.25 0.97 4.13 3.12 2.67 2.37 0.55 1.32 0.27 3.33	McLachlan, et al. (1990)[1]

Table 4-5. (Cont'd)

Animal	Days	Compound	BF:Diet	MF:Diet	Reference
Cows 4 cows and three times during milking for each cow	 28, 42, 56	2378-TCDD 12378-PCDD 123478-HxCDD 123678-HxCDD 123789-HxCDD 1234678-HpCDD OCDD 23478-PCDF 123478-HxCDF 123678-HxCDF 234678-HxCDF 1234678-HpCDF 1234789-HpCDF OCDF		7.1 5.0 3.1 (3.6) 3.7 (3.2) 2.6 (2.2) 0.68 (0.3) 0.08 (0.05) 3.5 (3.5) 3.0 (1.1) 3.1 (2.2) 1.9 (1.6) 0.72 (0.3) 0.87 0.07 (0.01)	Fries, et al. (1999)[2]

[1] McLachlan, et al. (1990) was not a dosed feeding study; the single cow studied was given normal rationing. The first sample was taken Feb 16, 1989, two months after the last calving on Dec. 22, to maximize the possibility that steady state had been reached. The 92 days listed was from Dec. 22 until the last sample on Mar. 24.
[2]Fries, et al. (1999) were derived from a study where ground up PCP-treated wood was added to the cows' feed. Results are presented only for congeners where concentrations were above background for both milk and feed. Comparison with BCFs derived for other cows which were fed a normal diet (without PCP-treated wood) setting were comparable to the feeding experiment; these background BCFs are shown in parenthesis

Source: Fries and Paustenbach (1990), McLachlan, et al. (1990), and Fries, et al. (1999)

Table 4-6. Ratios of PCBs in milk fat (MF) and body fat (BF) to concentrations in diets of lactating cows[a].

Animal	Days	Compound	Concentration in diet, ppm	BF:diet	MF:diet	Reference and Comments
Lactating Cows	20	Aroclor 1254	12.1	-	3.1	Fries, et al (1973)
	40	Aroclor 1254	12.1	-	4.4	
	60	Aroclor 1254	12.1	3.4	4.8	
Lactating Cows	56					Tuinstra et al (1981), data is:
		dichloro-PCBs	0.05	-	0.4	average of 2 congeners
		tetrachloro-PCBs	0.001	-	5.9	one congener
		pentachloro-PCBs	0.003	-	1.2	average of 2 congeners
		hexachloro-PCBs	0.009	-	2.2	average of 7 congeners
		heptachloro-PCBs	0.010	-	2.3	average of 8 congeners
		octachloro-PCBs	0.005	-	3.8	average of 5 congeners
		nanochloro-PCBs	0.001	-	4.0	one congener
Lactating Cows	60	Aroclor 1254	0.51	2.8	3.7	Willett, et al. (1987)
	120	Aroclor 1254	2.82	2.4	3.9	values at left reflect different
	180	Aroclor 1254	18.97	3.7	4.8	average intake over 3 periods.
Lactating Cows	20	Aroclor 1254	2.56	-	1.2	Willett and Liu (1982)
Lactating Cows	32	Aroclor 1254	10.25	-	4.2	Perry, et al (1981)

[a] see text for full details of noted studies.

Table 4-7. BCFs for liver, adipose, thigh meat, and eggs calculated from the Cal-EPA experiments.

Congener	Low Exposure Group				High Exposure Group			
	Liver	Adipose	Thigh	Egg	Liver	Adipose	Thigh	Egg
2378-TCDD	NA	NA	NA	NA	63.4	28.8	28.7	11.3
12378-PCDD	13.7	11.7	6.8	6.0	44.3	23.7	21.5	8.9
123478-HxCDD	6.7	7.6	3.6	5.4	37.3	18.3	15.9	8.5
123678-HxCDD	10.7	11.0	5.6	10.2	26.8	12.5	9.9	7.0
123789-HxCDD	6.1	5.1	2.4	4.5	16.0	7.4	5.4	4.4
1234678-HpCDD	7.6	2.7	1.4	4.8	22.3	4.1	3.3	4.8
OCDD	3.1	0.6	0.3	4.3	14.9	0.7	0.4	1.8
2378-TCDF	8.1	2.7	3.1	2.7	42.6	18.0	21.9	6.8
12378-PCDF	36.2	27.7	18.0	20.5	NA	NA	NA	NA
23478-PCDF	16.2	13.1	7.4	7.8	59.8	26.7	28.4	10.6
123478-HxCDF	13.8	11.9	4.8	7.4	46.8	15.1	13.4	8.5
123678-HxCDF	10.9	11.7	5.3	8.2	37.8	16.9	14.2	8.5
123789-HxCDF	NA	NA	NA	NA	NA	NA	NA	NA
234678-HxCDF	8.2	4.8	2.1	3.0	33.4	8.3	6.8	5.1
1234678-HpCDF	4.2	2.4	1.0	3.1	15.3	3.3	2.7	3.9
1234789-HpCDF	3.8	1.8	0.9	2.2	26.5	5.2	4.2	4.6
OCDD	1.9	0.5	0.3	1.4	11.4	0.8	0.1	1.5

NA = described as “not applicable” for derivation of BCFs by Stephens, et al. (1995) because one or both measurements were below the quantification limit.

Table 4-8. Chicken and egg BCFs for Aroclor mixtures.

Aroclor Mixture	Low Exposure Group		High Exposure Group	
	Egg	Body Fat	Egg	Body Fat
1221	NA	NA	0.4	1.2
1232	NA	NA	1.2	2.6
1242	3.5	2.9	7.2	4.5
1248	3.5	9.8	4.7	4.5
1254	6.5	7.4	5.7	6.2
1268	NA	NA	10.8	2.6

NA = data was not taken for the low, 2 ppm, concentration exposure for these Aroclors

Table 4-9. Ranges of concentrations of PCDDs, PCDFs, and PCBs in municipal waste combustor ash (results in ng/g or ppb; ND = Not detected; NR = not reported; Tr = trace; DL between 0.01 and 0.1 ng/g).

Constituent	Fly ash	Combined ash	Bottom ash	Constituent	Fly ash	Combined ash	Bottom ash
I. DIOXINS				III. PCBs			
MCDD	2.0	ND	NR	Mono CB	0.29-9.5	ND	ND-1.3
DCDD	0.4 - 200	ND-120	NR	Di CB	0.13-9.9	0.13-1.35	ND-5.5
T_3CDD	1.1 - 82	ND-33	NR	Tri CB	ND-110	0.35-14.3	ND-80
T_4CDD	ND - 250	0.14-14	<0.04-410	Tetra CB	0.5-140	16.5	ND-47
PCDD	ND - 722	0.07-50	ND-800	Penta CB	0.8-225	ND	ND-48
H_6CDD	ND - 5,565	0.07-78	ND-1000	Hexa CB	0.45-65	ND-39	NR
H_7CDD	ND - 3,030	0.07-120	ND-290	Hepta CB	ND-0.1	ND	NR
OCDD	ND - 3,152	0.07-89	ND-55	Octa CB	ND-1.2	ND	NR
2378-TCDD	ND - 330	0.02-0.78	<0.04-6.7	Nona CB	ND	ND	NR
Total PCDD	5 - 10,883	6.2-350	ND-2800	Deca Cb	ND	ND	NR
II. FURANS				Total PCB	ND-360	ND-32.15	ND-180
MCDF	41	1.1	NR				
DCDF	ND - 90	ND-42	NR				
T_3CDF	0.7 - 550	ND-14	NR				
T_4CDF	ND - 410	2.3-9	10.1-350				
PCDF	ND - 1800	1.6-37	0.07-430				
H_6CDF	Tr - 2,353	1.2-35	ND-920				
H_7CDF	Tr - 887	0.62-36	ND-210				
OCDF	ND - 398	0.18-8.4	ND-11				
2378-TCDF	0.05-5.4	0.41-12	ND-13				
Total PCDF	3.73 - 2,396	6.14-153.9	ND-1600				

Source: EPA (1991)

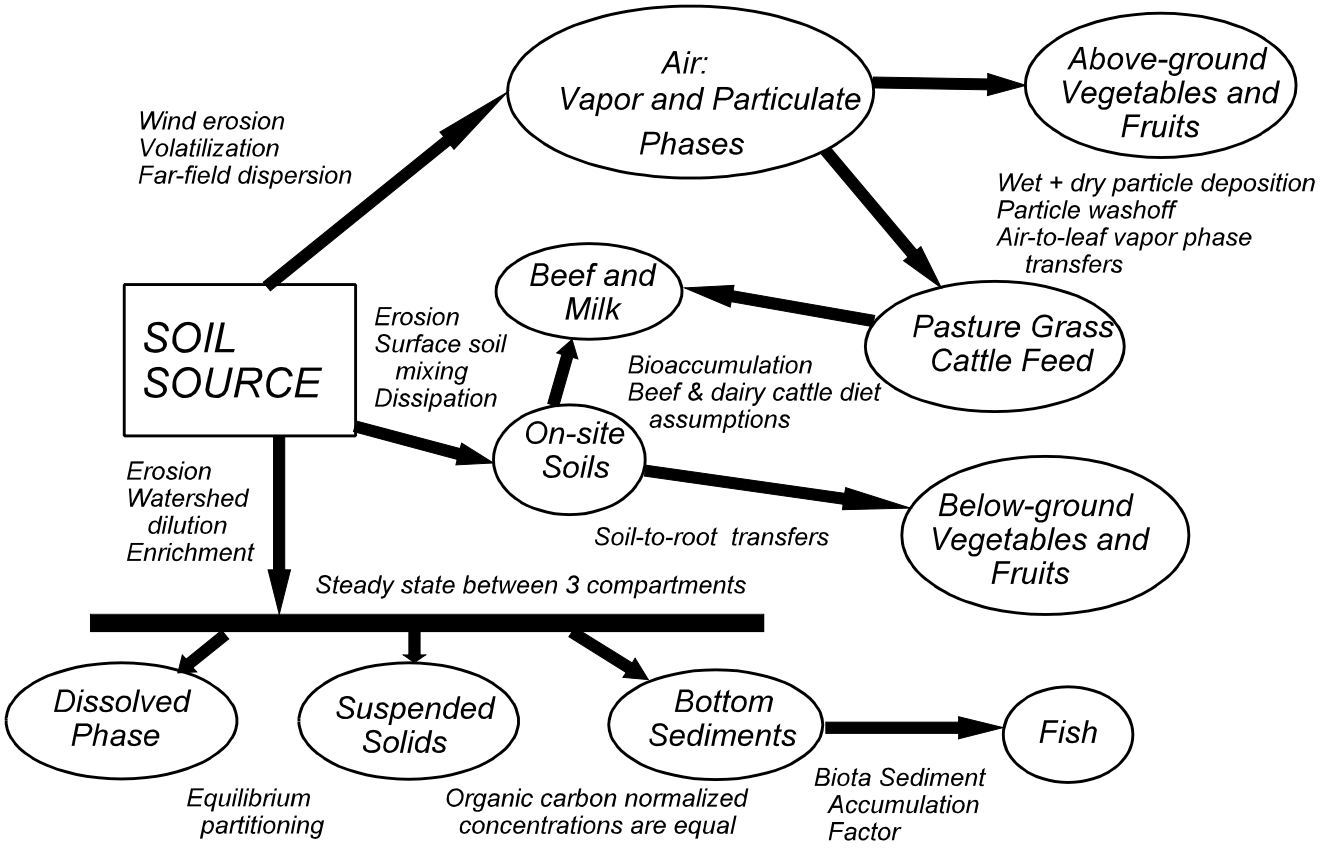


Figure 4-1. Diagram of the fate, transport, and transfer relationships for the soil contamination source category.

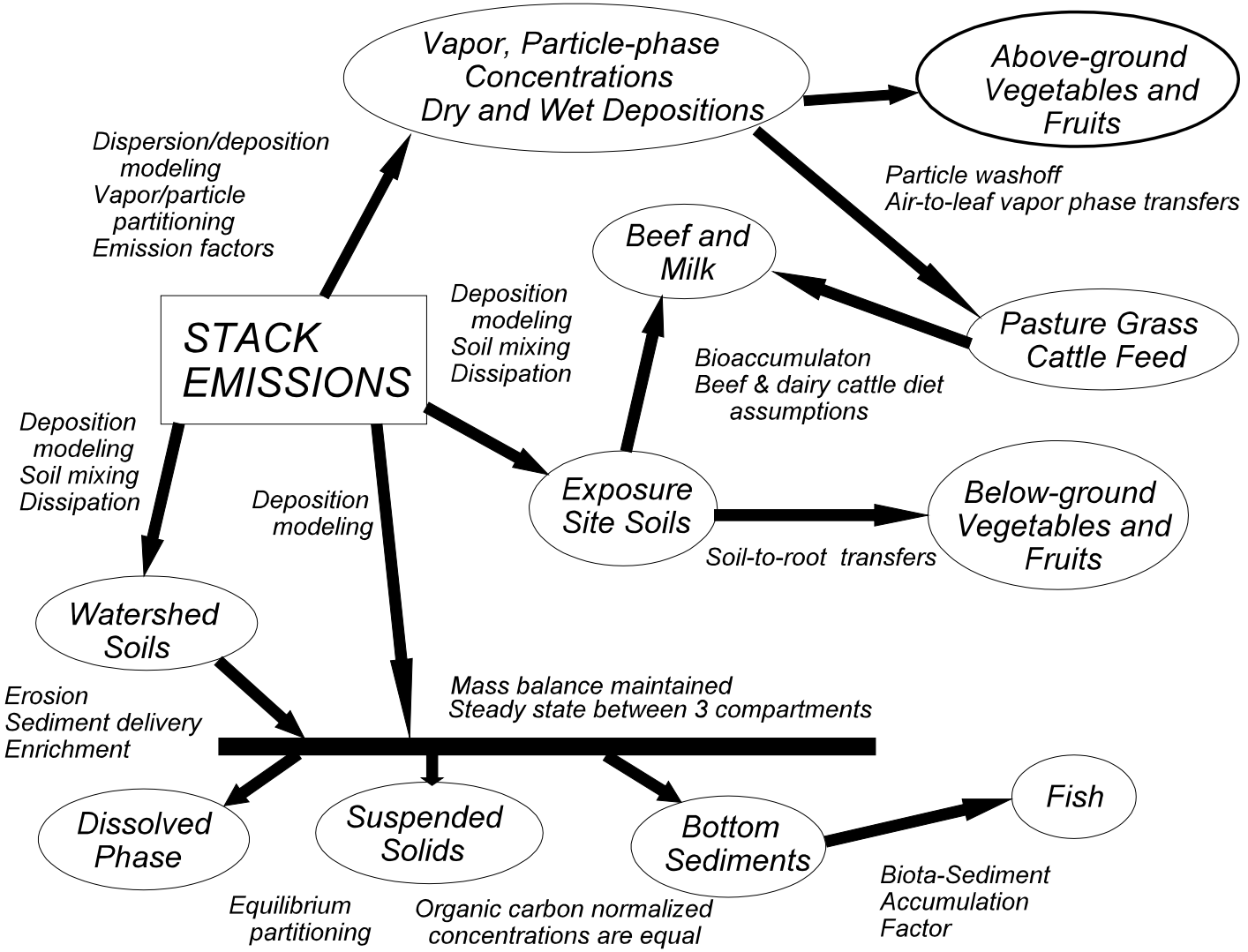


Figure 4-2. Diagram of the fate, transport, and transfer relationships for the stack emission source category.

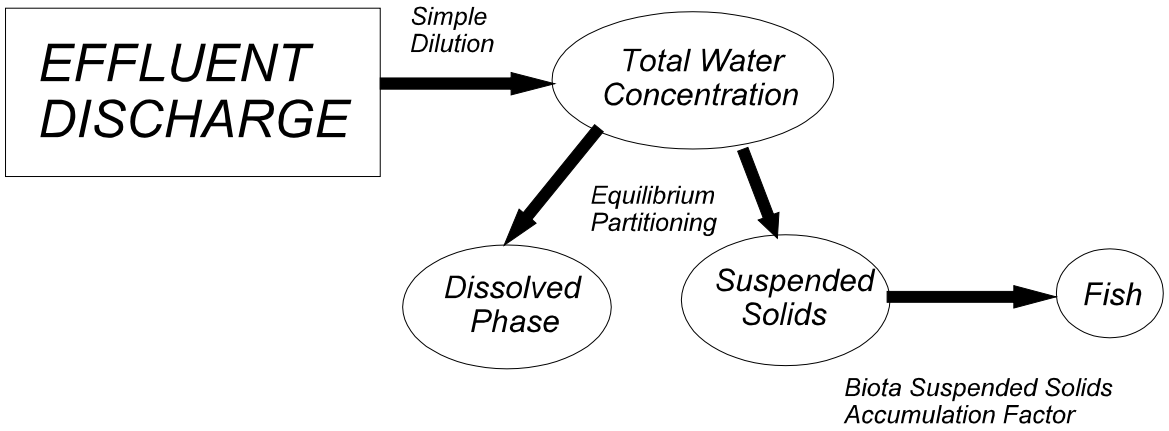
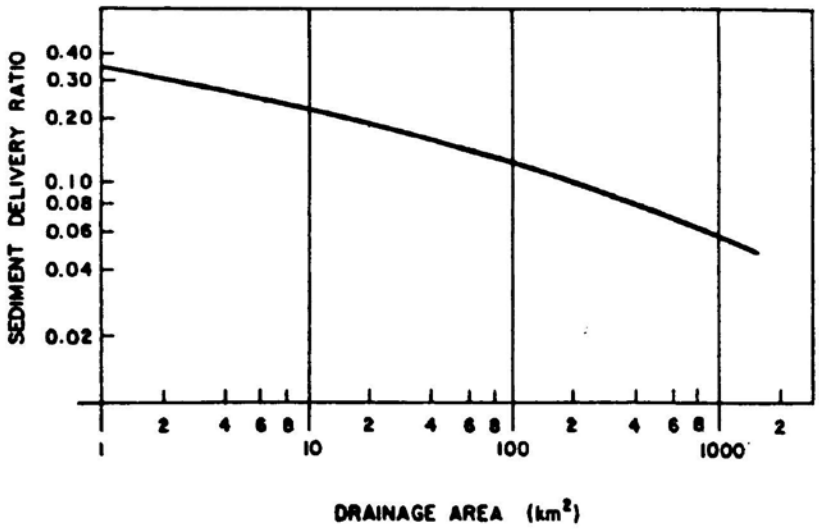


Figure 4-3. Diagram of the fate, transport, and transfer relationships for the effluent discharge source category.



Source: Vanoni, 1975

Figure 4-4. Watershed delivery ratio, SD_w, as a function of watershed size.

5. DEMONSTRATION OF METHODOLOGY

5.1. INTRODUCTION

This document has provided methodologies and background information for conducting site-specific exposure assessments for dioxin-like compounds. Chapter 2 summarized an overall exposure assessment framework, Chapter 3 described mechanisms of formation of dioxin-like compounds in stack emissions and the fate and transport modeling of releases from the stack to a site of exposure, and Chapter 4 provided methodologies to estimate exposure media concentrations for three sources of contamination, which were termed source categories.

The purpose of this chapter is to put all this information together and demonstrate the methodologies that have been developed. For this demonstration, exposure scenarios are developed which are associated with the three source categories. These categories were defined in Chapter 4, and are:

- **Soil Contamination**: The source of contamination is soil. The contaminated soil could occur at the site of exposure, such as in worker exposure scenarios at Superfund sites or contaminated soil at a residence, or the contaminated soil could occur distant from the site of exposure, such as a residence near a Superfund site.
- **Stack emissions:** Exposed individuals reside in the vicinity of the site where stack emissions occur and are exposed to resulting air-borne contaminants, and soil and vegetation on their property is impacted by deposition of contaminated particulates.
- **Effluent discharge:** A discharge of dioxin-like compounds in effluents impacts surface water and fish. Exposure occurs through consumption of the impacted fish and water.

An additional and important scenario is developed which merges the fate and transport algorithms of the soil contamination and emission source categories. This scenario is called, "background conditions". Further details on the structure and fate algorithms of the background conditions scenario are provided in Sections 5.3 through 5.5 below.

The demonstration in this chapter is structured around what are termed exposure scenarios. As defined in Chapter 2, an exposure scenario includes a description of the physical setting of the source of contamination and the site of exposure, behavior of exposed individuals, and exposure pathways. Chapter 2 also described the objective of exposure assessors to

determine "central" and "high end" exposure scenarios. This objective was an important one for this demonstration, and the strategy to design such scenarios is detailed in Section 5.2 below.

For the soil contamination and the effluent discharge source categories, three dioxin-like compounds are demonstrated for each exposure scenario, including 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, and 2,3,3',4,4',5,5'-HPCB. For the stack emission source and the background conditions demonstrations, a different approach is taken with regard to compounds demonstrated. The 17 dioxin and furan compounds of non-zero toxicity are demonstrated; no dioxin-like PCBs are demonstrated. Exposure media concentration results are developed for all 17 congeners. As well, a "toxic equivalent" exposure media concentration, or TEQ concentration, is calculated as the sum of the individual congener concentrations multiplied the congener's Toxicity Equivalency Factor, or TEF. As described in Chapter 1, TEQ concentrations are determined using the WHO 1998 scheme, and the TEQs of this chapter are therefore further identified as WHO_{98}-TEQ_{DF}. Final exposure estimates (Lifetime Average Daily Doses, or LADDs) are developed based on the WHO_{98}-TEQ_{DF} exposure media concentrations for these demonstrations.

Section 5.2 describes the strategy for development of the demonstration exposure scenarios. Section 5.3 gives a complete summary of the demonstration scenarios. Section 5.4 provides some detail on the example compounds demonstrated. Section 5.5 describes the source strength terms for the scenarios. Section 5.6 summarizes the results for all scenarios, which are exposure media concentrations for all exposure pathways, and exposure estimates which are Lifetime Average Daily Doses (LADDs) for all pathways. Also, several observations and additional analyses are provided in Section 5.6.

5.2. STRATEGIES FOR DEVISING EXPOSURE SCENARIOS

Chapter 2 of this document described procedures to assess individual exposures to known sources of contamination. Central and high end exposure patterns, and exposure parameters consistent with these definitions were proposed in that chapter. The demonstration in this chapter attempts to merge procedures for estimating individual exposures to known sources of contamination and current thoughts on devising central and high end exposure scenarios.

An exposure assessor's first task in determining patterns of exposure is to fully characterize the exposed population in relation to the source of contamination. If the extent of contamination can be characterized, then the exposed population would be limited to those within the geographically bounded area. An example of this situation might be an area impacted by stack emissions. Chapter 3 demonstrated the use of ISCST3 atmospheric dispersion model to predict ambient air concentrations and depositions rates for all points surrounding the stack.

Results listed in Tables 3-16 through 3-19 were only for the prevailing wind direction. As can be seen on these tables, the points of maximum impact were within 1 km of the stack. By overlaying the concentration isopleths onto a population density map, the exposed population can be identified. If the extent of contamination is not as clearly defined, such as extent of impact of nonpoint source pollution (impacts from use of agricultural pesticides, e.g.) or the compound is found ubiquitously without a clearly defined source, then the emphasis shifts from geographical bounding to understanding ambient concentrations, exposure pathways and patterns of behavior in general populations. The background conditions scenarios do, in fact, focus on the development of realistic ambient concentrations for its source strength terms.

After identifying the exposed population, the next task is to develop an understanding of the continuum of exposures. The exposures faced by the 10 percent of the population most exposed has been defined as high end exposures. Those faced by the middle of the continuum are called central exposures. Another important estimate of exposure level is a bounding exposure, which is defined as a level above that of the most exposed individual in a population. Arriving at such an understanding can be more of an art than a science. One consideration is the proximity of individuals within an exposed population to the source of contamination. For the incinerator example discussed above, one might begin an analysis by assuming that bounding or high end exposures occur within a kilometer from the stack, in the prevailing wind direction. Another important consideration is the relative contribution of different exposure pathways to an individual's total exposure. While individuals residing at this distance from the incinerator might experience the highest inhalation exposures, they may not experience other exposure pathways associated with contaminated soil on their property - such as consumption of home grown vegetables, dermal contact, or soil ingestion. Families with home gardens and individuals who regularly work in those gardens may reside over a kilometer from the incinerator and possibly be more exposed because of their behavior patterns. Screening tools, such as the algorithms of this assessment which are amenable to spreadsheet analysis (except for the ISCST3 modeling), can be used in an iterative mode to evaluate the interplay of such complex factors. When applied to a real world situation, information should be sought as to the makeup and behavior patterns of an exposed population.

The third principle task for evaluating impacts on an exposed population is to understand the relationship between impacts attributed to the source in question and the background exposures faced by the identified population. Assessors should attempt to answer the following question for dioxin-like compounds: What exposures to dioxin-like compounds would the identified populations have if the source in question were not in existence? The exposures faced

by the identified in the absence of the source in question can be termed "background" or "cumulative" exposures; cumulative in two senses: that the exposures faced by the identified population result from the cumulative impacts of all sources in their environment and from all pathways. Chapter 2 describes approaches to determining background exposures to dioxin-like compounds, and this chapter demonstrates one way to evaluate background/cumulative exposures for a specific site.

The demonstration in this chapter attempts to be consistent with the goal of quantifying central and high end exposures, and properly considering background exposures. However, it is not exhaustive in its analysis, nor should it be construed as a case study with widely applicable results. All the scenario definitions, parameter values, and so on, were construed to be plausible and reasonable, and to demonstrate the application of a site-specific methodology, not to set any regulatory precedent.

Following are bullet summaries of key features of the structure and intent of the demonstrations.

- **Exposed populations:** Exposed individuals are assumed to reside in a rural setting. Exposures occur in the home environment, in contrast to the work environment or other environments away from home (parks, etc.). The presumption is made that the sources of contamination of this assessment can occur in rural settings in the United States. It is further assumed that the behavior patterns associated with the exposure pathways can exist in rural settings. Several of these behaviors characterized as high end relate to individuals on farms as compared to behaviors characterized as central for individuals not on farms. The exposed population for this demonstration, therefore, consists of rural individuals in farming and non-farming residences.
- **Plausibility of source strength terms:** The objective to determine plausible levels of source strength contamination was an important one for this demonstration. Sources demonstrated include small areas of soils with concentrations that have been found in industrial sites, stack emissions with emission rates typical of facilities containing state-of-the-art emission controls, and effluent discharges where characteristics of the effluent stream including rate of contaminant discharges were developed from recent data from pulp and paper

mills. Also, the background conditions scenarios include watershed soils and air concentrations which have been measured in an actual rural background setting. Section 5.5 describes the source terms in detail.

- **Proximity to sources of contamination:** The background scenarios use soil and air concentrations which have been measured in an actual background setting. Therefore, proximity to the source of contamination is not an issue. The effluent discharge source category is unique from the others in that soils or air are not impacted by the source. Only the surface water body into which the effluent is discharged is impacted. The only exposure pathways considered for this source category are drinking water and fish ingestion. Like the demonstration of background conditions, proximity is not an issue for this source category because the simple dilution model does not model fish and water concentrations as a function of distance from the source. It is felt that the water movement of a river or stream receiving the effluent discharge allows for sufficient mixing such that the simplistic dilution approach is reasonable for the dioxin-like compounds. As well, fish are not stationary so that a relationship between distance to source and where the fish are caught would be hard to develop or defend. Individuals in the effluent discharge demonstration simply exhibit behaviors associated with an impacted water body - they fish and they consume the water. Proximity to a stack emitting dioxin-like compounds was identified as an important determinant for identifying the continuum of exposures. Assuming there is a uniform distribution of exposure-related behaviors among exposed populations, i.e., their behavior patterns are not a function of where they live in relation to the stack, the most exposed individuals will be those exhibiting high end exposure behavior nearest the stack. This was the assumption made for purposes of this demonstration. A set of high end exposure behaviors and pathways were demonstrated for individuals residing 500 meters east of the stack, and a set of central exposure pathways were demonstrated for individuals residing 5000 meters east of the stack. The highest ambient air concentrations, and dry and wet deposition rates were simulated to occur at 200 to 1000 meters downwind, justifying 500 meters as an appropriate point for assuming high end impacts. Tables 3-16 through 3-19 listing concentrations and depositions rates as a function show that air concentrations and dry depositions rates at 5000 meters are only about half of what they are at 500 meters, although wet deposition rates are about 20 times

higher at 500 meters as compared to 5000 meters. Without rigorous justification, the model output (concentrations and deposition rates) at 500 and 5000 meters was felt to appropriately characterize high end and central exposures. The site of contamination in the demonstration of the soil contamination source category is 10 acres in size and has concentrations that have been found in industrial sites. A working hypothesis is made that the population most exposed are those residing very near the site. Their soil is assumed to become contaminated over time due to the process of erosion; these processes normally do not carry contaminants long distances across land, particularly land developed with residences or where erosion is interrupted with ditches or surface water bodies. People from the surrounding community can be impacted by visiting or trespassing on the contaminated land, volatilized residues may reach their home environments, they may obtain water and fish from impacted water bodies, and so on. It seems reasonable to assume that those residing near these sites comprise the principally exposed individuals, or equivalently, the individuals experiencing the high end or bounding exposures associated with these areas of soil contamination. The soil contamination source category will be demonstrated with a single, high end scenario. The exposure site is assumed to be located 150 meters downgradient from the site of soil contamination.

- **Central and high end exposure patterns:** Chapter 2 described the exposure pathways that are considered in this methodology, and justified assignment of key exposure parameters (contact rates and contact fractions, exposure durations, and so on) as central or high end estimates. The bullet above discussing exposed populations indicated that several of the behavior assumptions were specific to individuals on farms, and that these behavior patterns were evaluated as "high end". "Central" behavior patterns were those for individuals residing in a non-farm residence. High end behaviors assumed to be different for individuals on farms versus central behaviors for individuals not on farms include, for example, residing on larger tracts of land (10 acres assumed for farmers; 1 acre assumed for non-farmers) and ingestion of home produced and impacted beef. Other patterns of behavior modeled as central and high end are not specifically associated with farming and not farming, but are assumed to be plausible for individuals in rural settings. These include home gardening for fruit and vegetables, inhalation exposures, children that ingest soil, and the use of impacted surface water bodies

for drinking and fish to be ingested. Finally, a set of additional exposure pathways are modeled which are outside the scenarios altogether. These include the pathways of milk ingestion, chicken, and egg ingestion. Like the beef ingestion pathways, these pathways involve home production of the food products. Since an objective of the scenario development was to be realistic, it was felt that a scenario involving home production of the four animal food products: beef, milk, chicken, and eggs (not to mention fruits and vegetables), was highly unlikely. However, a scenario involving production of at least one animal terrestrial food product is more realistic.

- **Consideration of background exposures**: Background scenarios are devised which include the same exposure pathways and exposure parameters as the source-specific scenarios. The difference is that the exposure media concentrations are "background" or "cumulative" as contrasted to concentrations that result only from the source being modeled. Specifically, the background scenarios use, as input, "background" air and soil concentrations, and model all subsequent terrestrial and aquatic impacts. By structuring the background scenarios in this way, the key question, "What would be the exposure of individuals if the source in question did not exist?" is most specifically answered. Chapter 2 described a second approach to the issue of background exposures, and that was the comparison of source/scenario specific exposures to a generic background exposure. Volume II of this assessment has estimated that a general background exposure to WHO_{98}-TEQ_{DFP} is about 60 pg/day. One could, therefore, compare any source-specific estimates to this overall background estimate. Further detail on the specifics of the background scenarios is given below.
- **Realism of modeled concentrations:** The air and soil concentrations of the background scenarios are, by definition, realistic since they were derived from actual measured concentrations from a background site. For all other exposure media of the background scenarios, and in all other scenarios, the exposure media concentrations were modeled. The realism of modeled exposure media concentrations is dependent on the appropriateness of the models used for such estimations and the assignment of parameter values for those models. One way to arrive at a judgement as to the realism of estimated concentrations is to compare predictions with observations. To the extent possible (i.e., given the availability of appropriate data), model predictions of exposure media concentrations are

compared with occurrence data in Chapter 7, which describes several model validation exercises. As is shown, predictions fell within the realm of observed data. Chapter 4 describes the justification of all model parameter values. Many of the parameters are specific to the contaminants. Some contaminant properties were estimated as empirical functions of contaminant-specific parameters: the root concentration factor, RCF, was estimated as a function of the octanol water partition coefficient, Kow, for example. Other parameters were measured values, such as the vapor pressure or some of the bioconcentration factors. For non-contaminant parameters such as soil and sediment properties, patterns of cattle ingestion of soil (and other bioaccumulation/biotransfer parameters), and many others, selected values were carefully described and crafted to be plausible.

5.3. EXAMPLE EXPOSURE SCENARIOS

As noted above, all exposures occur in a rural setting. Exposure pathways were those which could be associated with places of residence in contrast to the work place or other places of exposure. The example scenarios are structured so that some (but not all) of the behaviors associated with high end exposures are included in the "high end" scenarios and all the central behaviors are in the scenarios characterized as "central". To summarize, the components which distinguished the high end exposure scenarios in contrast to the central scenarios include:

- Individuals in the central scenarios lived in their homes and were exposed to the source of contamination for only 9 years, in contrast to individuals in the high end scenarios, who were exposed for 30 years (except for the exposure pathway of soil ingestion, where the individuals are assumed to be children ages 2-6, and in both the central and high end scenarios, the exposure duration is 5 years).
- Individuals in the central scenarios lived on properties 1 acre in size, whereas individuals in the high end scenarios lived on properties 10 acres in size.
- Individuals in the high end scenario associated with the stack emission source category lived 500 meters from the incinerator, whereas individuals in central scenario lived 5000 meters from the incinerator.
- Individuals in high end scenarios obtained a portion of their beef from home-raised cattle stocks - such individuals are obviously farmers. Consumption of terrestrial animal food products were not assessed for non-farming rural individuals, representing the central scenarios.

- On the other hand, farming individuals in the high end scenarios were not assumed to recreationally fish. A fish pathway was included only in the central scenarios.
- Ninety percent of the inhaled air and ingested water by the high end individuals were assumed to be contaminated, whereas only 70% of these exposures were with impacted media for the central individuals. This is based on time at home versus time away from home assumptions for central versus high end individuals. Also, individuals in high end scenarios were assumed to consume 2.0 L/day of water and breathe 20 m^3/day of air as compared to 1.4 L/day and 13 m^3/day for individuals in central scenarios.
- Both the central and high end scenarios included a fruit/vegetable ingestion pathway. Although patterns of home production and consumption of fruits and vegetables differ within a population, average behaviors for individuals who home produce fruit and vegetables was assumed for both the central and high end scenarios in this assessment.
- The rates of ingestion of soil by children were higher for the high end individuals than the central individuals.

These are the distinguishing features for the central and high end exposure scenarios. For the sake of convenience mainly, all the scenarios defined below as high end are called "farms", and all central scenarios are called "residences". In addition to the scenarios, high end behaviors including fish, milk, chicken and egg consumption are separately modeled for the background conditions farm setting, the stack emission high end farm setting, and the soil contamination farm setting.

Again, the reason for separating these four pathways from the scenarios is that it is important for assessors to develop scenarios which combine a series of behaviors which are plausible to occur simultaneously in a real world setting. If such a strategy is followed, than the assessor is able to sum the exposures over all pathways to arrive at a total scenario exposure. It does not seem reasonably common in the real world that a single farm would include home production of several terrestrial animal food products (along with recreational fishing), which is why such a scenario is not developed in this assessment. In an exhaustive site-specific analysis, one might begin by evaluating all possible pathways, further evaluating pathways of most exposure, and then determining what pathways occur simultaneously for identified individuals in the exposed population. Only then can be the assessor begin to define a continuum of exposures.

The following bullets describe six exposure scenarios that are demonstrated. The numbering scheme and titles will be referenced for the remainder of this chapter:

Exposure Scenarios 1 and 2: Background conditions, Residence and Farm

Surface soils within the watershed are initialized to soil concentrations of the 17 dioxin-like congeners (no dioxin-like PCBs) which have been found in an actual rural setting. Also, air concentrations of the 17 congeners are initialized to air concentrations which have been found in this same rural setting. More details on this setting are provided in Section 5.5 below. Scenario 1 is the central residential scenario, and Scenario 2 is the high end farming scenario. Bottom sediment in a nearby river becomes impacted by long term erosion and atmospheric deposition. Water and fish in that stream are subsequently impacted. The exposure pathways for Scenario 1 are: water ingestion, air inhalation, fish ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion. The exposure pathways for Scenario 2 are: water ingestion, air inhalation, beef ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion. It is noted that for a background condition, it could be argued that all exposure is to background concentrations in exposure media. In other words, all contact fractions would be 1.00. However, if an assessor wished to compare the incremental impacts from a specific source of dioxin release with impacts an individual would receive by contact with the same exposure media which has only background concentrations of dioxins, than the assessor would assume all the same exposure behaviors (rates of contact, contact fractions). This demonstration takes this approach. When evaluating non-cancer risks using a margin-of-exposure approach, which is also demonstrated in this chapter, it is most appropriate, however, to compare incremental impacts with all background impacts, not only the same source-specific incremental impacts. This is discussed in more detail in Section 5.7, which demonstrates cancer and non-cancer risk assessments.

Exposure Scenario 3: Soil Contamination, Farm

A 40,000 m^2 rural farm is located 150 m (500 ft roughly) from a 40,000 m^2 area of bare soil contamination; an area that might be typical of contaminated industrial property. The surface soil at this property is contaminated with three example dioxin-like compounds to the same concentration of 1 part per billion (ppb). These compounds are: 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, and 2,3,3',4,4',5,5'-HPCB. The 1 ppb soil concentration is reasonable for industrial sites of contamination of dioxin-like compounds, and generally about three orders of magnitude higher than the concentrations of these congeners in background settings. As in the above and all scenarios, bottom sediment in a nearby river is impacted, which impacts the water and fish. The

exposure pathways include: water ingestion, air inhalation, beef ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion.

Exposure Scenarios 4 and 5: Stack Emissions, Residence and Farm

A 4,000 m^2 rural residence (Scenario 4) is located 5000 meters from an incinerator, and a 40,000 m^2 (Scenario 5) rural farm is located 500 meters downwind from an incinerator. Emission data of the suite of 17 dioxin-like dioxin and furan congeners (no dioxin-like PCBs) is available from stack testing of an actual incinerator. This allows for estimation of impacts from each congener individually, and estimation of WHO_{98}-TEQ_{DF} impacts. The modeling of the transport of these contaminants from the stack to the site of exposure and other points in the watershed used the ISCST3 model. Details on the stack emission source for this demonstration and the ISCST3 model application are found in Chapter 3. A nearby impacted river provides drinking water and fish for recreational fishing. The exposure pathways for Scenario 4 are: water ingestion, air inhalation, fish ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion. The exposure pathways for Scenario 5 are: water ingestion, air inhalation, beef ingestion, fruit/vegetable ingestion, soil dermal contact, and soil ingestion.

Exposure Scenario 6: Effluent Discharge into a River

As has been discussed, this source category is different from others in that the air, soil, and vegetation at a site are not impacted. Rather, only surface water impacts are considered. Therefore, central and high end behaviors associated with places of residence are less pertinent for this source category. Exposure parameters associated with central behaviors for the water and fish ingestion pathways were chosen to demonstrate this source category. The source strength was developed from data on pulp and paper mill discharges of 2,3,7,8-TCDD; more detail on this source strength term development is provided in Section 5.5 below. The discharges of the other two example compounds are assumed to be the same for purposes of demonstration. Obviously, however, there is less of a tie to real data for the discharge rate for these other two example compounds. Also noteworthy for this source category as compared to the others is the size of the surface water body into which discharges occur. The other source categories all were demonstrated on water bodies with annual flow rates of $4.8 * 10^{11}$ L/yr. The river size into which the example effluent was discharged was developed from data from the 104 pulp and paper mill study (as discussed in Section 5.5 below). This river size was $4 * 10^{12}$ L/yr, one order of magnitude larger than the river of the other scenarios.

Food pathway analyses outside of the scenario framework: The food consumption pathways of fish, milk, chicken, and eggs are demonstrated using source strength characteristics of the three high end scenarios above: Scenarios 2 (background conditions), 3 (soil contamination), and 5 (stack emission). These food pathways were not modeled in the scenarios themselves. In these analyses, exposure media concentrations are calculated for each source and the pathway exposure estimates are provided. The purpose of these external pathway analyses was to provide further demonstration and to compare impacts from the various food pathways where methodologies have been provided in this assessment.

5.4. EXAMPLE COMPOUNDS

Three compounds were demonstrated for the soil contamination source and for the effluent discharge source category. For purposes of illustration, one compound was arbitrarily selected from each of the major classes of dioxin-like compounds. They are: 2,3,7,8-tetrachlorodibenzo-p-dioxin, 2,3,4,7,8-pentachlorodibenzofuran, and 2,3,3',4,4',5,5'-heptachloro-PCB. For the remainder of this chapter, these compounds will be abbreviated as 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, and 2,3,3',4,4',5,5'-HPCB.

These compounds demonstrate a range of expected results because of the variability of their key fate and transport parameters. The log octanol water partition coefficients (log Kow) for 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, and 2,3,3',4,4',5,5'-HPCB were 6.80, 6.50, and 7.71, respectively. Whereas the span of reported log Kow ranged from less than 6.00 to greater than 8.00, only a few reported values were at these extremes. Increasing log Kow translates to the following trends: tighter sorption to soils and sediments and less releases into air and water, less accumulation in plants and in cattle products (beef, milk), and more accumulation in fish. The Henry's Constants for the three compounds span the range of reported values, with the value of the PCB compound the highest of all reported at $6.6 * 10^{-5}$ atm-m^3/mole. There were few values less than the $4.98 * 10^{-6}$ atm-m^3/mole reported for 2,3,4,7,8-PCDF. Higher Henry's Constants translate to greater amounts of volatilization flux. The fate parameters for these three compounds and the 15 other dioxin and furan congeners are provided in Table 5-1.

For the background conditions and the stack emission demonstrations, Scenarios 1, 2, 4, and 5, a different approach was taken. All 17 of the dioxin-like dioxin and furan congeners were modeled. The ISCST3 modeling exercise described in Chapter 3 allowed for the generation of deposition amounts (wet and dry) and ambient air concentrations of all 17 congeners at sites of exposure for the demonstration of the stack emission source. For the background conditions demonstration, air concentrations were taken from an actual rural site (see Section 5.5). The dry

depositions of particle-bound congeners were estimated as the particle-bound air concentration times a deposition velocity. Based on the measurements of Koester and Hites (1992), this deposition velocity was assumed to be 0.2 cm/sec. Also based on Koester and Hites (1992), who measured wet and dry deposition and showed these two quantities to be roughly equal for settings in Indiana, wet deposition was set equal to dry deposition.

The individual deposition rates and air concentrations for the 17 congeners in Scenarios 1, 2, 4, and 5 were used to model the exposure media concentrations for each congener individually with unique fate and bioaccumulation parameters. The exposure media concentrations include: air, soil, fruit/vegetables, water, fish, and the terrestrial animal food products including beef, milk, chicken, and eggs. A final WHO_{98}-TEQ_{DF} exposure media concentration was estimated using the 1998 WHO TEFs (Van der Berg, 1998):

$$C_{TEQ} = \Sigma\ TEF_i\ C_i \qquad (5\text{-}1)$$

where:

C_{TEQ}	=	Toxic Equivalent concentration
TEF_i	=	Toxicity Equivalency Factor for congener i
C_i	=	concentration of congener i

The final results which are displayed for these scenarios are the WHO_{98}-TEQ_{DF} results only.

5.5. SOURCE TERMS

This section describes the source terms for the example scenarios. The source terms for the demonstration of background conditions, Scenarios 1 and 2, include both the initial air concentrations and the initial soil concentrations. The source terms for the soil contamination source demonstration, Scenario 3, include the area of contamination and soil concentrations. The source terms for the stack emission scenarios, 4 and 5, are the emission rates of contaminants from the stacks. These are described in Chapter 3. What will be detailed here, instead, are the deposition rates, air concentrations, and predicted soil concentrations at the site of exposure. In this way, scenarios 4 and 5 can be compared to the background scenarios, 1 and 2. The source term for the effluent discharge example scenario is the rate of discharge of dioxin-like compounds. This is briefly discussed in this section, with reference to a more detailed discussion in Chapter 7. Following now are discussions on these terms for all scenarios.

Scenarios 1 and 2

The 1994, the Ohio EPA (OEPA) conducted air monitoring in the city of Columbus in order to evaluate the impact of the Columbus Municipal Solid Waste Incinerator (MSWI). This incinerator operated between June, 1983 and December, 1994. Air samples were taken in March and April, 1994, at 6 sites in the city in Columbus and in a background site 28 miles southwest of Columbus. This background site is in the upwind direction from the facility. The air concentrations were higher in the urban air of Columbus as compared to the air concentrations in the background site: the average I-TEQ (I is short for "international"; see Chapter 1 for a discussion of the WHO TEFs versus the I TEFs) air concentration from 10 samples (6 sites, 2 sample dates, but only 5 sites sampled each sample date) in Columbus was 0.092 pg I-TEQ/m^3 as compared to 0.023 pg I-TEQ/m^3 from 2 samples (1 site, 2 sample dates) at the background site. The Ohio EPA visited these same sites in April, 1995, to measure air concentrations once the incinerator was no longer operating. The average air concentration from the 6 urban sites (all 6 sites sampled in 1995) was 0.046 pg I-TEQ/m^3 as compared to the background site of 0.018 pg/m^3. Further details on the 1994 sampling can be found in OEPA (1994) and details on the 1995 sampling can be found in OEPA (1995), and an overall summary of all sampling, including soil sampling, can be found in Lorber, et al. (1998). For the demonstration of background conditions, concentrations of the 17 dioxin-like congeners from the three sample dates at the rural site will be averaged to give the air concentration source terms.

The I-TEQ results discussed above were calculated assuming non-detects were equal to ½ the detection limit. Typically, non-detects are either assumed to be 0.0 or ½ detection limit. For TEQ concentrations, assumptions on the treatment of the detection limit can be an important issue if concentrations are consistently less than the detection limit and/or quantified concentrations are near the detection limit. For many samples of the OEPA sampling at Columbus, it turned out that I-TEQ concentrations did not differ significantly assuming non-detects equal 0.0 or non-detects equal ½ detection limit. For example, for the 10 Columbus samples in Mar/Apr of 1994, the average I-TEQ concentration would be 0.088 pg/m^3 at ND equal to 0.0 instead of 0.092 pg/m^3 at ½ detection limit. Likewise, for most of the congeners, the assumption on handling of non-detects is not critical as most of the samples were positively quantified, and/or the concentrations were sufficiently high such that assumptions on the values used for non-detects was not critical.

This was not the case, however, for 2,3,7,8-TCDD, the most toxic of congeners. For six sites and three sampling dates in the city of Columbus, or 16 data points (5 sites sampled for 2 dates, 6 sites sampled for one date), 6 were positive ranging from 0.0027 to 0.0262 pg/m^3. With

non-detect equal to 0.0, the average of these 16 data points was 0.0048 pg/m^3; with non-detect equal to ½ detection limit, the average concentration was 0.0065 pg/m^3. Although seemingly small, this kind of difference can be important in the calculation of TEQ media concentrations. There were no positive occurrences of 2,3,7,8-TCDD in the three dates of sampling in the rural site.

The detection limit for 2,3,7,8-TCDD varied by sampling, but was always in the narrow range of 0.0043 to 0.0074 pg/m^3 at the rural site. At ½ the detection limit for the three rural samples, the 2,3,7,8-TCDD average concentration would be 0.0029 pg/m^3, but the range of possible concentrations would be 0.00 (ND=0) to 0.0058 pg/m^3 (ND=½ DL).

An examination of the available quantified concentrations at the rural site and in Columbus suggests that assuming ½ detection limit for 2,3,7,8-TCDD would overestimate the air concentration of this congener in the rural site. Concentrations were more available for the penta dioxin congener, 1,2,3,7,8-PCDD, which are now examined to lend some insight about the difference in concentrations between Columbus and the rural site for the lower chlorinated congeners. To estimate the "true" 2,3,7,8-TCDD concentration, it will be assumed that the difference in the urban 1,2,3,7,8-PCDD concentration and the rural 1,2,3,7,8-PCDD concentration is assumed to be similar to the difference in the urban and rural 2,3,7,8-TCDD concentration. Of 16 samples of 1,2,3,7,8-PCDD in Columbus, 10 were quantified. The average concentrations at non-detect equal 0.0 and non-detect equal ½ detection limit for these 10 samples were 0.0151 and 0.0159 pg/m^3, respectively. One of 3 rural samples was quantified, leading to averages of 0.0037 and 0.0045 pg/m^3 at non-detect equal 0.0 and non-detect equal ½ detection limit. This would suggest that the rural concentration of 1,2,3,7,8-PCDD is about 1/4 that of the urban concentration (i.e., 0.0037/0.0151 = 0.245, and 0.0045/0.0159 = 0.28).

For 2,3,7,8-TCDD, where the urban concentration ranges from 0.0048 to 0.0065 pg/m^3, the "true" rural concentration is speculated to range from 0.0012 (0.0048/4) to 0.0016 (0.0065/4) pg/m^3, somewhat smaller than the 0.0029 pg/m^3 by the traditional non-detect equal to ½ detection limit method. For this example, the rural concentration of 2,3,7,8-TCDD will be assigned a value of 0.0014 pg/m^3, the midpoint of the hypothesized range.

All other air concentrations were calculated as the average of the three air samples, assuming ½ the detection limit for non-detects. The WHO_{98}-TEQ_{DF} air concentration for this profile was 0.021 pg/m^3.

In 1995, a soil sampling program was undertaken to evaluate the soils in the vicinity of the Columbus MSWI. This program was sponsored by the EPA with participation of the Agency for Toxic Substances Disease Registry (ATSDR), Ohio EPA and the Ohio Department of

Agriculture, and other state and local agencies. The purpose of the study was to determine whether the soils in the vicinity and also distant from the incinerator were impacted by the operation of the incinerator. Twenty-five samples were available for analysis, including 22 in the city of Columbus, and 3 in the same rural site 28 miles upwind of Columbus where air concentrations were taken. A full discussion of the soil sampling program can be found in EPA (1996), and an overview can be found in Lorber, et al. (1998).

This background scenario will, however, take advantage of the samples which were taken in the background setting. The soil concentration at the background site will be calculated as the average of the three background samples. The final WHO_{98}-TEQ_{DF} soil concentration for the background scenarios was 1.3 ppt. This soil sampling program took soil samples to a depth of 7.5 cm. Therefore, the concentrations as analyzed will be used to represent the "untilled" soil concentration. They will also be used to represent watershed soils for calculation of water body impacts. The question exists as to whether they should also be used to represent the tilled concentrations for the high end farming scenarios and for calculation of below ground vegetable concentrations. Brzuzy and Hites (1995) reported on the concentrations of dioxin in soil profiles from undisturbed background locations. Measuring the concentration in 2 cm increments, they generally found uniform concentrations to a depth of about 5 cm, with dropoffs thereafter. For two sandy soils, they found increasing concentrations which peaked at approximately 30 and 40 cm. Based on this information, the soil concentrations from the rural site used here will be divided by 2 to estimate tilled soil concentrations. A division by 3 to estimate the average concentration over the approximate 20 cm depth of the tilled soil depth for other scenarios in this assessment (stack emissions, soil contamination) would assume no dioxins exist below 7.5 cm in background soils. This was not found in the Brzuzy and Hites (1995) data. That is why the tilled concentration is calculated as the 7.5 cm concentration divided by 2.0 rather than 3.0. Recall that tilled soil concentrations are used to estimate concentrations in below ground vegetables, as well as in the dermal contact pathways, which assume gardening or farming as the cause for soil contact.

In summary, the background scenarios 1 and 2 use air concentrations averaged from three points in time and soil concentrations corresponding to the air samples from an actual rural setting.

It has been stated earlier in this chapter that the fate algorithms for this demonstration of background conditions would merge the fate and transport algorithms for the contaminated soil source with the stack emission source. In particular, the following will be done. First, deposition to soils will not be evaluated; soil concentrations will be supplied as source terms and are not

assumed to change over the course of the time period of the demonstration, as in the soil contamination source category. In the same vein, air concentrations are not assumed to be impacted by soil emissions; the air concentrations will be assumed to be constant and supplied as source terms as in the stack emission source category. Above ground vegetative impacts will be evaluated given the estimated depositions of particle-bound dioxins and the transfer of vapor phase dioxins from the air profile. Below ground vegetative impacts will be based on soil-to-plant transfer algorithms assuming the tilled concentration supplied as a source term. Surface water impacts (water and fish) are a function of direct depositions of particle bound contaminants onto the water body and erosion from watershed soils. The soil concentration used for calculation of water body impacts will be the untilled soil concentration. Terrestrial animal food products are calculated as a function of above ground terrestrial vegetation (impacted only by air to plant transfers) and the initialized untilled soil concentrations.

Table 5-2 summarizes the source terms used for Scenarios 1 and 2, which include the deposition rates, the air concentrations, and the soil concentrations.

Scenario 3

This scenario was designed to be plausible for properties located near inactive industrial sites with contaminated soil. The selection of 1 µg/kg (ppb; or 1000 ppt) for the three compounds was based on 2,3,7,8-TCDD findings associated with the Dow Chemical site in Midland, MI (EPA, 1985; Nestrick, et al. 1986) as well as the 100 industrial sites evaluated in the National Dioxin Study (which included the Dow Chemical site; EPA, 1987). In that study, most of the sites studied had soil concentrations in the parts per billion range. The other key source information is the size of the contaminated area. This scenario will assume a contaminated site 40 hectares, or 40,000 m^2.

Scenarios 4 and 5

Chapter 3 described the application of the ISCST3 atmospheric dispersion model to estimate air-borne concentrations and deposition rates of the contaminants in the vicinity of the hypothetical incinerator, given contaminant emission rates in units of g/sec. As discussed in Chapter 3, the emission factors (mass compound emitted per mass feed material combusted) and resulting emission rates and concentrations (rate = mass compound emitted per time period and concentration = mass compound emitted per unit volume of air emitted) for all the congeners was typical of incinerators with a high level of air pollution control, e.g., scrubbers with fabric filters. The I-TEQ emission factor for the hypothetical incinerator, 4.5 ng I-TEQ/kg material combusted,

was within a range of 0.3 ng I-TEQ/kg municipal solid waste incinerated, to 200 ng I-TEQ/kg hospital waste incinerated. This range was developed from representative test data for source-specific incinerators with a similar high level of pollution control technology. Two hundred metric tons per day of material was assumed to be incinerated at the hypothetical incinerator in order to arrive at emissions in appropriate units of g/sec. The TEQ emission rate was $1.5*10^{-9}$ g/sec. Wet and dry particle-bound deposition rates, in units of pg/m^2 -yr, were determined for all dioxins and furans, at various distances from the stack and in the prevailing wind direction. The exposure sites of Scenarios 4 and 5 are located downwind at 500 and 5000 meters, respectively, from the emission source. Other deposition rates needed for the stack emission source category were those used to estimate average watershed soil concentrations and direct deposition onto the impacted water body. For both the central and high end scenarios, rates of deposition at 5000 meters were used for these purposes. Since the watershed is 100,000 ha, which would be 10,000,000, meters long if it was square, assuming rates of deposition at 5000 meters might translate to an assumption that the stack was located relatively near the impacted water body.

Key source terms for Scenarios 4 and 5 are shown in Table 5-3. To facilitate comparison with the background scenarios, #1 and #2, these terms include the depositions, air concentrations, and soil concentrations.

Scenario 6

All key parameters used in Scenario 6 demonstrating the effluent discharge source category were developed using data associated with the 104 pulp and paper mill study (EPA, 1990). Derivation of the physical parameters including the flow rate of the receiving water body, flow rate of the effluent stream, suspended solids concentrations of the receiving water body and the effluent stream, and so on, are described in Section 4.5 of Chapter 4. An exercise evaluating the simple dilution model for predicting impacts to suspended solids in water body and subsequently to fish tissue concentrations resulting from discharges from these mills is described in Chapter 7. The bottom line conclusion from that exercise was that the simple dilution model appears to work satisfactorily for a screening model: predicted whole fish tissue concentrations for the majority of mills averaged about half as much as measured fish tissue concentrations. This could be due to an underestimate of the uncertain bioconcentration factor, BSAF, or it could be due to other factors. For the minority of mills, those with the highest volumes of receiving water, the model did not work as well. Predicted fish tissue concentrations were around an order of magnitude lower than measured concentrations. The precise reason for this discrepancy is not known, but the most likely explanation that larger water bodies have more uses and more sources

of dioxin-like input - assuming that the fish tissue concentrations result singly from the mill discharge and a few proximate mills may be inappropriate.

Parameters for Scenario 6 were derived from the mills for which the model best performed. The average discharge rate from these mills was 0.197 mg 2,3,7,8-TCDD/hr. However, this data was valid for the time of sampling, which was 1988. Since then, pulp and paper mills have reduced the discharge of dioxin-like compounds in their effluents by altering the pulp bleaching processes. Gillespie (1992) reports that data on effluent quality from all 104 mills demonstrate reductions in discharges of 2,3,7,8-TCDD of 84% overall. On this basis, the discharge rate assumed for 2,3,7,8-TCDD was 0.0315 mg/hr (16% of 0.197 mg/hr). This same rate was assumed for the other two example compounds, although the claim is not being made that they are emitted by pulp and paper mills.

It is important to note that these discharge assignments are not intended to reflect current discharges of dioxin-like compounds from pulp and paper mills, even for 2,3,7,8-TCDD. Data from the 104-mill study did allow for development of a "composite" effluent discharger in certainly a plausible setting (receiving water body and discharge flow rates, suspended solids, etc.) for pulp and paper mills. Assigning what might be evaluated as a reasonable discharge rate of 2,3,7,8-TCDD from pulp and paper mills for current conditions allows for the example scenario to placed in some context, which was a primary objective of crafting all example scenarios. Individual sources must be evaluated on an individual basis.

In summary, the key source term for the demonstration of the effluent source category include a discharge rate of 0.0315 mg/hr for all three compounds demonstrated, and the discharge of this rate into a water body of size $4.65*10^9$ L/yr.

5.6. RESULTS

The results of this exercise include the exposure media concentrations for all exposure pathways and scenarios, and the LADD exposure estimates. These two categories of results are summarized in Tables 5-4 through 5-10. Following now are several observations from this exercise. As a reminder for the background conditions scenarios, #1 and #2, and stack emission demonstration scenarios, #4 and #5, individual dioxin and furan congeners with non-zero toxic equivalency factors (TEFs) were modeled with unique fate and transport parameters until estimates of exposure media concentration were made. At that point, the WHO_{98}-TEQ_{DF} exposure media concentrations were estimated. For the sake of brevity, the WHO_{98}-TEQ_{DF} results are emphasized in this chapter.

It is important to understand that all observations made below are not general comments. Different results would arise from different source strength characteristics, proximity considerations, model parameter values, different models altogether, and so on. Chapters 6, 7, and 8 on User Considerations, Model Validation and Model Comparisons, and Uncertainty describes many areas of this assessment which should be considered when evaluating the methodology or viewing the results.

5.6.1. Observations Concerning Exposure Media Concentrations

Exposure media results are given in Tables 5-4 through 5-6.

- ***Soil Concentrations***:

1. The lowest exposure site soil concentrations resulted from deposition of particles 5000 m away from the example stack emission source. This was the location of the exposure site in the central stack emission demonstration scenario, Scenario 5. The highest exposure site soil concentrations were predicted for the demonstration of the soil contamination scenario. About 6 orders of magnitude separate the exposure site soil concentrations of 2,3,7,8-TCDD predicted for the central stack emission demonstration scenario, Scenario 4, and the soil contamination scenario, Scenario 5.

2. Concentrations for the stack emission central and high end scenario were about 3 and 2orders of magnitude lower than the central and high end scenarios demonstrating background conditions, respectively. This suggests that the example stack emission source, which was a single emission source with a high level of pollution control, would contribute little to overall background levels in soil.

3. The order of magnitude difference in distance from the stack between the central (5000 meters away) and high end (500 meters) scenarios is matched by the same order of magnitude difference in soil concentrations.

4. For both the background scenarios, 1 and 2, and the stack emission scenarios, 4 and 5, WHO_{98}-TEQ_{DF} soil concentrations were over an order of magnitude higher than 2,3,7,8-TCDD concentrations. The difference in 2,3,7,8-TCDD and WHO_{98}-TEQ_{DF} impacts to all media mirrors the difference in stack emissions of 2,3,7,8-TCDD and stack emissions of WHO_{98}-TEQ_{DF}. This

trend in differences between 2,3,7,8-TCDD and TEQ impacts occurs in all exposure media estimations for both the background scenarios and the stack emission scenarios.

5. For the demonstration of the soil contamination source, exposure site soil concentrations resulting from erosion were the same for all three compounds. This is because the same initial soil concentration was assumed at the site of contamination, and the erosion algorithm contains only one chemical specific parameter. This is the rate of dissipation for eroding contaminants. It was assigned a value of 0.0277 yr^{-1} (25-year half life) for all three example compounds. The stack emission source also has only one contaminant-specific parameter in the algorithm, the soil dissipation rate, and it was also assigned a value of 0.0277 yr^{-1} for all congeners.

- ***Vapor and Particle-Phase Air Concentrations***:

1. The partitioning of air-borne dioxins is modeled differently for the stack emission and the soil contamination sources. For the stack emission source, dioxins are assumed to be in equilibrium between the particle and the vapor phase from stack to receptor. The equilibrium partitioning model is explained in detail in Chapter 3. The application of this model in the demonstration scenario resulted in the 2,3,7,8-TCDD to be approximately 51% in the vapor phase and 49% in the particle phase. For the WHO_{98}-TEQ_{DF} air concentration, the partitioning, as seen in Table 5-4, is about 88% in the particle phase and 12% in the vapor phase for the background scenario, and about 71% particle/29% vapor for the stack emission source category. However, the modeling of dioxins above a site of soil contamination does not result in partitioning that approaches these equilibrium calculations. The volatilization, wind erosion, and dispersion algorithms are described in Chapter 4. As seen in Table 5-5, the vapor phase dominates the total air concentration and is about 95% of the total concentration. Residues which volatilize from the soil are assumed to remain in the vapor phase. However, it is possible that dioxin-like compounds released into the air this way would not remain in vapor phase, but would partly sorb to air-borne particles. An alternate approach to the one take for this assessment would be to sum the total concentrations of dioxins modeled to be emitted from soil, and to repartition them according to the equilibrium calculations. This is not done in this assessment.

2. The background WHO_{98}-TEQ_{DF} air concentration was 0.021 pg/m^3. In contrast, the WHO_{98}-TEQ_{DF} air concentration for the stack emission source was 2 orders of magnitude lower at 500

meters from the stack, at 0.00024 pg/m^3, and was over 2 orders of magnitude lower at 5000 meters from the stack, at 0.000085 pg/m^3.

3. The air concentration of 2,3,7,8-TCDD is highest in the soil contamination source category at 0.0042 pg/m^3. The background air concentration of this congener, used in Scenarios 1 and 2, is actually not that much lower at 0.0014 pg/m^3. There is the same 2 and 3 order of magnitude difference in the stack emission air concentrations of this congener compared to background that is seen in the comparison of other media concentrations - at 5000 m, the 2,3,7,8-TCDD concentration is $4.8*10^{-6}$ pg/m^3, and at 500 m, it is $1.4*10^{-5}$ pg/m^3.

4. The vapor phase air concentration over a site of soil contamination is a function of contaminant-specific parameters including the partition coefficient, Koc, and the Henry's Constant, H. As seen in Table 5-5, the vapor phase concentrations of the three demonstration congeners are different: 0.004 pg/m^3 for 2,3,7,8-TCDD, 0.007 pg/m^3 for 2,3,4,7,8-PCDF, and 0.002 pg/m^3 for 2,3,3',4,4',5,5'-HPCB. The particle phase concentrations were not different, however, since the wind erosion algorithm was not a function of contaminant specific properties.

- ***Water Impacts Including Water, Sediment, and Fish***:

1. There was a 2 order of magnitude difference in all water impacts between the background scenario and the stack emission scenario. This is easily seen in Table 5-4.

2. For the stack emission source category, surface water impacts were not a function of the location of the exposure site, unlike other media concentrations associated with the exposure site including air, soil, and home grown foods. Therefore, the media concentrations will be the same for the central and high end scenarios.

3. The surface water impacts are comparable for the contaminated soil demonstration, Scenario 3, the effluent discharge scenario, Scenario 6, and the background scenarios (#1 and #2). Examining the 2,3,7,8-TCDD fish lipid concentrations, they are: 6.4 ppt for the effluent discharge scenario, 4.3 ppt for the soil contamination scenario, and 3.0 ppt for the background scenarios. The surface water impacts are much lower for the stack emission scenarios, #4 and #5 - the fish lipid concentration is 0.0003 ppt for the stack emission scenarios. This observation is

particularly noteworthy in that the assumed effluent discharge rate is 84% lower than originally measured in the 104-mill study in 1989.

4. The PCB concentrations were between 1 and 2 orders of magnitude higher than the dioxin and furan because the key bioaccumulation variables estimating fish tissue concentrations, the Biota Sediment Accumulation Factor, BSAF, and the Biota Suspended Solids Accumulation Factor, BSSAF (used only for the effluent discharge source category), is 2.0 for the example PCB while it is 0.09 for the example dioxin and and 0.14 for the example furan.

5. Concentrations of WHO_{98}-TEQ_{DF} in water in the background and stack emission scenarios were all less than 0.01 pg/L (ppq), and for the individual congeners in the soil contamination and effluent discharge scenarios was less than 0.1 pg/L. These very low concentrations are the result of high lipophilicity of the dioxins, furans, and PCBs. The water ingestion pathway had the lowest exposure estimates of all pathways.

- ***Terrestrial Vegetation Concentrations***:

1. At first glance, there appears to be roughly a 2-3 order of magnitude difference in above ground vegetables/fruits and above ground leafy vegetation. In fact, this is due to two modeling differences: 1) the fruit/vegetable concentrations are presented in fresh weight. The dry weight to fresh weight conversion factor is 0.15, or equivalently, a dry weight concentration is about 6.7 times higher than fresh weight concentration, and 2) fruit/vegetables are bulky above ground vegetation. Literature data and experimental studies supported the hypothesis that dioxins impacted mainly the outer portions of bulky above ground vegetation and did not translocate to inner plant parts. The vapor phase air-to-plant algorithm, meanwhile, was calibrated to predict leafy vegetation, whole plant, concentrations. Therefore, to reduce predicted leafy whole plant concentrations to more appropriate dilute whole plant concentrations for bulky vegetation, an empirical parameter, VG_{ag}, was introduced. It was assigned a value of 0.01 for bulky above ground fruits/vegetables and 1.00 for leafy vegetation. With these two modeling differences, leafy vegetation dry weight concentrations are 666 times greater than bulky vegetable/fruit fresh weight concentrations. Other differences in concentrations are explained by differences in the particle phase impact algorithms of the two types of vegetation.

2. A more significant difference is found in the algorithms predicting below and above ground vegetation concentrations for the different source categories. Below ground vegetables are higher in concentration as compared to above ground vegetables, as seen in Tables 5-4, for the background and stack emission demonstrations, and in Table 5-5, for the soil contamination source category. However, the degree of difference is significantly more for the soil contamination source category as compared to the stack emission category or background demonstration scenarios. For these latter two cases, below ground vegetables are only between 1 and 2 times higher than above ground vegetables, but for the soil contamination source category demonstration, below ground vegetables are over 3 orders of magnitude higher than above ground vegetables.

The explanation for this trend is found in the air-to-soil model validation exercise which is described in Chapter 7. In that exercise, the background air profile used in the demonstrations in this chapter was modeled to deposit onto soil and mix in a 7.5-cm reservoir. The predicted soil concentrations were shown to match the measured soil concentrations, also used in the demonstrations in this chapter, reasonably well. Therefore, it would appear that the overall model seems to mimic air to soil relationships when air is the principal source of the dioxins in soil. Except for cases of specific soil contamination, this will often be the case, and certainly is expected to be case for background settings where there are no major sources for soil contamination. However, when the soil concentrations were assumed to be the source for air concentrations, and the soil contamination algorithms were used to predict air concentrations above the background soil, it was found that the predicted air concentrations were much lower than the measured air concentrations. Two possible explanations were offered for this trend: 1) the models predicting volatilization and dispersion were underpredicting air concentrations, and/or 2) measured air concentrations in the specific background setting used in the demonstration, and for background settings in general, are not only due to soil emissions, but also from the long range transport of residues from distant sources. In fact, it may be the case that distant sources of dioxin emissions to the air, such as stack emissions, followed by long range transport, explain significantly more of the background air concentrations found than local soil emissions from soils with background concentrations. If so, than a model prediction of background air concentration based on background soil emission will be significantly lower than background air concentrations.

For the purpose of this explanation, one can develop a ratio of air to soil concentration to more fully understand this difference. For the background scenario, and taking air and untilled soil concentrations from Table 5-4, an air to soil WHO_{98}-TEQ_{DF} concentration ratio is, 0.14 for

the background scenario (total air concentration divided by untilled soil concentration, Table 5-4), 0.008 for the high end stack emission scenario, and 0.02 for the central stack emission scenario. The same ratio for the soil contamination scenario is on the order of $1*10^{-5}$. Therefore, the relative strength of air dioxins to soil dioxins is about three to four orders of magnitude higher when air is the source, as in the background scenarios, than when soil is the source, as in the soil contamination scenario.

Since above ground vegetables are a function of air concentrations, it then stands to reason that the discrepancy between below and above ground vegetables will be much higher when soil is the source of contamination as compared to when air is the source of contamination.

3. For the soil contamination demonstration, the tilled and untilled soil concentrations were the same for the three contaminants demonstrated. As noted in the observations for soil concentrations, this is because the parameters predicting exposure site soil concentrations from a distant site of soil contamination are the same for the three contaminants. However, there are differences in the predicted above and below ground vegetation for the three contaminants. Transfers from soil to plant are driven by chemical parameters, particularly the octanol water partition coefficient, Kow. 2,3,3',4,4',5,5'-HPCB and 2,3,7,8-TCDD had similar Kow, with 2,3,4,7,8-PCDF at a lower Kow. Higher Kow translates to tighter sorption to soil, and less transfer to plant, either through root uptake or air-to-leaf transfer. This trend translated to the lower fruit/vegetable concentrations for 2,3,3',4,4',5,5'-HPCB and 2,3,7,8-TCDD as compared to 2,3,4,7,8-PCDF.

- ***Terrestrial Animal Product Lipid Concentrations***:

1. Within each demonstration scenario, there appears to be a reasonably narrow range of predicted lipid concentrations among beef, milk, chicken, and egg fat. The difference is about a factor of 3 to 4. The lowest concentrations are noted for the stack emission demonstration scenarios, in the 10^{-3} to 10^{-2} pg WHO_{98}-TEQ_{DF}/g (ppt) range. The background concentrations were next highest, about two orders of magnitude higher in the 10^{-1} to 10^{0} ppt range, and the soil contamination demonstration was the highest at about two orders of magnitude higher still, at 10^{2} to 10^{3} pg 2,3,7,8-TCDD/g lipid.

2. The differences within a scenario can be explained by a combination of three factors: the apportioning of dry matter intake by the animal between soil and terrestrial vegetation, the

differences in the bioconcentration factors between beef/milk, chicken, and eggs, and the relationships between soil and vegetation as described above. For example, milk fat concentrations were lower than beef fat concentrations in all cases, but within about a factor of two. This was due to assumptions concerning apportioning of total dry matter intake between contaminated soil, contaminated pasture grass, and home-grown contaminated feeds. Beef cattle were assumed to take in twice as much soil as lactating cattle, 4% of their dry matter intake versus 2%, and much more leafy vegetation than lactating cattle, 48% pasture grass versus 8% pasture grass. Another interesting trend is that the chicken and egg fat concentrations are much higher than the beef/milk fat concentrations for the contaminated soil demonstration scenario, but the chicken and egg fat concentrations are lower or comparable for the background and stack emission scenarios. This is due to two factors: the free range chickens had 10% of their diet in soil as compared to 4 and 2% for beef and dairy cattle - this obviously will be important in a contaminated soil scenario, and the above ground vegetation were substantially less impacted, relatively speaking, in the soil contamination scenario as compared to the background or stack emission scenarios, as explained above in the vegetation observations. This would tend to minimize the importance of the vegetation in the diet of beef or dairy cattle in the soil contamination scenario.

3. In the observations concerning surface water impacts, it was noted that the fish lipid concentration of the PCB congener was much higher than the dioxin or furan congener. This was because the BSAF/BSSAF of the PCB congener was much higher at 2.10 as compared to the BSAF/BSSAF of the dioxin and furan congeners, 0.09 and 0.14, respectively. However, the literature suggests that the terrestrial animal bioconcentration factors are more similar for the three congeners. Hence, and as seen in Table 5-5, the beef, milk, chicken, and egg fat concentrations are comparable among the three congeners.

4. Table 5-6 shows the individual congener concentrations in beef for the high end background and stack emission scenarios. Recall that the TEQ beef concentration was about two orders of magnitude higher for the background as compared to the stack emission scenario. For all congeners except the tetra congeners, the difference is this same two order of magnitude difference, and up to 3 orders of magnitude difference for the higher chlorinated congeners. For the tetra congeners, 2,3,7,8-TCDD and 2,3,7,8-TCDF, the difference is an order of magnitude and less. This suggests that the congener profile in the hypothetical incinerator is distinctly

different than the background profile: the incinerator emissions would appear to have a greater proportion of emissions in the tetra congeners as compared to background air or soil.

5.6.2. Observations Concerning LADD Exposure Estimates

Much of the differences between exposure pathways and scenarios is due to differences in exposure media estimation. Therefore, much of the above discussion is also appropriate for analysis of Lifetime Average Daily Dose, LADD, estimates. What will be noted below are unique observations. LADD results are given in Tables 5-7 through 5-11.

1. Like in exposure media estimation, LADDs for the stack emission scenarios, 4 and 5, were the lowest at 10^{-11} to 10^{-7} ng WHO_{98}-TEQ_{DF}/kg-day, followed by the background scenarios, 1 and 2, at 10^{-8} to 10^{-5} ng/kg-day, the effluent discharge scenario which had a fish ingestion LADD in the 10^{-5} range, and finally the soil contamination scenario with the highest LADDs ranging from 10^{-8} to 10^{-3} ng/kg-day for all three compounds demonstrated - the dioxin, furan and PCB.

2. Tables 5-7 and 5-8 also show the percent of total scenario exposure which is accounted for by each pathway. The total scenario LADD was calculated simply as the sum of the pathway LADDs in the scenario, without accounting for any differences in body absorption. It should be remembered, however, that the amount of dioxin absorbed by the soil dermal contact pathway is estimated at 3%. This was accounted for in the calculation of LADD, so that the LADD for the soil dermal contact pathway was "absorbed" dose, while for all other pathways, the LADD was the "administered" or "potential" dose. As discussed in Chapter 2, the absorption for these other pathways was in the neighborhood of 80%, except for soil ingestion, where the absorption is on the order of 30%. Because of this 3% absorption accounted for in the dermal contact pathway, the LADD for this pathway is almost always the lowest of all pathways. From Tables 5-7 and 5-8, it is seen from the individual percentages that the food pathways dominate the scenarios, with fish ingestion dominating the central scenarios and beef ingestion dominating the high end scenarios. Furthermore, the beef ingestion pathway LADD was over an order of magnitude higher than the fish ingestion pathway LADD. This was more due to differences in the exposure parameters including the ingestion and contact rates, and the differences in the lipid content of the full product, rather than lipid concentrations themselves since the fish lipid concentrations tended to be higher than the beef lipid concentrations for a given source. For example, in the background scenario, the fish lipid concentration was modeled as 6.33 ppt WHO_{98}-TEQ_{DF}, while the beef lipid concentration was about one-fourth of that at 1.58 ppt WHO_{98}-TEQ_{DF}.

3. Differences between analogous "central" and "high end" exposure pathway estimates for the background demonstration scenarios, 1 and 2, were near or less than an order of magnitude (inhalation exposure for the central background scenario and the inhalation exposure for high end on-site scenario are analogous exposures). This is because the exposure parameters used to distinguish typical and high end exposures, the contact rates, contact fractions, and exposure durations, themselves did not differ significantly, and these were the only distinguishing features for analogous pathways in the background demonstrations. For the total exposure, however, there was a difference of a factor of 20 between high end and central exposure in the background demonstration scenarios. This is because the high end scenario included consumption of beef, which was the highest exposure pathway and exceeded the fish pathway of the central scenario by over an order of magnitude.

4. In the stack emission scenarios, placing exposed individuals either 500 or 5000 meters away from the incinerator did significantly impact the results. The order of magnitude difference in distance added about an order of magnitude difference in exposure media concentrations and hence LADD estimates. Therefore, the full difference in analogous pathways between the central and high end was closer to 2 orders of magnitude for the stack emission demonstration scenarios.

5. Tables 5-9 and 5-10 show results for the food ingestion pathways that were not included in the scenarios. One observation here is that the terrestrial animal product pathways, including milk, chicken, and egg ingestion pathways, are all less than the beef ingestion pathway, by up to an order of magnitude, despite the fact that the terrestrial food product lipid concentrations were fairly near each other. For example, the chicken fat concentration in the background scenario was 0.61 ppt WHO_{98}-TEQ_{DF}, compared to the beef fat concentration for that scenario of 1.58 ppt. The chicken ingestion pathway LADD was over an order of magnitude less than the beef ingestion pathway, however. This was due to the differences in the four other exposure related parameters which differ for chicken and beef: 1) beef was assumed to be 19% fat while chicken was assumed to be 13% fat, 2) the whole product ingestion rate of beef was 2.45 g/kg-day while the whole product ingestion rate of chicken was 0.97 g/kg-day, 3) according to the analysis of the National Food Consumption Survey described in Chapter 2, the beef ingestion pathway had a higher contact rate of 0.478 compared to the chicken contact rate of 0.151, and 4) the chicken and beef pathways had an additional food preparation factor which considers discarded portions

(bones, etc.) and cooking loss. This factor did not differ greatly for the two food products, 0.55 for beef and 0.49 for chicken.

6. Table 5-11 relates all the pathways considered in this demonstration for the background, the stack emission, and the soil contamination demonstrations. This table includes the food ingestion pathways that were not in the demonstration scenarios. It was constructed by assigning a value of 1.00 to the beef ingestion pathway, and then determining the ratio of the other pathways to the beef pathway. This table again shows the domination of beef and milk exposures, at least given the exposure parameters, lipid contents, and so on, assigned to the demonstration scenarios. The fish pathway was very important in the background scenario as compared to the other two scenarios. The main reason for this was how the models predicted bottom sediments. For the background scenario, the predicted sediment concentration was nearly three times higher at 3.4 ppt WHO_{98}-TEQ_{DF} than the soil to which the cattle were exposed, 1.3 ppt. In contrast, the sediment concentration was nearly an order of magnitude lower at 0.0024 ppt WHO_{98}-TEQ_{DF} than the soil concentration to which cattle were exposed in the high end stack emission scenario, at 0.035 ppt WHO_{98}-TEQ_{DF}. Even more dramatic, there was a two order of magnitude difference in the sediment and soil concentration for the soil contamination site scenario - 1.4 vs. 357 ppt 2,3,7,8-TCDD. Table 5-11 also shows that a childhood pattern of soil ingestion can be an important pathway, ranking along with chicken and egg exposures in the background and stack emission demonstrations. The chicken and egg pathways were considerably more important in the soil contamination scenario as compared to the other two pathways. This is due to the trend of predicting much higher chicken and egg concentrations in the soil contamination scenario as compared to the background and stack emission scenarios; this was discussed earlier in the observations for the exposure media concentrations. Vegetable ingestion was also more important in the soil contamination scenario, which was driven by high below ground vegetable concentration. Vegetable ingestion and inhalation were comparable to the chicken, egg, and soil ingestion pathways in the background and stack emission scenarios. Fruit ingestion, dermal exposure, and water ingestion are all relatively minor compared to the animal ingestion pathways and were less than 1% of the exposures estimated for beef ingestion.

7. Fish was the principal impacted media for the effluent discharge source category, with fish ingestion 19 times higher than water ingestion, the only two pathways considered for the effluent discharge category. Fish was an important route of exposure in the central scenarios for the

background and stack emission scenarios, 1 and 3, explaining over half of all exposures estimated for those scenarios.

5.7. HEALTH RISK DEMONSTRATIONS

Chapter 2 described the procedures to generate estimates of excess cancer risks and the ratio IOB to evaluate potential non-cancer impacts. This section will demonstrate these health risk assessment procedures, using the background and the high end stack emission scenarios.

Recall that excess cancer risk is estimated as the product of the LADD and cancer potency factor, q_1^*. For 2,3,7,8-TCDD, the q_1^* is 1.0 kg-day/ng, and this value is also used for TEQ LADDs. Table 5-12 shows the cancer risk estimates for the background and the stack emission high end scenarios, where LADDs are for WHO_{98}-TEQ_{DF} exposures.

As seen in Table 5-12, there is a 2 order of magnitude difference between the total cancer risk of both scenarios, the same 2 order of magnitude difference in the total LADDs as noted earlier. The cancer risk associated with the high end scenario for the incinerator was $9*10^{-7}$, while the background high end cancer risk was $9*10^{-5}$.

The cancer risk for the background scenario corresponds to a lifetime average daily dose, LADD, of 6 pg WHO_{98}-TEQ_{DF}/day. This is about a factor of seven lower than the background dose of 43 pg WHO_{98}-TEQ_{DF}/day generated in Volume II, Chapter 4 of the Exposure Reassessment Document. The reasons for this difference are: 1) the Volume II background exposure estimate was an average daily dose, ADD, not an LADD calculated in the demonstration scenarios here. The LADD estimated in this chapter assumes 30 years of exposure. The ADD during the exposure period would be just over twice, or 70/30, the LADD; 2) the Volume II background exposure considered additional pathways including fish, dairy ingestion (milk and otherwise), eggs, pork, and poultry. If one adds the additional pathways for the background high scenario - milk, chicken, egg, and fish shown in Table 5-9 - the LADD (and ADD) roughly doubles; 3) the exposure factors are different, with the most important difference being that in the exposure scenarios considered in this chapter, contact fractions of less than 1.0 were assumed - less than 0.5 for the terrestrial animal pathways, in fact.

Some of these differences also are relevant for the procedures demonstrated here to characterize non-cancer risk. Specifically, the procedures described in Chapter 2 require the assignment of a “background body burden” in the calculation of an Increment Over Background, IOB, ratio. The IOB is defined as the ratio of the incremental of body burden due to the source being evaluated (IBB) and the background body burden (BB_{bk}) times 100%. As described in Chapter 2, the BB_{bk} can be a generic U.S. background body burden, or a site-specific background.

The generic adult background body burden is currently evaluated as 5 ng WHO_{98}-TEQ_{DF}/kg. However, this quantity represents the full range of the current adult population; an assessor could consider the background body burden for younger adults rather than the full range of adult ages (younger adults would have a lower background body burden), whether to consider specific populations such as women of child-bearing age (which again might imply a lower concentration as compared to a full population average), and so on. As well, one could develop a body burden that is specific to the site being evaluate. This could be a non-trivial exercise and could involve estimating quantities that have not been considered when evaluating only an increment of exposure due to a specific source. Chapter 2 went into some of the issues to consider when developing a site-specific estimate of background exposure dose/intake or background body burden.

If an assessor could determine an appropriate background exposure dose for a specific site being evaluated, he could then use the simple first order pharmacokinetic model to convert this site-specific dose to a site-specific BB_{bk}. To do so, an assessor needs to estimate the total exposure of an individual (or individuals) to dioxins as though the nearby source being evaluated was not in existence. In a farm family scenario, the family would still be consuming home produced foods, but these foods would only be impacted by background dioxins in the environment, and no longer by the source being evaluated. But they would also be consuming store-bought or restaurant-bought foods. The "total" exposure would include all pathways considered in the scenarios of this chapter, but other pathways as well.

For the purposes of this demonstration, it will be assumed that the farming family in the background scenario consumes foods at similar rates whether or not they are consuming home-produced or store-bought food products, and that their exposure is characterized by all the pathways in the formal scenarios of Table 5-7, as well as the additional scenarios shown in Table 5-9. To estimate their average background daily dose over a lifetime, the exposure duration will increase from 30 to 70 years, and the contact fractions will all rise to 1.00. The resulting daily exposure is 1.16 pg WHO_{98}-TEQ_{DF}/kg-day. This 1.16 pg WHO_{98}-TEQ_{DF}/kg-day will be used here as the "site-specific background dose" against which one can develop IOBs for the incinerator source.

For generation of the increment of body burden due to the incremental exposure, one needs to estimate the ADD during the period of exposure. The total LADD for the stack emission high end scenario, as displayed in Table 5-7, is $1.01 * 10^{-3}$ pg WHO_{98}-TEQ_{DF} /kg-day. The ADD can be simply calculated as this LADD times 70/30, or $2.36 * 10^{-3}$ pg WHO_{98}-TEQ_{DF}/kg-day. It is now possible to calculate the site-specific background body burden, BB_{bk},

and the increment of body burden due to the site-specific source, IBB, using this generalized equation:

$$BB_i = \frac{DD\ AF}{k\ CF_1}(1 - e^{-kt}) \quad (5\text{-}2)$$

where:

BB_i = body burden of interest, either BB_{bk} or IBB, pg/g (ppt) whole weight basis

DD = dose quantity for calculating the BB, either the site-specific lifetime average daily dose, LADD, or the daily dose during the period of exposure to the specific source, ADD, pg/kg-day (whole body weight basis)

AF = absorption fraction

k = first-order rate of decline of dioxin residues from the body, day^{-1}, calculated as $(\ln 2/t_{1/2})$, where $t_{1/2}$ is the half-life, days

CF = conversion factor, 1000 g/kg

t = time of exposure, either lifetime for BB_{bk} or the exposure duration for ADD, days

Using assumptions used in the Risk Characterization as first approximations for pharmacokinetic modeling of TEQs, AF will be assumed to be 0.8, $t_{1/2}$ will be 7.1 years so that k is calculated as 0.000267 day^{-1}. The appropriate values for t include the exposure duration corresponding to the ADD described above for the high end scenario, which is 30 years (10950 days), and the 70 year (25550 days) lifetime assumed for calculation of BB_{bk}. Finally, the DDs equal the 1.16 and 0.00236 pg WHO_{98}-TEQ_{DF}/kg-day, as discussed above.

Substituting these values yields body burdens of 0.007 pg WHO_{98}-TEQ_{DF}/g for IBB and 3.5 pg WHO_{98}-TEQ_{DF}/g for BB_{bk}. The IOB is then easily solved for as, 0.2 % ([0.007/3.5]*100). This increment of body burden increase is very low and can probably be characterized as insignificant. It is also interesting to note that the BB_{bk} at 3.5 ppt TEQ is lower than the general US population background body burden of 5.0 ppt TEQ. As discussed in Volume II of these Exposure Documents, and as alluded to in discussions above, the general US population background body burden is influenced by higher concentrations in older individuals who experienced higher doses in the past. The "steady state" body burden at the current general US background exposure dose of 1.0 pg WHO_{98}-TEQ_{DFP}/kg-day is also lower than 5.0 ppt, at 3.0 ppt. The assessor can choose either the general US background exposure, this steady state exposure at

current US background doses, a site-specific background exposure, or even another background quantity in developing the IBB term for non-cancer risk assessing at specific sites.

It is once again emphasized that the scenarios and all exposure parameters, and the fate modeling with their parameters, used in this demonstration chapter, are not being offered as default values or recommendations for all uses. Chapter 6 contains additional information pertaining to these models, including sensitivity analysis exercises and discussions of model parameters. Chapter 7 provides a critical evaluation of the fate models selected in this methodology, including model comparisons and model validation exercise. Chapter 8 on Uncertainty critically evaluates the fate and exposure modeling approaches and parameters used in this assessment. Information in these three Chapters should be reviewed when evaluating the validity of the approaches demonstrated in this Chapter.

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Table 5-1. Fate and transport parameters for the dioxin-like congeners demonstrated in this chapter (see bottom of table for column definitions).

Congeners	TEF	H	$p°_L$	V/P	Log Kow	Koc	Bvpa	BSAF/ BSSAF	RCF	BCF	CCF	ECF
2378-TCDD	1.0	$3.29*10^{-5}$	$6.27*10^{-10}$	51/49	6.80	$3.98*10^{6}$	$6.55*10^{4}$	0.090	5200	5.76	8.8	7.8
12378-PCDD	1.0	$2.60*10^{-6}$	$9.20*10^{-11}$	13/87	6.64	$2.69*10^{6}$	$2.39*10^{5}$	0.083	3916	5.55	6.8	6.0
123478-HxCDD	0.1	$1.07*10^{-5}$	$2.01*10^{-11}$	3/97	7.80	$3.89*10^{7}$	$5.20*10^{5}$	0.028	30600	2.69	3.6	5.4
123678-HxCDD	0.1	$1.10*10^{-5}$	$2.01*10^{-11}$	3/97	7.30	$1.23*10^{7}$	$5.20*10^{5}$	0.011	12600	2.32	5.6	10.2
123789-HxCDD	0.1	$1.10*10^{-5}$	$2.01*10^{-11}$	3/97	7.30	$1.23*10^{7}$	$5.20*10^{5}$	0.013	12600	2.99	2.4	4.5
1234678-HpCDD	0.01	$1.26*10^{-5}$	$5.05*10^{-12}$	1/99	8.00	$6.17*10^{7}$	$9.10*10^{5}$	0.003	43700	0.48	1.4	4.8
OCDD	0.0001	$6.75*10^{-6}$	$1.32*10^{-12}$	0.2/99.8	8.20	$9.77*10^{7}$	$2.36*10^{6}$	0.001	62200	0.69	0.3	4.3
2378-TCDF	0.1	$1.44*10^{-5}$	$6.80*10^{-10}$	47/53	6.10	$7.76*10^{5}$	$4.57*10^{4}$	0.072	1500	1.25	3.1	2.7
12378-PCDF	0.05	$5.00*10^{-6}$	$1.96*10^{-10}$	25/75	6.79	$3.80*10^{6}$	$9.75*10^{4}$	0.020	5110	0.97	18.0	20.5
23478-PCDF	0.5	$4.98*10^{-6}$	$1.15*10^{-10}$	16/84	6.50	$1.95*10^{6}$	$9.75*10^{4}$	0.144	3050	4.13	7.4	7.8
123478-HxCDF	0.1	$1.43*10^{-5}$	$4.21*10^{-11}$	7/93	7.00	$6.17*10^{6}$	$1.62*10^{5}$	0.007	7410	3.12	4.8	7.4
123678-HxCDF	0.1	$7.31*10^{-6}$	$4.21*10^{-11}$	7/93	7.00	$6.17*10^{6}$	$1.62*10^{5}$	0.017	7410	2.67	5.3	8.2
123789-HxCDF	0.1	$1.10*10^{-5}$	$2.56*10^{-11}$	4/96	7.00	$6.17*10^{6}$	$1.62*10^{5}$	0.060	7410	2.67	4.1	6.2
234678-HxCDF	0.1	$1.10*10^{-5}$	$2.56*10^{-11}$	4/96	7.00	$6.17*10^{6}$	$1.62*10^{5}$	0.057	7410	2.37	2.1	3.0
1234678-HpCDF	0.01	$1.41*10^{-5}$	$1.13*10^{-11}$	2/98	7.40	$1.55*10^{7}$	$8.30*10^{5}$	0.001	15100	0.55	1.0	3.1
1234789-HpCDF	0.01	$1.40*10^{-5}$	$6.51*10^{-12}$	1/99	8.00	$6.17*10^{7}$	$8.30*10^{5}$	0.035	43700	1.32	0.9	2.2
OCDF	0.0001	$1.88*10^{-6}$	$1.24*10^{-12}$	0.2/99.8	8.80	$3.89*10^{8}$	$2.28*10^{6}$	0.001	180000	0.27	0.3	1.4
233'44'55'-HPCB	0.0001	$6.60*10^{-5}$	$1.46*10^{-11}$	42/58	7.71	$3.16*10^{7}$	$1.49*10^{5}$	2.10	26100	2.30	6.5	7.4

Table 5-1. (con't.)

Definitions for Table 5-1:

TEF:	Toxicity Equivalency Factor	Log Kow:	log octanol water partition coefficient
H:	Henry's Constant, atm-m^3/mole	Koc:	Organic carbon partition coefficient, L/kg
$p°_L$:	liquid sub-cooled vapor pressure, 20°C, atm	B_{vpa}:	Air-to-leaf biotransfer factor, (pg PCDD/g leaf dry)/(pg PCDD/g air)
V/P:	Vapor phase/particle phase percentages	BSAF/BSSAF:	Biota-to-(suspended) sediment accumulation factor, unitless
RCF:	Root concentration factor, unitless	BCF/CCF/ECF:	Beef/milk, chicken, egg fat bioconcentration factor, unitless

Table 5-2. Summary of key source terms for the background scenarios, 1 and 2.

Congeners	TEF	Dry Dep, pg/m^2-yr	Wet Dep, pg/m^2-yr	C_{air}, pg/m^3	C_{soil}, pg/g
2378-TCDD	1.0	43	43	0.0014	0.37
12378-PCDD	1.0	286	286	0.0052	0.14
123478-HxCDD	0.1	482	482	0.0079	0.35
123678-HxCDD	0.1	570	570	0.0093	0.82
123789-HxCDD	0.1	826	826	0.0135	1.23
1234678-HpCDD	0.01	14,170	14,170	0.227	17.73
OCDD	0.0001	56,900	56,900	0.904	160.89
2378-TCDF	0.1	82	82	0.0028	0.64
12378-PCDF	0.05	308	308	0.0065	0.17
23478-PCDF	0.5	394	394	0.0074	0.21
123478-HxCDF	0.1	780	780	0.0133	0.15
123678-HxCDF	0.1	909	909	0.0155	0.11
123789-HxCDF	0.1	168	168	0.0028	0.15
234678-HxCDF	0.1	555	555	0.0092	0.64
1234678-HpCDF	0.01	4277	4277	0.0692	4.06
1234789-HpCDF	0.01	893	893	0.0143	0.27
OCDF	0.0001	4198	4198	0.0667	10.72
WHO_{98}-TEQ_{DF}		1180	1180	0.021	1.29

Table 5-3. Summary of key source terms for Scenarios 4 and 5, the stack emission demonstration scenarios.

Congeners	TEF	Scenario 4 - Central; 5000 meters downwind				Scenario 5 - High End; 500 meters downwind			
		Wet Dep pg/m^2-yr	Dry Dep pg/m^2-yr	C_{air}, pg/m^3	C_{soil}, pg/g	Wet Dep $pg/-m^2$-yr	Dry Dep pg/m^2-yr	C_{air} , pg/m^3	C_{soil}, pg/g
2378-TCDD	1.0	0.05	0.10	$4.84*10^{-6}$	$1.72*10^{-4}$	0.68	0.44	$1.37*10^{-5}$	$1.36*10^{-3}$
12378-PCDD	1.0	0.17	0.36	$1.01*10^{-5}$	$6.40*10^{-4}$	2.54	1.65	$2.87*10^{-5}$	$5.04*10^{-3}$
123478-HxCDD	0.1	0.25	0.52	$1.30*10^{-5}$	$9.22*10^{-4}$	3.66	2.38	$3.71*10^{-5}$	$7.27*10^{-3}$
123678-HxCDD	0.1	0.33	0.69	$1.72*10^{-5}$	$1.22*10^{-3}$	4.85	3.14	$4.89*10^{-5}$	$9.66*10^{-3}$
123789-HxCDD	0.1	0.36	0.75	$1.89*10^{-5}$	$1.34*10^{-3}$	5.33	3.46	$5.39*10^{-5}$	$1.06*10^{-2}$
1234678-HpCDD	0.01	3.30	6.92	$1.70*10^{-4}$	$1.23*10^{-3}$	48.9	31.8	$4.84*10^{-4}$	$9.71*10^{-2}$
OCDD	0.0001	6.85	14.4	$3.50*10^{-4}$	$2.56*10^{-2}$	102.0	66.0	$9.98*10^{-4}$	$2.02*10^{-1}$
2378-TCDF	0.1	2.89	6.07	$3.17*10^{-4}$	$1.08*10^{-2}$	42.8	27.8	$8.97*10^{-4}$	$8.50*10^{-2}$
12378-PCDF	0.05	0.30	0.62	$2.02*10^{-5}$	$1.10*10^{-2}$	4.38	2.85	$5.74*10^{-5}$	$8.70*10^{-3}$
23478-PCDF	0.5	0.54	1.14	$3.31*10^{-5}$	$2.03*10^{-3}$	8.04	5.22	$9.40*10^{-5}$	$1.06*10^{-2}$
123478-HxCDF	0.1	0.87	1.83	$4.80*10^{-5}$	$3.25*10^{-3}$	12.9	8.40	$1.36*10^{-4}$	$2.56*10^{-2}$
123678-HxCDF	0.1	0.83	1.73	$4.54*10^{-5}$	$3.07*10^{-3}$	12.2	7.95	$1.29*10^{-4}$	$2.42*10^{-2}$
123789-HxCDF	0.1	0.56	1.18	$2.94*10^{-5}$	$2.10*10^{-3}$	8.32	5.40	$8.50*10^{-5}$	$1.65*10^{-2}$
234678-HxCDF	0.1	0.33	0.69	$1.74*10^{-5}$	$1.22*10^{-3}$	4.84	3.14	$4.94*10^{-5}$	$9.60*10^{-3}$
1234678-HpCDF	0.01	1.15	2.42	$6.01*10^{-5}$	$4.30*10^{-3}$	17.1	11.1	$1.71*10^{-4}$	$3.39*10^{-2}$
1234789-HpCDF	0.01	0.51	1.06	$2.61*10^{-5}$	$1.88*10^{-3}$	7.48	4.86	$7.41*10^{-5}$	$1.48*10^{-2}$
OCDF	0.0001	2.27	4.77	$1.16*10^{-4}$	$8.47*10^{-3}$	33.7	21.9	$3.31*10^{-4}$	$6.69*10^{-2}$
WHO_{98}-TEQ_{DF}		**1.12**	**2.35**	**$8.12*10^{-5}$**	**$4.17*10^{-3}$**	**17.7**	**11.5**	**$2.30*10^{-4}$**	**$3.29*10^{-2}$**

Table 5-4. WHO_{98}-TEQ_{DF} environmental and exposure media concentrations for the background conditions scenarios, #1 and #2, and the stack emissions demonstration scenarios, #4 and #5.

Description	Background, Scenarios 1 and 2	Emission, Central Scenario 4	Emission, High End Scenario 5
Air, vapor phase, pg/m^3	$2.59*10^{-3}$	$2.45*10^{-5}$	$6.94*10^{-5}$
Air, particle phase, pg/m^3	$1.87*10^{-2}$	$6.04*10^{-5}$	$1.74*10^{-4}$
Soil, untilled, pg/g	1.29	$4.46*10^{-3}$	$3.51*10^{-2}$
Soil, tilled, pg/g	0.65	$4.46*10^{-4}$	$3.51*10^{-3}$
Soil, watershed, pg/g	1.29	$8.91*10^{-4}$	$8.91*10^{-4}$
Surface water, pg/L	$2.63*10^{-3}$	$3.80*10^{-5}$	$3.80*10^{-5}$
Sediment, pg/g	3.37	$2.39*10^{-3}$	$2.39*10^{-3}$
fish lipid, pg/g*	6.33	$5.64*10^{-3}$	$5.64*10^{-3}$
leafy vegetation, pg/g dry	0.45	$1.86*10^{-3}$	$6.39*10^{-3}$
above ground fruit/veg, pg/g fresh	$5.74*10^{-3}$	$1.20*10^{-5}$	$6.37*10^{-5}$
below ground vegetables, pg/g fresh	$1.94*10^{-2}$	$1.63*10^{-5}$	$1.29*10^{-4}$
beef fat, pg/g*	1.58	$4.35*10^{-3}$	$1.65*10^{-2}$
milk fat, pg/g*	1.10	$3.05*10^{-3}$	$1.11*10^{-3}$
chicken fat, pg/g*	0.61	$2.02*10^{-3}$	$1.38*10^{-2}$
egg fat, pg/g*	0.71	$2.25*10^{-3}$	$1.55*10^{-2}$

* These food concentrations were not uniformly required for all scenarios. For example, the central scenarios did include a fish ingestion pathway, but the high scenarios did not. Similarly, chicken, milk, and egg pathways are demonstrated outside the context of a scenario. These concentrations are presented here for completeness.

Table 5-5. Environmental and exposure media concentrations for 2,3,7,8-TCDD ("dioxin"), 2,3,4,7,8-PCDF ("furan") and 2,3,3',4,4',5,5'-HPCB (PCB) for the soil contamination demonstration, scenario #3, and the effluent discharge demonstration, scenario #6 (NA = not applicable).

Description	Scenario 3 - Soil Contamination			Scenario 6 - Effluent Discharge		
	dioxin	furan	PCB	dioxin	furan	PCB
Air, vapor phase, pg/m^3	0.004	0.007	0.002	NA	NA	NA
Air, particle phase, pg/m^3	0.0002	0.0002	0.0002	NA	NA	NA
Soil, untilled, pg/g	357	357	357	NA	NA	NA
Soil, tilled, pg/g	61	61	61	NA	NA	NA
Sediment, pg/g*	1.44	0.53	1.56	4.91	3.84	6.40
Surface water, pg/L	0.012	0.091	0.0016	0.018	0.029	0.0029
fish lipid, pg/g**	4.3	2.6	108.9	6.4	8.0	195.7
leafy vegetation, pg/g dry	0.23	0.60	0.26	NA	NA	NA
above ground fruit/veg, pg/g fresh	0.0006	0.0011	0.0006	NA	NA	NA
below ground vegetables, pg/g fresh	2.0	23.4	1.30	NA	NA	NA
beef fat, pg/g**	54.4	40.1	21.8	NA	NA	NA
milk fat, pg/g**	27.5	20.4	11.0	NA	NA	NA
chicken fat, pg/g**	204.1	171.8	171.7	NA	NA	NA
egg fat, pg/g**	180.9	181.1	.150.8	NA	NA	NA

* The sediment concentration given for Scenario 3 is the bottom sediment, while the concentration for Scenario 6 is the suspended sediment. These are the concentrations used in the prediction of fish tissue concentrations.

** These food concentrations were not uniformly required for all scenarios. For example, the central scenarios did include a fish ingestion pathway, but the high scenarios did not. Similarly, chicken, milk, and egg pathways are demonstrated outside the context of a scenario. These concentrations are presented here for completeness

Table 5-6. Individual congener and Toxic Equivalent (WHO_{98}-TEQ_{DF}) concentrations for predicted beef concentration for the background high scenario, scenario # 2, and the stack emission high scenario, scenario 5.

Congeners	TEF	Scenario 2: Background high, pg/g lipid	Scenario 5: Stack emission high, pg/g lipid
2378-TCDD	1.0	0.25	0.021
12378-PCDD	1.0	0.74	0.005
123478-HxCDD	0.1	0.37	0.002
123678-HxCDD	0.1	0.40	0.003
123789-HxCDD	0.1	0.75	0.004
1234678-HpCDD	0.01	1.59	0.004
OCDD	0.0001	9.08	0.011
2378-TCDF	0.1	0.08	0.023
12378-PCDF	0.05	0.13	0.001
23478-PCDF	0.5	0.50	0.008
123478-HxCDF	0.1	0.57	0.008
123678-HxCDF	0.1	0.56	0.007
123789-HxCDF	0.1	0.09	0.004
234678-HxCDF	0.1	0.27	0.002
1234678-HpCDF	0.01	0.71	0.002
1234789-HpCDF	0.01	0.24	0.002
OCDF	0.0001	0.25	0.001
WHO_{98}-TEQ_{DF}		**1.58**	**0.017**

Table 5-7. Lifetime average daily doses, LADD, of Toxic Equivalents (TEQs), for the background scenarios, #1 and #2, and for the stack emission scenarios, #4 and #5.

Scenario/Pathway	LADD, ng/kg-day	Percent of total scenario exposure
Scenario 1 - Background Central		
Soil Ingestion	$5.42*10^{-7}$	6
Soil Dermal Contact	$3.23*10^{-9}$	<1
Inhalation	$4.57*10^{-7}$	5
Water Ingestion	$8.70*10^{-8}$	1
Fish Ingestion	$6.51*10^{-6}$	78
Vegetable Ingestion	$6.95*10^{-7}$	8
Fruit Ingestion	$1.09*10^{-7}$	1
Total	$8.40*10^{-6}$	100
Scenario 2 - Background High		
Soil Ingestion	$3.25*10^{-6}$	4
Soil Dermal Contact	$4.40*10^{-8}$	<1
Inhalation	$2.34*10^{-6}$	3
Water Ingestion	$2.90*10^{-8}$	<1
Beef Ingestion	$8.30*10^{-5}$	91
Vegetable Ingestion	$2.32*10^{-6}$	2
Fruit Ingestion	$3.65*10^{-7}$	<1
Total	$9.16*10^{-5}$	100

Table 5-7. (Cont'd)

Scenario/Pathway	LADD, ng/kg-day	Percent of total scenario exposure
Scenario 4 - Stack Emission Central		
Soil Ingestion	$1.87*10^{-9}$	18
Soil Dermal Contact	$3.22*10^{-12}$	<1
Inhalation	$1.43*10^{-9}$	14
Water Ingestion	$6.85*10^{-11}$	1
Fish Ingestion	$5.81*10^{-9}$	57
Vegetable Ingestion	$8.28*10^{-10}$	8
Fruit Ingestion	$2.29*10^{-10}$	2
Total	$1.02*10^{-8}$	100
Scenario 5 - Stack Emission High		
Soil Ingestion	$8.86*10^{-8}$	9
Soil dermal contact	$2.55*10^{-10}$	<1
Inhalation	$2.68*10^{-8}$	2
Water ingestion	$4.19*10^{-10}$	<1
Beef ingestion	$8.65*10^{-7}$	86
Vegetable ingestion	$1.83*10^{-8}$	3
Fruit ingestion	$4.05*10^{-9}$	<1
Total	$1.00*10^{-6}$	100

Table 5-8. Lifetime average daily doses, LADD, for 2,3,7,8-TCDD ("dioxin"), 2,3,4,7,8-PCDF ("furan") and 2,3,3',4,4',5,5'-HPCB (PCB) for the soil contamination demonstration, scenario #3, and the effluent discharge demonstration, scenario #6.

Scenario/Pathway	Dioxin, ng/kg-day	Furan, ng/kg-day	PCB, ng/kg-day	Percent of total scenario exposure*
Scenario 3 - Soil Contamination				
Soil Ingestion	$8.99*10^{-4}$	$8.99*10^{-4}$	$8.99*10^{-4}$	23
Soil dermal contact	$4.20*10^{-6}$	$4.20*10^{-6}$	$4.20*10^{-6}$	<1
Inhalation	$4.75*10^{-7}$	$8.12*10^{-7}$	$2.40*10^{-7}$	<1
Water ingestion	$1.33*10^{-7}$	$1.00*10^{-6}$	$1.81*10^{-8}$	<1
Beef ingestion	$2.85*10^{-3}$	$2.10*10^{-3}$	$1.14*10^{-3}$	73
Vegetable ingestion	$1.71*10^{-4}$	$2.05*10^{-3}$	$1.08*10^{-4}$	4
Fruit ingestion	$3.75*10^{-8}$	$7.25*10^{-8}$	$4.04*10^{-8}$	<1
Total	$4.06*10^{-3}$	$5.19*10^{-3}$	$2.29*10^{-3}$	100
Scenario 6 - Effluent Discharge				
Water ingestion	$3.22*10^{-8}$	$5.15*10^{-8}$	$5.29*10^{-9}$	<1
Fish ingestion	$6.60*10^{-6}$	$8.26*10^{-6}$	$2.01*10^{-4}$	100
Total	$6.63*10^{-6}$	$8.31*10^{-6}$	$5.01*10^{-5}$	100

* Results in this column are for dioxin

Table 5-9. Lifetime Average Daily Doses, LADD, of Toxic Equivalents (WHO_{98}-TEQ_{DF}) for exposure pathways evaluated outside of the scenarios for background conditions and stack emissions.

Setting/Exposure Pathway	WHO_{98}-TEQ_{DF} LADD, ng/kg-day
Background Conditions, high end setting	
Milk ingestion	$4.09*10^{-5}$
Chicken ingestion	$2.64*10^{-6}$
Egg ingestion	$3.79*10^{-6}$
Fish ingestion, high ingestion rate	$6.78*10^{-5}$
Stack emissions, high end setting	
Milk ingestion	$4.12*10^{-7}$
Chicken ingestion	$5.92*10^{-8}$
Egg ingestion	$8.31*10^{-8}$
Fish ingestion, high ingestion rate	$6.05*10^{-8}$

Table 5-10. Lifetime Average Daily Doses, LADD, of 2,3,7,8-TCDD ("dioxin"), 2,3,4,7,8-PCDF ("furan") and 2,3,3',4,4',5,5'-HPCB ("PCB") for exposure pathways evaluated outside of the scenarios for the soil contamination and the effluent discharge settings.

Setting/Pathway	Dioxin, ng/kg-day	Furan, ng/kg-day	PCB, ng/kg-day
Soil Contamination			
Milk ingestion	$1.19*10^{-3}$	$8.89*10^{-4}$	$4.77*10^{-4}$
Chicken ingestion	$8.79*10^{-4}$	$7.48*10^{-4}$	$7.39*10^{-4}$
Egg ingestion	$1.09*10^{-3}$	$1.09*10^{-3}$	$9.09*10^{-4}$
Fish ingestion, high ingestion rate	$4.62*10^{-5}$	$2.74*10^{-5}$	$1.17*10^{-3}$
Scenario 6 - Effluent Discharge			
Fish ingestion, high ingestion rate	$2.06*10^{-5}$	$3.44*10^{-5}$	$6.28*10^{-4}$

Table 5-11. Relative magnitude of all exposure pathways evaluated for the background setting and the stack emission, high exposure scenario setting (see table bottom for notes).

Exposure Pathway	Background conditions	Stack emissions	Soil Contamination
Beef Ingestion	1.00	1.00	1.00
Milk Ingestion	0.49	0.48	0.42
Fish Ingestion	0.82	0.07	0.02
Egg Ingestion	0.05	0.10	0.38
Soil Ingestion	0.04	0.10	0.31
Chicken Ingestion	0.03	0.07	0.31
Inhalation	0.02	0.03	<0.01
Vegetable Ingestion	0.02	0.02	0.06
Soil Dermal - high end	<0.01	<0.01	<0.01
Fruit Ingestion	<0.01	<0.01	<0.01
Water ingestion	<0.01	<0.01	<0.01

Notes:
1. 1.00 is the highest pathway, and the values less than 1.00 describe the relation of that pathway to the highest pathway.
2. This table is for the high exposure farm setting only. For the stack emission scenario, the farm was located 500 meters from the stack. Also, the fish ingestion pathway was for the high ingestion rate, 25 g/day, and the soil pathways - dermal and soil ingestion - were for the high contact assumptions only.
3. For the background and stack emission scenarios, results are for TEQs; for the soil contamination scenario, results are for 2,3,7,8-TCDD.

Table 5-12. Cancer risk estimates for the background and stack emission high end scenarios.

Setting/Exposure Pathway	Cancer Risk
Background Conditions, high end setting	
Soil Ingestion	$1.22*10^{-6}$
Soil Dermal Contact	$5.27*10^{-8}$
Inhalation	$2.34*10^{-6}$
Water Ingestion	$2.90*10^{-7}$
Beef Ingestion	$8.30*10^{-5}$
Vegetable Ingestion	$2.36*10^{-6}$
Fruit Ingestion	$3.65*10^{-7}$
Total	$8.96*10^{-5}$
Stack emissions, high end setting	
Soil Ingestion	$3.32*10^{-8}$
Soil Dermal Contact	$3.19*10^{-10}$
Inhalation	$2.68*10^{-8}$
Water Ingestion	$4.19*10^{-10}$
Beef Ingestion	$8.65*10^{-7}$
Vegetable Ingestion	$1.83*10^{-8}$
Fruit Ingestion	$4.05*10^{-9}$
Total	$9.48*10^{-7}$

6. USER CONSIDERATIONS

6.1. INTRODUCTION

The methodology in this document has been earlier described as screening level in terms of theoretical sophistication, but site specific in its application. Chapter 2 described concepts of exposure and assigned values to exposure parameters which define, for purposes of demonstration, a central and a high end exposure pattern. Chapters 3 and 4 described algorithms for the fate, transport, and transfer of dioxin-like compounds, and also assigned parameter values for purposes of demonstration. The methodology was demonstrated in Chapter 5, using exposure and fate and transport parameters which had been laid out in earlier chapters. Those who wish to use the methodology for further analysis of incremental exposures to sources of dioxin-like compounds are now in a position to use the same algorithms, perhaps many of the same parameter values. The purpose of this chapter is to provide guidance on some key issues for potential users.

Section 6.2 discusses the use of the parameter values selected for the demonstration scenarios in Chapter 5 for other applications. Section 6.3 is a sensitivity analysis exercise on the parameters required for algorithms estimating exposure media concentrations. Section 6.4 addresses the issue of mass balance with regard to the source strength terms of the four source categories.

6.2. CATEGORIZATION OF METHODOLOGY PARAMETERS

Table 6-1 lists all the parameters, including names, definitions, and units, that are required for the methodologies of this assessment except the exposure parameters. Exposure parameters are given in Table 2-1 of Chapter 2. Table 6-1 also gives four additional pieces of information for each parameter listed. Three are numerical values which were used in the sensitivity analysis exercises that are described in Section 6.3. below. The parameter values labeled "selected" were the ones used in the demonstration of the methodologies in Chapter 5. Section 6.3. below justifies the high and low values of parameters selected for sensitivity analysis. Other users of this methodology may wish to view these high and low values as reasonable high and low possible values for their applications; note however that the chemical specific parameters are those only for 2,3,7,8-TCDD. The fourth piece of information is a qualitative judgement on the part of the authors of this document as to the appropriateness of using the "selected" parameter values for other assessments. This judgement is categorized in three ways:

1) **First Order Defaults, or FOD:** As defaults, these parameters are independent of site specific characteristics and can be used for any assessment. Also, as first order defaults, it is felt that the values selected for the demonstration scenarios carry a sufficient weight of evidence from current literature such that these values are recommended for other assessments. Several of the chemical specific parameters, such as the Henry's Constant, H, and the organic carbon partition coefficient, Koc, fall into this category. The qualifier above, "current literature", indicates that new information could lead to changes in these values.

2) **Second Order Defaults, or SOD:** Like the above category, these parameters are judged to be independent of site specific characteristics. However, unlike the above category, the current scientific weight of evidence is judged insufficient to describe values selected for demonstration purposes as first order defaults. SOD parameters of principal note are the bioconcentration parameters specific to the chemicals, such the Biota Sediment Accumulation Factor, or BSAF. This parameter translates the ratio of a bottom sediment concentration to a fish tissue concentration. The science is evolving for this parameter, including thought on the extent to which BSAFs generated for one species at one site can be generalized to other sites and/or species, the differences in BSAF between column and bottom feeders, the differences between past and ongoing contamination, and so on. Users should carefully review the justification for the SOD values selected for the demonstration scenarios before using the same values.

3) **Site Specific, or SS:** These parameters should or can be assigned values based on site-specific information. The information provided on their assignment for the demonstration scenarios, and for selection of high and low values for sensitivity analysis testing, is useful for determining alternate values for a specific site. A key class of SS parameters included in Table 6-1 above are the source strength terms - the soil concentrations, effluent discharge rates, and stack emission rates. There are likely to be site-specific applications of this methodology for which detailed information is unavailable. Often the midrange values selected for the demonstration scenarios are suitable for site specific applications when data is unavailable. An example of this category of parameters would be the soil characteristics, such as the porosity, bulk density, and so on.

The exposure parameters have not been categorized as have the contaminant fate and transport/transfer parameters. Assignment of these values are critical as LADD estimates are linearly related to parameter assignments - doubling exposure duration assumptions double LADDs, and so on. All exposure parameters were developed based on information and recommendations in EPA's *Exposure Factors Handbook* (EPA,1989;1997) and *Dermal Exposure Assessment: Principals and Applications* (EPA, 1992). Some of the exposure parameters of

Table 2-1, Chapter 2, are appropriately described as FOD. These include: lifetime, body weights, water ingestion rates, inhalation rates, and an exposure duration for a childhood pattern of soil ingestion. All of the other exposure parameters are better described as either SOD or SS. Attaining site-specific information is recommended for them. However, this is often difficult for site specific assessments and impractical if the procedures in this assessment are used in general assessments. In the absence of site specific information, the following parameters can be considered SOD: adult exposure durations of 9 years for central scenarios (whether they be modeled after "residential" settings or not) and 30 years for high end scenarios (whether "farming" be the model for high end exposures or not), childhood soil ingestion rates, the fruit/vegetable food ingestion rates, the fraction of fruit/vegetable consumption that comes from a home garden, the food preparation factors that were developed for home produced meats, and the fractions of time spent at home (which are applied to inhalation and water ingestion pathways). The remaining exposure parameters pertain to the exposure pathways evaluated as most critical to dioxin exposures. For this reason, users should either pursue site specific information or carefully justify parameter selections in the absence of site specific information. These include the rate of beef, milk, and fish ingestion and the fraction of these food products which are produced at home and hence impacted by the source. Fish ingestion rates for the demonstration of methodologies in this assessment were 8 g/day as the central assumption and 25 g/day for the high end assumption. These were the mean values for the central and upper end ingestion rates from several fish consumption studies characterized as “recreational” fishing studies in EPA (1997). These rates are both more than a national average estimate of fish consumption that was published in an water quality criteria document for 2,3,7,8-TCDD, 6.5 g/day (EPA, 1984). The setting for the demonstration scenarios was a rural setting which contained farm and non-farm residences, and which contained a major water body for recreational fishing purposes. The other parameters are the ingestion rates and contact fractions for beef, milk, chicken, and egg ingestion. The ingestion rates for these food products were developed in EPA (1997) from the 1987-88 National Food Consumption Survey (NFCS) conducted by USDA, and specifically, they were from the “household” portion of the NFCS. This portion of the survey included questions on consumption of home produced foods, which was why it was felt to be appropriate for the demonstration scenarios of this assessment. The contact fractions assigned for the high end scenarios were also developed from information in the household survey of the NFCS.

In addition to the above qualifications, the parameters of this methodology have been categorized in terms of their role in the methodology. The following is a brief description of three principal categories.

Category 1. Human behavior exposure parameters

These are the contact rates, contact fractions, exposure durations, lifetime and body weights used in the following equation for lifetime average daily dose:

$$\text{Lifetime Average Daily Dose (LADD)} = \frac{(\text{exposure media concentration} \times \text{contact rate} \times \text{contact fraction} \times \text{exposure duration})}{(\text{body weight} \times \text{lifetime})} \quad (6\text{-}1)$$

Category 2. Fate, transport, and transfer parameters

These parameters are all the parameters required to estimate exposure media concentrations, except those specifically associated with a contaminant - chemical-specific parameters are included in Category 3 below. All fate, transport, and transfer parameters are listed, defined, and further subcategorized in Table 6-1. Not included in the discussions in Section 6.3 are perhaps the most important terms in this category, and these are critical source strength terms: the concentrations of dioxin-like compounds for the soil contamination scenario, and the release quantities of dioxin-like compounds into the air for the stack emission source category and into the surface water for the effluent discharge source category. A general comment that can be made for fate and transport parameters is that values for the demonstration scenarios were selected to be midrange and plausible, and that this document provides information on selecting alternate values for site-specific applications. Most of the parameters in this category fall under the SS qualification. Subcategories within the fate and transport category include:

- Contaminated and exposure site characteristics: These are areas, soil properties, and depths of tillage (which are depths to which residues transported by erosion or deposition are mixed in conditions of tillage such as agriculture or gardening, and no tillage). Like the soil concentration term, the area of contamination is a site-specific parameter. Soil properties were assigned to be midrange and typical of agricultural soils. Depths of mixing for tilled and untilled circumstances are not known with certainty, and these two parameters were characterized as SOD.

- Soil and sediment delivery parameters: These include parameters associated the erosion of contaminated soil from a site of contamination to a nearby site of exposure and/or to a

nearby surface water body. All but one of the parameters in this subcategory are physical, site-specific parameters which should be evaluated for site specific applications. The one parameter not of this description is the enrichment ratio, which describes the enrichment of eroded soil with dioxin-like compounds, and was assigned a rating of SOD. Geometric parameters include watershed drainage area, water body volumes, and distances. Physical parameters include soil loss estimates, organic carbon contents, water body suspended solids, and background watershed contaminant concentrations.

- Volatilization and dust suspension parameters: These parameters are associated with suspension, dispersion, and transport of contaminants from contaminated soils. One parameter included in this category is the exposure duration, which appears to be misplaced. In fact, the exposure duration is used to determine the average vapor phase air concentration - this is further discussed in Section 6.3 below. Parameters in this category are site-specific and should be evaluated for specific methodology applications.

- Bioconcentration and biotransfer parameters: These include parameters describing the biota and the media surrounding the biota which influence the transfer of dioxin-like compounds from the media to the biota. Some of these parameters are site-specific, although obtaining values may be difficult. Included here are annual rainfall, fish lipid contents, a fresh to dry vegetable weight conversion factor, and yields and intercept fractions for vegetation categories. Others are theoretical; values for these were determined from the literature and can be used for other assessments if better information is unavailable. Included here are atmospheric deposition velocities of particles, washout of wind-suspended particles from the atmospheric, the retention of wet particle depositions on vegetation, empirical correction factors for vapor-phase air-to-plant transfers and soil-to- plant transfers, and the bioavailability of soil as compared to vegetation as a vehicle of transfer of dioxin-like compounds to terrestrial animals. These were given a rating of SOD. A third group describes exposure of the terrestrial animals to dioxin-like compounds through their diet. These include fractions of animal diet which are soil, pasture grass, and feed, and the extent to which these three are impacted by the source of contaminant. Sensitivity analysis below was conducted on beef parameters only, not on the dairy cow, chicken, or egg parameters. It is expected that, in general, the trends should be the same for all the terrestrial animals. The analysis below shows how beef concentrations are impacted by changes in assumptions of how cattle are exposed to dioxin-like compounds through their diet. Since terrestrial animal exposures are most critical for human exposure, the animal exposure assumptions made for demonstrating the methodologies of this assessment should be carefully considered before using them for other assessments.

- Effluent discharge source category: These are three physical parameters that can be determined on a site-specific basis, and include flow rates of the effluent and receiving water body, organic carbon contents of suspended solids in the effluent and the receiving water body, and suspended solids content of the effluent and the receiving water body.

- Stack emission source category: In fact, most of the parameters required to evaluate the impact of stack emissions to a nearby site of exposure have been included in other categories. Sensitivity analysis only focuses on parameters and issues unique to this category. One set of input values are contaminant wet and dry deposition rates. Three depositions are required: one for the site of exposure, one to represent depositions on watershed soils which drain into the water body, and one to represent direct deposition onto the water body. These were all generated using the ISCST3 model, as described in Chapter 3. Two other key inputs generated by the ISCST3 model are the ambient air vapor phase and particle phase concentrations of contaminant at the site of exposure. All such quantities are a function of that model's algorithms and parameter input requirements, particularly the release rate from the stack. Information on the ISCST3 model and its application is given in Chapter 3 and not discussed further in this chapter. Users can determine air concentrations and contaminant deposition rates in other ways, and use those in the methodologies to determine impacts and exposures. The no-till depth of mixing at the site of exposure, d_{not}, is required for the contaminated soil source algorithm as well. It's selected value for the stack emission source category was 2 cm, similar to the 2 cm used in the soil contamination source demonstration. The only other unique parameters not included in other subcategories are the average watershed mixing depth (used for determining watershed soil concentrations, which are then used to determine impacts to water bodies) and the fraction of particles depositing on water bodies which remain in suspension. These are both theoretical values and can be used in other assessments lacking better information.

Category 3. Chemical properties of dioxin-like compounds

The thirteen chemical-specific parameters required for the algorithms of this assessment fall under two categories, FOD and SOD. As such, they are all independent of the specifics of the site. The parameters deemed FOD are chemical fate and transport parameters, some of which are common and often determined in laboratory conditions. These include the Henry's Constant, the organic carbon partition coefficient, and the molecular diffusivity in air. The selected values for these parameters are, in the authors' opinion, the best values derivable from current data. A second set of chemical specific parameters are associated with bioconcentration/biotransfer algorithms. Some of them are determined from field data (data on dioxin-like compounds or

other compounds), and others are determined by experimentation and with that experimentation, development of empirical relationships between a critical transfer factor and the chemical's octanol water partition coefficient. The authors cannot be definitive in a judgement that values given to these parameters be considered default, hence the SOD rating. For these compounds, field/experimental data is conflicting or there simply is a lack of appropriate data. Parameters included in this category are a soil to below ground vegetation transfer factor, two air-to-plant factors: the air-to-leaf vapor phase transfer coefficient and the plant washoff rate constant, two water body to fish parameters: the biota to sediment accumulation factor and the related biota to suspended solids accumulation factor, and the bioconcentration factors for beef, milk, chicken, and eggs. The sorbed fraction was given a "SOD/SS" rating because its assignment is a function of chemical properties as well as an assumption regarding particle density in the airshed. This assessment assumed, "background plus local sources" as the appropriate descriptor for particle density in the airshed. This particle density selection is the site-specific aspect to this parameter assignment. Therefore, for other applications where this airshed particle density is appropriate, users may consider the values for the particle density to be, SOD.

6.3. SENSITIVITY ANALYSIS

Sensitivity analysis was undertaken in order to evaluate the impact of model results with changes in model parameters. The following sections describe the limitations, methodology and parameter selections, and results.

6.3.1. Limitations of the Sensitivity Analysis Exercises

The exercises were not comprehensive and/or definitive. Following are some key limiters:

- **The ISCST3 model was not evaluated in this section.** Chapter 3 describes the ISCST3 model. No sensitivity analysis runs were performed on ISCST3 model output for this chapter. This section does evaluate the impact of different deposition rates and modeled ambient air concentrations on exposure sites soils, surface water, and biota. Chapter 7 describes a model validation exercise on the ISCST3 model, and this exercise includes an evaluation of the impacts of selecting different meteorological data and different source strength terms (i.e., different stack emission rates of dioxins).

- **Sensitivity to changes in exposure parameters was not evaluated.** The basic equation for evaluating lifetime average daily dose was given above as Equation (6-1).

Chapter 2 described all terms in this equation except the exposure media concentration, which was the focus of Chapter 4. Because LADD estimates are a linear function of all exposure parameters, sensitivity analysis was not performed on LADD exposure estimates. The focus of this section instead is on the fate, transport, and bioconcentration/biotransfer algorithms used to estimate the exposure media concentration term in Equation (6-1).

- **The analysis was not exhaustive in its coverage.** Principal algorithms in the fate, transport, and transfer of dioxin-like compounds were evaluated, and all parameters required for algorithms were tested at least once. However, not all possible tests were conducted. Before noting those, following is a list of algorithms which were tested:

  - Volatilization/suspension and transport/dispersion of vapor/particle phase airborne residues from a site of contamination to a site of exposure (using algorithms for the soil contamination source category);

  - Transport via erosion of contaminants at a site of soil contamination to a nearby site of exposure to impact exposure site soils (soil contamination source category);

  - Transport via erosion of contaminants at a site of soil contamination to a nearby surface water body, to impact bottom sediments, water, and fish (soil contamination source category);

  - Transfers of contaminants from soils to below ground vegetables and from air to above ground vegetation (soil contamination source category);

  - Transfers of contaminants from soils to vegetation to beef (soil contamination source category) and from air to vegetation to beef (stack emission source category);

  - Direct discharges of dioxin-like compounds into surface water bodies, and the effect of surface water and effluent parameters on fish and water concentration estimation (effluent discharge source category); and

  - Particle depositions and ambient air concentrations, which result from stack emissions, onto exposure site soils, watershed soils, surface water bodies, and biota (stack emission source category);

The exercise was purposefully limited since several possible exercises would have been duplicative. For example, impacts to terrestrial animal products was limited to an evaluation of the algorithm estimating beef concentrations. Similar trends are expected for the milk, chicken, and egg bioconcentration algorithms. For all the animal pathways, including fish ingestion, the impact to changes in the lipid, or fat, contents was not evaluated in this exercise. All the bioconcentration algorithms estimate the concentration of the dioxin-like compound in fat tissue. The fraction of fat parameters are all required simply to translate a fat concentration to a whole product concentration for purposes of exposure estimation. Therefore, changes to the assumption

of fat contents will translate to a linear change in the estimation of the whole animal product concentration.

A related limitation has to do with the cascading effect of certain parameters. For example, a key contaminant parameter is the organic partition coefficient, Koc, which impacts (among other concentrations) vapor phase air concentrations. Air concentrations are used to estimate above ground vegetation concentrations, including those of grass and cattle feed. Beef concentrations are a function of concentrations in grass and cattle feed. The impact of Koc is evaluated in the context of the soil contamination source category. What is not done in the sensitivity analysis below for this important model parameter (and others as well) is to evaluate the impact of changes in Koc to beef concentrations. What is done, however, is as follows. The sensitivity of air concentration predictions to changes in the partition coefficient are evaluated. Then, the sensitivity to grass and cattle feed concentrations to plus and minus one order of magnitude differences in estimated vapor phase air concentrations are evaluated. In this way, any possible parameter change(s) which influences air concentrations within a plus/minus order of magnitude range is evaluated for grass and feed concentrations. Finally, beef concentration estimations are evaluated within a similar plus/minus order of magnitude change for grass and feed concentrations. With some examination, therefore, the effect of cascading impacts can be determined.

The impact of changing soil concentrations (in the soil contamination source category) to estimates of exposure media concentrations (air, water, biota) is linear and direct in all cases - i.e, increasing soil concentrations by a factor of five increases all impacted exposure media by the same factor of five. For this reason, soil concentrations are not displayed in the sensitivity graphs displayed in the next section, with one exception. This was in the estimation of beef concentrations from soil contamination. Beef concentrations are a function of concentrations in the dry matter diet of the cattle, including soil, grass, and cattle feed. Therefore, if soil concentrations were to change and concentrations on the other intakes were to not change, than beef concentrations would not be a linear and direct function of soil concentrations. However, and in the context of this sensitivity analysis, when changing only soil concentrations, vegetative concentrations are linearly and directly impacted by the same order of magnitude change. Therefore, beef and milk concentrations turn out to be linearly related to soil concentrations.

A final limitation to note is that this exercise does not evaluate the multiple effects of changing more than one independent parameter simultaneously. Other numerical methods, particularly Monte Carlo, can be used to evaluate the impact of simultaneous changes to model

parameters. Applications of this technique to dioxin exposure assessments are discussed in Chapter 8 of this volume.

There are instances where parameters were evaluated as dependent and changes were made simultaneously. One example is in three parameters which are related to the size of a watershed (also termed the "effective drainage area" since such an area might be smaller than a surrounding river system watershed), and which are important in determining the impact of a bounded area of soil contamination to a nearby surface water body. These three include the watershed size, the watershed sediment delivery ratio (which decreases as watershed size increases), and the surface water body volume (which increases as watershed size increases, assuming sources of water - surface runoff, interflow, and groundwater recharge - remain the same on a per unit area basis). To test the impact of watershed size to surface water and sediment concentrations, all three parameters were changed simultaneously in modeling a small and a large watershed. One set of parameters which might not be independent, but which were treated as such in the sensitivity testing, are the chemical specific parameters. For example, a higher organic carbon partition coefficient might be associated with a lower Henry's Constant - tighter binding to soils means less of a tendency to volatilize. Empirical relationships between such chemical specific parameters have not been established, and since there is uncertainty in precise values selected for the dioxin-like compounds, chemical specific parameters were treated as independent parameters.

- **Only a high and a low value for model parameters were tested; no discussions of likelihood for parameter values or distributions of parameter values are included.** Certainly the identification of all model parameters and the justification for assignment of high and low values will be helpful to others using the methodology. Assignment of parameter values for purposes of demonstrating the methodologies in Chapter 5 should be carefully considered when users apply this methodology for specific purposes or specific sites.

6.3.2. Methodology Description and Parameter Assignments

Only two of the six example scenarios of Chapter 5 served as "baselines" in the sensitivity analysis exercises. The single scenario for the soil contamination source category, Scenario 3 in Chapter 5, served as the basis for testing on these algorithms: 1) transport of vapor and particulate phase airborne contaminants from a site of contamination to a nearby site of exposure, 2) transport of soils via erosion to nearby sites of exposure and to surface water bodies to impact bottom sediments, fish, and water, 3) impacts of soil concentrations and other parameters to below ground vegetation, and air concentrations and other parameters to above

ground vegetation, and 4) impacts of soil, grass, and feed concentrations, and other parameters, to beef concentrations. The source strength for this scenario, in summary, was a 40,000 m^2 (4 ha, 10 ac) area of soil concentrations of 1 μg/kg (ppb) within a watershed of size 4,000 ha (40,000,000 m^2; 10,000 ac; 15.5 mi^2) with soils otherwise at 0.0 ppb. Most of the sensitivity analyses focused on predictions that were to occur at the exposure site, which was a farm located 150 meters away. The high end example scenario for the stack emission source category, example scenario #5, served as the basis for the testing the impact of particle depositions and ambient air concentrations on soils and biota. The ambient air concentrations and deposition rates at the site of exposure 500 meters from the stack served as the baseline source strength terms. The single scenario for the effluent discharge source category, example scenario #6, was used to evaluate the impact of parameters required for that source category on fish and water concentrations. The source strength in that case was a discharge of 0.0315 mg/hr into a surface water body with a harmonic mean flow rate of $4.7x10^8$ L/hr. Assignment of that baseline discharge was based on data from the 104 pulp and paper mill study, and then considering reductions is discharges which have occurred in these pulp and paper mills since the 104 mill study in 1988.

The baseline chemical for all these sensitivity runs was 2,3,7,8-TCDD; i.e., all the chemical specific parameters were those assigned to this example compound. The high and low values for parameter testings were determined starting with the 2,3,7,8-TCDD assignments. Care was not taken to encompass a range of possible values for all dioxin-like compounds. However, the ranges that were tested are mostly inclusive of the dioxin-like compounds. What will be noted and discussed below is that mostly the model response to chemical-specific parameters is linear or nearly linear, so that model responses to values outside the ranges tested can be evaluated easily.

All the initial parameter values required for all four source categories, and the values selected for high and low sensitivity analysis were listed above in Table 6-1. Following are brief discussions on the selection of these high and low values. Longer discussions on all parameter values can be found in Chapter 4, which included justifications for all parameter values selected for the demonstration of the methodologies in Chapter 5. Often, ranges of possible values were discussed in Chapter 4; those ranges were the basis of high and low parameter values selected below. Discussions in Chapter 4 are not repeated here, but are referenced below. The summaries below are organized in the same order as the parameter listings in Table 6-1.

● Contaminated and exposure site characteristics: These are the area and distance parameters, and the soil characteristic parameters of the site of contamination and the site of exposure. The "site of contamination" refers to the bounded area of high soil concentration for the soil contamination source category. The "site of exposure" for these sensitivity runs is the small farm which was the basis for the definition of the "high end" example scenarios demonstrated in Chapter 5. The area of the site of exposure, **AES**, and site of contamination, **ASC**, are both 40,000 m^2 in the demonstration scenarios, which is equal to 4 ha or 10 ac. Low and high values tested were 4,000 m^2 (0.4 ha, 1 ac) and 400,000 m^2 (40 ha, 100 ac). The soil description parameters include soil porosity, **ESLP**, particle bulk density, **Psoil**, soil bulk density, **Bsoil**, and the organic carbon fraction, **OCsl**. The assignment of high/low values to these parameters were developed from Brady (1984) and cover a reasonable range of agricultural field soils. The no-till and tillage depths, $\mathbf{d_{not}}$ **and** $\mathbf{d_t}$, refer to the depth to which eroded soil or depositing particulates mix at the site of exposure. The no-till depth was set at 2 cm and was varied between 1 and 10 cm, and the tilled depth was varied between 10 and 30 cm. The no-till concentrations were used to estimate soil concentrations for soil related exposures: soil ingestion and soil dermal contact, and also for the beef and milk bioconcentration algorithm. The tilled concentrations were used only to estimate the concentration in below ground vegetation.

● Soil and Sediment Delivery Parameters: Contaminated soil erodes from a site of contamination, a 4 ha site in the demonstration scenarios, to a nearby site of exposure and also to a nearby river. The distance to the site of exposure from a site of contamination, $\mathbf{DL_e}$, was set at 150 meters for the example scenarios, and varied between 50 and 1000 meters in this exercise. The same initial distance of 150 meters was the distance to the nearby river, $\mathbf{DL_w}$, and it was also varied between 50 and 1000 meters. The unit amount of soil eroding off the site of contamination, $\mathbf{SL_s}$, was initialized at 21520 kg/ha-yr, equal to 9.6 Eng. ton/ac-yr (abbreviated t/ac-yr hereafter). Assumptions inherent in this estimate include: midcontinent range of annual rainfall erosivity (which is also the middle of the range of rainfall intensities of the US), midrange agricultural soil erosivity, a gentle 2% slope, no man-made erosion protection (ditches, etc.), and bare soil conditions. A doubling of this amount to 42,000 kg/ha-yr (19 t/ac-yr) was used as a high erosion estimate off the site of contamination. This could reflect any number of different assumptions, such as more erosive soil, more erosive rainfall, steeper slopes, and so on. A low estimate of one-tenth the default value, at 2100 kg/ha-yr (1 t/ac-yr), could reflect all the same assumptions except a dense cover of grass or weeds, which changes the bare soil

assumption leading to a "C" (cropping management factor) of 1.0 to a C of 0.1. The erosion amount of 2152 kg/ha-yr was the initial amount assumed for a second unit erosion term needed in this assessment, a unit erosion typical of land area between the contaminated and the exposure site, $\mathbf{SL_{ec}}$. The critical assumption in this initialization was that all conditions for this land area were similar to the contaminated site, except that the ground was densely covered with grass or weeds. The value of SL_{ec} was reduced to 0 kg/ha-yr for the low value, which is unrealistically low but might give a sense of how the algorithm would perform if mixing with soil between the contaminated and exposure site were not considered. The high value was 21,000 kg/ha-yr, which is similar to the initial assumption for the contaminated site, could reflect similar erosion conditions between the contaminated site and the exposure site. The third unit soil loss parameter required is one which reflects average erosion conditions within the watershed draining into the water body, $\mathbf{SL_w}$. This was initialized at 6455 kg/ha-yr (2.88 t/ac-yr) which reflects similar erosion conditions as the contaminated site (soil erosivity, rainfall intensity, average slopes, lack of support practices) except some erosion protection due to vegetation - C equal to 0.3 instead of 1.0. It was reduced to 2100 kg/ha-yr, which might translate to C equal to 0.1, and increased to 21,000, which was equal to the initial higher erosion from the contaminated site. The range of the enrichment ratio, ER, was noted at between 1 and 5 for its application in agricultural runoff field data and model simulations, and was given an initial value of 3 in this application. High and low values tested were 5 and 1. An average watershed concentration of contaminant was set at 0 for the soil contamination demonstration scenarios, where the soil concentration of 2,3,7,8-TCDD (and the other example compounds) was set at 1 ppb. This was selected so that the impact to surface water bodies could be demonstrated as an incremental impact. A concentration of 2,3,7,8-TCDD of 1 ppt was chosen to represent "background" conditions. This value is near the 0.3 ppt that was measured in the background setting near Columbus, Ohio, and used in the demonstration of the background scenarios. The value was used to evaluate the impact of a bounded site at 1 ppb when a background concentration of 1 ppt is also assumed to exist. Four parameters reflect watershed size. These include the effective drainage area, $\mathbf{A_w}$, the watershed sediment delivery ratio, $\mathbf{SD_w}$, the volume of the receiving water body, $\mathbf{VOL_w}$, and the surface area of the water body, $\mathbf{AREA_w}$. These are related and should therefore be changed in tandem. The initial watershed size of 100,000 ha (385 mi^2) was reduced to 10,000 ha (39 m^2) and increased to 1,000,000 ha (3850 mi^2). Since the water body volume was estimated using a in/yr runoff times an area, it was concurrently reduced 1 order of magnitude for the small watershed test and increased one order of magnitude for the large watershed. The surface area of the water body was also increased or reduced by an order of

magnitude with the concurrent change in water body volume. The values of SD_w were estimated using Figure 4-4 (Chapter 4), which shows watershed delivery ratios as a function of watershed area. The remaining three parameters further described the water body, and were the total suspended solids, **TSS**, and the organic carbon contents of suspended and bottom sediments, $\mathbf{OC_{ssed}}$ and $\mathbf{OC_{sed}}$. The initial value of TSS of 10 mg/L is typical of a moving water body (stream, river) supportive of fish and other aquatic life. It was reduced to 2 mg/L, which is typical of a stationary water body (pond, lake, reservoir) and increased to 50 mg/L, which begins to be high for a water body expected to be supportive of fish. The organic carbon contents were initialized at 0.05 for OC_{ssed} and 0.03 for OC_{sed}. The premise was that they were related - that sediments in suspension were lighter and likely to be higher in organic carbon content than bottom sediments. They were also changed in tandem to 0.02 (OC_{ssed}) and 0.01 (OC_{sed}) for a low organic carbon sensitivity test and 0.10 and 0.05 for a high organic carbon test.

● Volatilization and Dust Suspension Parameters: Distances and areas are pertinent to estimating vapor-phase and particulate-phase air concentrations, and these have been discussed above in the first two categories. One parameter included for sensitivity testing in this category is the exposure duration, **ED.** It is included in these exercises because the estimation of average volatilization flux over a period of time is a function of that period of time. The derivation of the flux model assumed contamination originates at the soil surface at time zero, and over time, originates from deeper within the soil profile. Therefore, the flux decreases over time (because residues have to migrate from deeper in the profile), and the average flux over a period of time will decrease as that period of time increases. This is further discussed in Chapter 4, Section 4.3.3., and in the original citation for the volatilization flux algorithm, Hwang, et al. (1986). The exposure duration assumed in the high end scenarios was 30 years, this was changed to 1 and 70 years in sensitivity tests. A range of average windspeeds, $\mathbf{U_m}$, around the U.S. was noted at 2.8 and 6.3 m/sec, and these two values were used around the selected value of 4.0 m/sec. The frequency with which wind blows from a site of contamination to a site of exposure, **FREQ**, was set at 0.15, which is appropriate if one assumes that wind blows in all directions roughly equally. It was changed to 0.05 and 0.50, which might translate to an assumption of a prevailing wind direction, either away from or towards a site of exposure. The remaining parameters, fraction of vegetative cover, **V**, threshold wind speed, $\mathbf{U_t}$, and model specific function, **F(x)**, all refer to the wind erosion algorithm which suspends contaminated particulates into the air. Sensitivity tests were applied to this trio for the on-site and the off-site source categories. V for the off-site scenario was initialized at zero, implying bare ground cover; it was increased to 0.9 reflecting

dense ground cover in the single sensitivity test here. It was set at 0.5 for the on-site small farm demonstration scenario, reflecting some bare ground conditions (in the agricultural fields, e.g.) as well as some dense vegetation (in other grassed areas of the farm property). It was decreased to 0 and increased to 0.9. The parameters U_t and F(x) reflect intrinsic erodibility of the soil and were varied together. Values were selected to reflect a high and low wind erodibility soil, following guidance in EPA (1985), the primary reference for the wind erosion algorithm.

● Bioconcentration and Biotransfer Parameters: Several parameters are required for the vegetation concentration algorithm, most of which were associated with the algorithm for dry plus wet deposition of particulates in the soil contamination source category. One parameter not associated with fate and transport was the dry to fresh weight conversion factor, **FDW**. The algorithm calculates vegetative matter concentrations on a dry weight basis, which is appropriate for the role of vegetation in the beef/milk bioconcentration algorithm. However, ingestion rates of fruits and vegetables are on a fresh weight basis, so dry weight concentrations have to be converted to a fresh weight basis. The initial value of 0.15 assumes that fruits and vegetables are 85% liquid. The high and low values tested for this parameter were 0.30 (70% liquid) and 0.05 (95% liquid). Four parameters are described as empirical correction factors for the air-to-leaf algorithm adopted for vapor phase transfers to vegetation (three of the parameters), and for the soil-water-to-root algorithm adopted for below ground vegetation. There is one each for the four principal vegetation considered: below ground vegetables/fruits - $\mathbf{VG_{bg}}$, above ground vegetables/fruits - $\mathbf{VG_{vg}}$, grass - $\mathbf{VG_{gr}}$, and feed - $\mathbf{VG_{ctfd/chfd}}$ (cattle and chicken feed, respectively). The concept for assignment of values to these parameters was the same, and briefly is as follows. The principal biotransfer factors, vapor phase air-to-leaf and soil-water-to-root, were developed for relatively thin vegetation, grass leaves for air-to-leaf transfers and barley roots for soil-water-to-root transfers. Concurrently, there is evidence that the strongly hydrophobic/lipophilic dioxin-like compounds are found only in outer portions of vegetation and not inner portions of bulky vegetation; there is very little translocation of dioxin-like compounds into and within vegetation. Therefore, the full vegetation concentrations of bulky vegetation are expected to be much lower than the concentrations that would be found in their thin outer layers. For above ground bulky fruits/vegetables, two considerations were included in the final assignment of 0.01 to VG_{vg}: 1) a surface area to volume ratio based on this tendency not to translocate into innner portions of the vegetation, and 2) additional reductions in whole fruit/vegetable concentrations that would occur due to washing or peeling. For bulky below ground vegetation, a final value of 0.25 was selected based on: 1) again, this tendency not to translocate into inner portions of below ground

vegetation, and 2) experimental evidence on carrots and potatoes that did indicate more within plant translocations than have been measured for above ground vegetation. The above ground VG_{ag} was reduced to 0.001 and increased to 0.10 in sensitivity testing, and the below ground VG_{bg} was reduced to 0.01 and increased to 1.00. The VG_{gr} was set at 1.00 since the air-to-leaf vapor transfer factors were developed from data on grass, so no correction is warranted. Although there is no justification to change VG_{gr}, a lower value of 0.50 was chosen simply for illustration. The VG_{ctfd} was set at 0.50, recognizing that some cattle feed is unprotected and thin vegetation such as the leaves in silage, while others are protected grains such as corn grain. That value was changed to 0.25 and 0.75 in sensitivity testing. There is one required parameter for the dry deposition algorithm, and this is the particle deposition velocity by gravity settling, V_p, in m/yr. The initial value of 3.2×10^5 m/yr, from a velocity assumption of 1 cm/sec, was given by Seinfeld (1986) as the gravitational settling velocity for 10 μm particles. This is the appropriate size to consider since the wind erosion algorithm was developed only for inhalable size particulates, those less than 10 μm (EPA, 1985). This was reduced to 0.5 cm/sec and 2 cm/sec (transformed to m/yr) for sensitivity testing. Three of the vegetation bioconcentration parameters are associated with the particulate wet deposition algorithm. These are the atmospheric washout ratio, $\mathbf{W_p}$, the retention of particles on vegetation, $\mathbf{R_w}$, and the annual rainfall amount, **R**. The definition, derivation, and ranges for these values are described in Chapter 4, Section 4.3.4.2, and are not repeated here (the ranges are given in Table 6.1). The remaining bioconcentration parameters are the yield and crop intercept values for the three above ground vegetation: vegetables/fruits ($\mathbf{Y_{veg}}$, $\mathbf{INT_{veg}}$), grass ($\mathbf{Y_{gr}}$, $\mathbf{INT_{gr}}$), and cattle feed ($\mathbf{Y_{ctfd}}$, $\mathbf{INT_{ctfd}}$). Again, discussions of chosen, and high and low, values for these quantities are given in Chapter 4, Section 4, and displayed in Table 6.1. It is noted that these two terms are correlated - high yields are correlated with high interception amounts. In sensitivity testing, therefore, these parameters were changed in tandem.

The remaining bioconcentration/biotransfer parameters are for the terrestrial animal bioconcentration algorithms, for beef, milk, chicken, and eggs. For the sake of brevity, only the beef bioconcentration algorithm will be evaluated. The trends found in the testing of this algorithm are expected to be duplicated for the other terrestrial animal products. One of the parameters relates the bioavailability of soil relative to the bioavailability of vegetation, where bioavailability refers to the efficiency of transfer of a contaminant attached to a vehicle. Fries and Paustenbach (1990) developed the bioconcentration factor, BCF, from studies where cattle were given contaminated feed. The studies of McLachlan, et al. (1990), from which BCFs for dioxin congeners were derived and used for this assessment, also used standard cattle feeds. This

feed is assumed to be analogous to the vegetation in cattle diet; therefore, the experimental BCFs can be directly applied to vegetation in cattle diets. However, Fries and Paustenbach also hypothesized that soil is less bioavailable than feed, based on some rat feeding studies, and therefore the BCF developed from feed cannot directly be used on a soil concentration - it should be reduced. Information in Fries and Paustenbach led to an assignment of 0.65 for the soil bioavailability factor, $\mathbf{B_s}$. This was reduced to 0.30 and increased to 0.90 in sensitivity testing. Three parameters describe the proportion of the dry matter in the diet of beef cattle that is soil, **BCSDF**, grass, **BCGDF**, and feed, **BCFDF**. The sum of these three terms, by definition, equals 1.00. Beef cattle are principally pastured (where incidental soil ingestion occurs), with supplemental feeds including hay, silages, and grain, particularly in cooler climates where they are housed during the winter. Values of 0.04 for BCSDF, 0.48 for BCGDF, and 0.48 for BCFDF were used in the demonstration scenarios. A final set of two parameters describes the proportion of these dietary intakes that are contaminated. One is defined as the fraction of grazing land that is contaminated, **BCGRA** for beef cattle. The initial assumption of 1.00 for this parameter meant that all the grass as well as all the soil in which the cattle grazed was contaminated (since soil was assumed to be ingested during grazing). The last one similarly is defined as the proportion of feed that is contaminated, **BCFOD** for beef cattle. It were also set at 1.00, perhaps indicating that feed was grown on-site. Rather than change these diet fraction assumptions and extent of contamination assumptions individually or in tandem (if necessary), what is done instead is to model four different scenarios relating to cattle exposures. These four scenarios and the parameter changes made are:

1) *High and low soil ingestion*	Low: BCSDF = 0.01 BCGDF = 0.50 BCFDF = 0.49
No changes to BCGRA or BCFOD; diet assumptions changed to reflect high and low soil ingestion patterns	High: BCSDF = 0.15 BCGDF = 0.43 BCFDF = 0.42
2) *Low exposure conditions* Grazing is under lush conditions, so soil ingestion and diet pattern is modeled as "low" soil ingestion above; also, most feed is purchased externally and uncontaminated; BCFOD reduced from 1.00 to 0.25	BCSDF = 0.01 BCGDF = 0.50 BCFDF = 0.49 BCFOD = 0.25

3) *Low extent of contamination* Diet assumptions are unchanged from initial assumptions; only it is assumed that 25% instead of 100% of dry matter in cattle diet is contaminated	BCGRA = 0.25 BCFOD = 0.25
4) *High/low lifetime pasturing* Tests for beef cattle only assuming heavy lifetime pasturing, 90% grass, and light lifetime pasturing, 08% grass	Low: BCSDF = 0.02 BCGDF = 0.08 BCFDF = 0.90 High: BCSDF = 0.08 BCGDF = 0.90 BCFDF = 0.02

● Effluent Discharge Source Category: Section 4.6, Chapter 4, discusses briefly how data from the 104-mill pulp and paper mill study (EPA, 1990) were used to develop initial parameters required for this source category in its demonstration in Chapter 5. The use of the 104-mill data in a model evaluation exercise is expanded upon in Chapter 7, Section 7.3.6. The data is also used here to assign high and low values for four of the seven required parameters for this source category. Two have to do with flow rates: $\mathbf{Q_e}$ which is the effluent flow rate, and $\mathbf{Q_u}$ which is the receiving water flow rate. The range of Q_e is from 10^5 to 10^7 L/hr, which are the low and high surrounding the $4.1x10^6$ rate used in the demonstration scenario in Chapter 5. The range of Q_u is 10^7 to 10^9 L/hr (excluding the top ten receiving water bodies, which were in the 10^{10} L/hr range and for which model did not appear to perform adequately), and these were the low and high around the $4.7x10^9$ L/hr rate used in Chapter 5. Two parameters describe the suspended solids content of the effluent, $\mathbf{TSS_e}$, and the suspended solids content of the receiving water body, $\mathbf{TSS_u}$. TSS_e ranged from 10 to 250 mg/L in the 104-mill study, so this was the range around the 70 mg/L used as the initial value. Data from STORET used to develop TSS_u led to an average of 9.5 mg/L and a range of less than 1 to 50 mg/L; a range of 2 (a reasonable value for a stationary water body such as a pond or lake) to 50 mg/L was tested. One required parameter was, of course, the rate of contaminant discharge, **LD**, in units of mg/hr. The assumed value was 0.0315 mg/hr, and this decreased and increased an order of magnitude for low and high testing. The remaining two parameters are the organic carbon contents of effluent solids, $\mathbf{OC_e}$, and upstream river suspended solids, $\mathbf{OC_u}$. A range based on data was not available for these parameters. OC_e was assigned a value of 0.36 based on the fact that solids in effluent discharges are primarily biosolids, and this value was one cited for surface water algae; values of 0.15 and 0.50 were tested. The value of 0.05 for OC_u was the value assumed for demonstration of other

source categories, where the parameter was called OC_{ssed}. The same range of 0.02 to 0.10 for OC_{ssed} was used for OC_u.

● Stack Emission Source Category: The parameters in this category listed in Table 6-1 are the only ones which are unique to this source category. As seen, there are only a very few unique parameters. Most of these are associated with surface water impact, and one series of tests evaluated the impact of parameter changes to surface water concentrations and fish concentrations. These include the contaminant deposition rates, $\mathbf{RDEP_{wat}}$ and $\mathbf{RDEP_{sw}}$, which are depositions onto the watershed draining into the surface water body and the surface water body itself (units are $\mu g/m^2$-yr). The initial values for these were those modeled to occur 5000 meters from the stack. This assignment for the stack emission demonstration scenarios, #4 and #5 in Chapter 5, assumes that the stack is located reasonably distant from the impacted water body. These depositions rates are specific to 2,3,7,8-TCDD. Rates of 2,3,7,8-TCDD deposition at 200 meters and at 10,000 meters were used as high and low values, respectively. It should be noted that depositions are higher at 200 meters and lower at 10,000 meters as compared to 5,000 meters, but air concentrations are lower at 200 meters as compared to 5,000 meters. This trend occurs because wet deposition is highest nearest the stack. Total depositions are driven by these high wet deposition totals; hence total depositions at 200 meters exceed those at 5,000 meters. However, dispersion modeling shows that ambient air concentrations of contaminants in the vapor phase (given the wind data and all other parameters and assumptions in using the ISCST3 model for the demonstration scenarios) are highest 500-1000 meters from the stack. For sensitivity testing, differences in model performance as a function of distance from the stack will be evaluated. $\mathbf{RDEP_p}$ is the deposition of particles themselves and was supplied in order to maintain a mass balance of solid materials entering the water body. The default value of 0.03 g/m^2-yr was taken from Goeden and Smith (1989) for a study on the impacts of a resource recovery facility on a lake. They estimated a total deposition of particles to the lake from all sources was 74.4 g/m^2-yr. Assuming the stack is unlikely to contribute all sources of particles to a water body, a high value was chosen as 3 g/m^2-yr, and a low value was given as 0.003. The fraction of depositing particles remaining in suspension, $\mathbf{f_{sd}}$, was initialized as 1.00 (meaning that all directly depositing particles remain in suspension) based on an argument that the small particles emitted from the stack and transported directly to the surface water body would settle to surface water bottoms much more slowly than other solids entering water bodies. A low value of 0.00 was tested (meaning that all solids directly depositing within a year settle quickly to become bottom sediments). The average watershed mixing zone depth, $\mathbf{d_{wmx}}$, was initialized at 0.10 m

(10 cm) which is midway between the 2 cm assumed for non-tilled conditions and 20 cm assumed for tilled conditions. This assumption might translate to a rural watershed comprised equally of farmed and unfarmed land. It was reduced to 1 cm and increased to 20 cm in sensitivity testing. A second series of tests evaluated biota impacts at the site of exposure, vegetables/fruits and beef/milk. Parameter inputs for these tests include the ambient air concentration and depositions at the site of exposure, $\mathbf{C_{va}}$ and $\mathbf{RDEP_e}$, and the no-till depth of mixing, $\mathbf{d_{not}}$. The no-till depth of mixing was increased from 2 to 5 cm. Concentrations and depositions of 2,3,7,8-TCDD at 200 and 10,000 meters were tested. The baseline quantities at 5,000 meters were varied to reflect different vapor/particle partitioning assumptions. Currently, the assumption is that 2,3,7,8-TCDD emissions are 51% in the vapor phase and 49% in the particle phase. Linear adjustments to the emissions in vapor and in particle form can be made to stack emissions. Concentrations and depositions at specific locations are then adjusted in the same linear manner to reflect different vapor/particle partitioning assumptions. Two assumptions tested include 10% vapor/90% particle and 90% vapor/10% particle.

● Contaminant Physical and Chemical Properties: The initial values for testing of this category of parameters were the ones used for 2,3,7,8-TCDD. Generally, the high and low values tested are those which may represent a range for this contaminant only, not all dioxin-like compounds. However, several of the ranges also encompass values that could be pertinent to other compounds. It should be remembered that this is simply a model performance exercise and nothing else. Also, it could be argued that some of the parameters should be changed in tandem - that there may be a relationship between soil/water adsorption, as modeled by Koc, and bioconcentration. Such relationships were not explored in these exercises. Notes on the parameters are as follows:

1. **Henry's Constant, H** - The value of 3.29×10^{-5} atm-m^3/mole was used for 2,3,7,8-TCDD. Except for a heptachloro-PCB, Henry's Constants for the dioxin-like compounds ranged from 10^{-6} to 10^{-4}. Because of this, the initial value was reduced and then increased an order of magnitude for this test.

2. **Molecular Diffusivity in Air, $\mathbf{D_a}$** - This parameter is needed for the volatilization flux algorithm. Because no values were available for the dioxin-like compounds, values were estimated based on the ratios of molecular between a dioxin-like compound of interest and a compound for which a D_a was available - in this case, diphenyl. The range of values tested are 0.005 cm^2/s as a low and 0.10 cm^2/s around the initial value of 0.047 cm^2/sec.

3. **Organic Carbon Partition Coefficient, Koc**: The Koc is perhaps the single most influential parameter governing the fate and transport of the dioxins from contaminated soils in this assessment, impacting surface water concentrations, vapor phase air concentrations, and directly or indirectly, all biomass concentrations (fish, vegetation, beef/milk). The literature for 2,3,7,8-TCDD shows a range of Koc under 10^6 (from Schroy, et al., 1985) to over $2x10^7$ L/kg (Jackson, et al., 1986). The value selected for 2,3,7,8-TCDD was $3.98*10^6$, based on an examination of available literature on the subject. The values tested were one order of magnitude less ($4*10^5$) and one order of magnitude more ($4*10^7$) than the value initially assumed for 2,3,7,8-TCDD.

4. **Air-to-Leaf Vapor Phase Transfer Factor, B_{vpa}**: The initial value for 2,3,7,8-TCDD was developed in a calibration exercise using field data which included air concentrations and grass concentrations which corresponded to these air concentrations. Details of this calibration are provided in Chapter 4, and will not be repeated here. Plus or minus an order of magnitude will be tested as a high and low value for B_{vpa}.

5. **Particle-Phase Fraction, ϕ:** This fraction was used in the stack emission source category for determining the portion of emitted contaminant that was and remained in the particle phase from stack to exposure site. Details on the measured and theoretical partitioning is given in Chapter 3 of this Volume. As discussed there, measured partitioning of 2,3,7,8-TCDD in ambient air showed a very small amount in the particle phase, 13%. However, speculation was that the monitoring method itself could lead to an underestimate in the particle phase, and for that reason, a theoretical approach was used to partition the dioxin. This led to a ϕ of 0.49 for 2,3,7,8-TCDD. The stack emission demonstration will be used to evaluate the impact of assuming 0.20 or 0.80 for 2,3,7,8-TCDD ϕ.

6. **Root Bioconcentration Factor, RCF:** The initial value for 2,3,7,8-TCDD was estimated as a function of octanol water partition coefficient, Kow. Assuming a log Kow of 6.8, RCF was solved as 5,200. Different assumptions for log Kow were used to estimate high and low values of RCF for this exercise. Examining literature Kow for the dioxin-like compounds, no log Kow are less than 6.0 (the lowest at 6.2) and only one value estimated to exceed log Kow equal 8.5. A high and low RCF were estimated, therefore, using log Kow of 6 and 8.5. This led to tested values of RCF of 1,260 and 106,000.

7. **Beef/milk Bioconcentration Factor, BCF:** Unlike the RCF (but like the BSAF and BSSAF as noted blow), there are no empirical formulas developed for BCF as a function of more common parameters such as Kow. The literature summary and interpretation of 2,3,7,8-TCDD cattle feeding studies by Fries and Paustenbach (1990) led them to assign a value of 5.0 for

2,3,7,8-TCDD. The study by McLachlan, et al. (1990) allowed for generation of BCF values for 16 of the 17 dioxin and furan congeners of dioxin toxicity equivalency, and the results from that study are used for this assessment. Fries, et al. (1999) presented another set of field-derived BCFs for 14 of the 17 dioxin-like dioxins and furans, and the BCF he calculated for 2,3,7,8-TCDD was 7.1. The 2,3,7,8-TCDD BCF used in this assessment was 5.76, which is close to the value of 5.0 promoted by Fries and Paustenbach (1990). Their summary, included in Table 4-5 in Chapter 4, showed BCF less than 1.0 for higher chlorinated dioxin-like compounds. For sensitivity testing, values of 1.0 and 10.0 were used as low and high values for BCF.

8. **Biota Sediment and Biota Suspended Solids Accumulation Factors, BSAF and BSSAF**: EPA (1993; 1995) summarizes several water column based and sediment (both suspended and bottom) based empirical parameters used to estimate fish concentrations given a water or sediment concentration. Two of these are the BSAF and BSSAF, which are used in this assessment. Although no data exists to determine values of the suspended solids factor, BSSAF, EPA (1993) suggests that BSAF values could be used. The range of BSAF values for 2,3,7,8-TCDD discussed in EPA (1993; 1995) is 0.03 to 0.30, and this was the low and high values selected for both BSAF and BSSAF. The literature summary on BSAF included in Chapter 4 of this assessment does include studies which imply higher BSAF for 2,3,7,8-TCDD. One study, which focused on bottom feeders (carp, catfish, etc.), found a BSAF for 2,3,7,8-TCDD (CDEP, 1992) of 0.76, whereas the range of 0.03 to 0.30 focused on column feeders. A high value of 2.94 (Kjeller, et al., 1990) was found in a lake in Sweden speculated to be impacted by an active pulp and paper mill. This high value appears to be an outlier not found in other field data sets.

9. **First-order Plant Weathering Factor, kw**: This is used to simulate the weathering of contaminated particulates which have settled on plant matter via dry and wet deposition. Several modeling efforts have used the same kw as used in this effort; that kw is 18.01 yr^{-1}, which corresponds to a half-life of 14 days. Values of 51 (half-life of 5 days) and 8.4 (half-life of 60 days) yr^{-1} were used to test the impact of this parameter.

10. **Dissipation Rate Constant for Eroding or Depositing Contaminants, k**: Evidence for soil degradation of the dioxin-like compounds indicates that residues even millimeters below the soil surface degrade at a very slow rate, if at all (see Chapter 2, Volume 2 of this assessment). This was the basis for not considering degradation of soil sources of dioxin-like compounds in this assessment. However, when residues migrate to impact only a thin layer of soil at a distant site, the processes of volatilization or photolysis (the one degradation process which appears to transform dioxin-like compounds in the environment) are likely to impact delivered residues. A rate constant of 0.0277 yr^{-1}, which corresponds to a 25-year half-life, was

used in two instances for this methodology - for erosion of off-site soils onto exposure site soils, and for deposition of stack emissions onto exposure site soils. This value was changed to 0.277 yr^{-1} (half-life of 2.5 years) and 0.00277 yr^{-1} (half-life of 250 years) in sensitivity testing.

6.3.3. Results

The results of the sensitivity analysis are principally described in a series of high/low bar graphs. The Y-axis is on a log scale and shows changes in media concentration estimation when the high and low parameter substitutions are made. The Y=1 line is the value of the media concentration with all baseline parameter selections; the precise value of that media concentration is noted on each graph. Other y-axis values are arrived at as the ratio of the pertinent media concentration estimated with the altered parameter over the baseline concentration; a y-axis value of 0.1, for example, means that the concentration with the parameter substitution was one-tenth the concentration under baseline conditions. Also noted on each graph is the pertinent source strength term - for air concentration sensitivities, soil concentrations are noted, and so on. The parameters tested are named on the x-axis, and these names correspond to the names in Table 6.1. The definition and baseline value of these key parameters are noted below each graph. The high and low values tested are appropriately placed either above (when the concentration increases with the parameter change) or below the bar graphs. These parameters are the only ones which impact the tested media concentration. Of course, the soil concentration also impacts the media concentration, but as noted in the previous section, soil concentrations have a direct and linear impact in all cases, and so are not displayed on the figures. Observations from each figure now follow.

6.3.3.1. *Estimation of Vapor-Phase and Particle-phase Air Concentrations Distant from a Site of Soil Contamination*

Results for this test are shown in Figures 6-1 and 6-2. For the test of the vapor-phase algorithm, Figure 6-1, no single change resulted in estimations over an order of magnitude different from that made with baseline parameters. The model is insensitive to porosity and particle bulk density parameters, E_{slp} and P_{soil}. The results are also reasonably insensitive to ranges for organic carbon content of soil, OC_{sl}, and windspeed, U_m. For all other parameters, there appears to be roughly an order of magnitude spread over the range of parameters tested. Increasing the exposure duration to 70 years would decrease air concentration predictions by about 35% and decreasing the duration to 1 year would roughly double concentrations. As discussed earlier in Section 6.2, the volatilization algorithm assumes that contamination begins at

the soil surface at time zero, and residues available for volatilization originate from deeper in the profile over time. The result of this assumption is that the flux decreases as time increases. This is the only algorithm of this assessment where an assumption of a decreasing source strength over time is made.

Results from the test of the particle phase flux and dispersion algorithm are shown in Figure 6-2. The y-axis in this test spans two orders of magnitude since changes in the parameters describing the inherent wind erodibility of the soil, U_t and F(x), results in over an order of magnitude higher and lower than concentration estimations as compared to estimations using the selected values of U_t and F(x). The assumption of bare soil conditions at the site of contamination led to a value of 0.0 for V, the vegetative cover parameter. If the contaminated site had a reasonably dense vegetative cover leading to a V of 0.9, air concentrations at the nearby site of exposure would be about an order of magnitude less. The impact of area (ASC), distance (DL_e), and frequency (FREQ) on exposure site concentrations mirror those for vapor-phase air concentrations. That is because these three are used in the same far-field dispersion algorithm. Another parameter used for the far-field dispersion algorithm is windspeed, U_m. However, interestingly, the impact of that parameter is reversed between the vapor and particulate phase algorithms. For the particulate phase, the windspeed has more of an impact in increasing wind erosion and hence the reservoir of airborne contaminant - increasing windspeed increases air concentrations. For the vapor phase, windspeed does not play a role in estimating volatilization flux, but only a role in the far-field dispersion model. In that role, increasing wind speed increases dispersion and decreases concentrations.

Noteworthy for the particle phase algorithm is that estimated concentrations are independent of any chemical-specific parameters; wind erosion suspending the particles is only a function of climate, ground cover, and soil erodibility. Also noteworthy is that the baseline air concentration of contaminants on particles is over an order of magnitude lower than the baseline air concentration of contaminants in the vapor phase. Besides having implications for particle phase and vapor phase inhalation exposures, this difference also has implications for impacts to vegetation concentrations and subsequently to beef and milk concentrations.

The results shown in Figure 6-1 and 6-2 are specific to algorithms estimating emissions from soil, volatilization and wind erosion, and dispersion of those emissions to calculate an air concentration at a distant site. Chapter 4 also described an algorithm to estimate “near-field” dispersions, which can be used to estimate air concentrations above a site of soil contamination. Brief tests were conducted to evaluate the difference in impacts when the near field dispersion model is used instead of the far field dispersion model. One observation was that all parameters

associated with flux calculations had identical impacts to near-field air concentrations as compared to far-field concentrations. Included in this group were: for the volatilization algorithm - the exposure duration, ED, the organic carbon content, OC_{sl}, soil porosity, E_{slp}, particle bulk density, P_{soil}, and the three chemical-specific parameters, Henry's Constant, H, organic carbon partition coefficient, Koc, and molecular diffusivity, D_a, and for the wind erosion algorithm - fraction of vegetative cover, V, average windspeeds, U_m, and the parameters associated with the erodibility of the soil, U_t and F(x). The impact of area is different for concentrations calculated with the near-field algorithm compared to the far-field algorithm. This is because the area term, ASC, has a different role for the near field as compared to the far field algorithms. For the far field algorithm, ASC in effect impacts the source strength, with an order of magnitude increase in ASC increasing exposure site air concentrations by a little over 2 times (>200%). For the near field dispersion, ASC impacts the dispersion algorithm, and the same order of magnitude increase in area only increases concentrations by around 30%.

6.3.3.2. *Estimation of Soil Erosion Impacts to Nearby Sites of Exposure*

Results from this test are shown in Figure 6-3. This model shows little sensitivity to two parameters, the bulk density of soil at the site of exposure, B_{soil}, and the amount of "clean" soil (that which is between the contaminated and exposure site) which erodes onto the exposure site, SL_{ec}, along with the contaminated soil. These will not be discussed further. In contrast to SL_{ec}, the model has a direct linear impact with the amount of soil eroding from the contaminated site, SL_s. Decreasing that amount by a factor of 10 decreases exposure site soil concentrations by the same amount, and doubling contaminated site erosion also doubles exposure site soil concentrations.

The model appears to show insensitivity to the distance between the exposure and contaminated site, DL_e. However, this result should be viewed cautiously. The sediment delivery ratio equation was developed to estimate sediment loads from construction sites to nearby surface water bodies, and from distances up to 250 m. Its application to distances beyond that are questionable, and applications from one land area to another land area rather than from one land area to surface water, should also be questioned. At the model baseline distance of 150 m, the SD_s (sediment delivery ratio) is 0.26. At 1000 m, it is 0.17, which is a marginal dropoff for what appears to be a significant increase in distance. The distance becomes increasingly important when there are obstructions between the contaminated and the exposure site such as ditches, roads, and so on. When using this methodology, one should consider not relying on the sediment delivery ratio equation for: 1) transport of soils beyond 250 meters, 2) when the

exposure site is upgradient from the site of contamination (in its development for construction sites, the assumption that a water body is downgradient soil concentration at the exposure site only doubled; it did not increase by an order of magnitude. It is unreasonable to assume that all the eroded soil would crowd into the smaller exposure site. When the contaminated site decreased an order of magnitude to 4,000 m^2, the exposure site soil concentration likewise decreased by an order of magnitude. In this case, like the case when the contaminated and exposure site were of the same size, all the contaminated soil eroding in the direction of the exposure site mixes into exposure site soil, so the resulting average soil concentration at the exposure site is linearly related to the concentration at the contaminated site. A similar trend is noted with changes in the exposure site area term..

The impact to changes in depth of tillage is nearly, but not quite, linear. Decreasing the no till depth of mixing, d_{not}, from 0.02 m to 0.01 m increased soil concentrations by a factor of 1.4 roughly, while increasing d_{not} to 0.10 decreased concentrations by 70%. A similar, nearly linear, impact is noted with the changes tested for tillage depth, d_t. For figure clarity, these results were left off Figure 6-3, but decreasing the depth from an initial 0.20 m to 0.10 m increased concentrations by just under a factor 2, and decreasing it to 0.30 m decreased concentrations by just under 33%.

The impact of changing the dissipation rate is not linear. Decreasing the rate by an order of magnitude, which is equal to increasing the half-life from 25 to 250 years, only about doubles the predicted soil concentrations, while increasing the dissipation rate by an order of magnitude, or reducing the half-life to 2.5 years, reduces the soil concentration by a factor of 5.

It is interesting that some of the tested model parameter changes, including manipulation of the areas of contamination and exposure sites, and the dissipation rate, result in increasing the exposure site soil concentration to nearly the same concentration as the contaminated site. This is a somewhat counterintuitive result; it seems unlikely that an off-site location would have concentrations close to the contaminated site. If, in fact, the model has a tendency to overpredict exposure site concentrations, there are several reasons why this might occur: 1) overestimation of the sediment delivery ratio, which was discussed above, 2) a shallow mixing depth for untilled situations, 3) a low dissipation rate (which translates to a long half-life), 4) high estimates of erosion from the contaminated site, and/or 5) use of a steady state solution.

Regarding this latter point, a steady state solution means that if erosion continues indefinitely and the contaminated site soil concentrations do not lessen during this time, than the exposure site soil concentrations reaches the level predicted by the model. This could lead to a significant overestimation if the soil contamination was relatively recent. For example, if the

erosion from a contaminated site to an exposure site has been occurring for 25 years, it can easily be shown that the full solution to the soil concentration, Equation (4-16) in Chapter 4, will result in a soil concentration that is 72% of the concentration estimated using the steady state simplification, Equation (4-17) in Chapter 4. At 50 years, the modeled soil concentration will be 92% of the steady state solution. These calculations assumed the half-life of 25 years. Therefore, if the soil contamination occurred within 20 years or so, assessors may wish to model a lower and perhaps more accurate soil concentration by using the full solution rather than the steady state solution to estimate exposure site soil concentrations and impacts.

6.3.3.3. *Estimation of Soil Erosion Impacts to Nearby Surface Water Bodies*

Results from this test are shown in Figure 6-4. One immediate point to make about this bar graph is that the results displayed are essentially identical for water, bottom sediment, and fish concentrations, with the exception of two trends which will be described below. Also, since bottom and suspended sediment concentrations are assumed to be linearly related by the equation: $C_{ssed} = (OC_{ssed}/OC_{sed}) * C_{sed}$, where C_{ssed} and C_{sed} are suspended and bottom sediment concentrations, respectively, and OC_{ssed} and OC_{sed} are suspended and bottom organic carbon fractions, than the relationships in Figure 6-4 apply to suspended sediment concentrations as well.

One of the exceptions has to with trends regarding partitioning of dioxins between sediments and water. The parameters involved in this algorithm are the organic carbon content parameters, OC_{ssed} and OC_{sed}, and the organic carbon partition coefficient, Koc. First, the direction of the change is not the same. The sorption, and hence concentration, of dioxin-like compounds onto sediments can be increased by increasing the organic carbon content of the sediments or increasing the Koc. However, doing either decreases the concentration in water. For the "low organics" test, water concentration increases by a factor of 2.7 rather than slightly decreases as in Figure 6-4, which for this case, displays only the impact to bottom sediments. For the "high organics" test, water concentrations decrease to 0.60 of what they were in baseline conditions. The high Koc decreases water concentrations to 0.1, and the low Koc increases water concentrations 7 times. Both these trends are distinctly different than the sediment trends; they were left out of the graph in order not to crowd the graph (or require another one be drafted), and also because water concentrations in the sub-ppq range are of minimal concern for exposure. The other exception has to do with the impact of changes to the organic carbon content of bottom and suspended sediments in the calculation of fish concentrations. Fish tissue concentrations for three of the four source categories of this assessment are a direct function of bottom sediment

concentrations; the one source category where this is not true is the effluent discharge source category, where fish tissue concentrations are a function of suspended sediment concentrations. As laid out in Chapter 4, whole fish tissue concentrations are estimated as: (C_{sed}/OC_{sed}) * BSAF * f(lipid), when fish tissue concentrations are a function of bottom sediment concentrations, and for the effluent source category, fish tissue concentrations are estimated as: (C_{ssed}/OC_{ssed}) * BSSAF * f(lipid). It is seen from Figure 6-4 that the concentration on bottom sediments, C_{sed}, is impacted by the value assigned to OC_{sed}. However, the impact to C_{sed} with changes to OC_{sed} is marginal and in the same direction. For example, reducing OC_{sed} from its baseline of 0.03 to 0.01, reduces C_{sed} by a small amount. The impact to fish tissue from changes in OC_{sed} is more pronounced and essentially in an inverse linear manner, as shown by the formulation above.

Other than these two exceptions, a principal message from Figure 6-4 is that all surface water impacts are identically impacted by surface soil and erosion parameters. The comments in the above section concerning the distance between the contaminated soil and the target site, which in the above section was the exposure site, but for here it is the surface water body, also pertains to this algorithm. Specifically, it was noted that the sediment delivery ratio equation seemed relatively insensitive to changes in distance. In Figure 6-4, this also seems to be the case, as little change in predicted water impacts occurs between the tested values of 50 and 1000 meters. However, if clear impediments such as roads or ditches are between the site and the target area as the distance increases, than it is quite possible that the sediment delivery ratio equation is not appropriate to use when predicting the delivery of contaminated soil to the water body. On the other hand, if a site is near a surface water body, it seems that the origins of the sediment delivery ratio equation - developed from data on construction sites near surface water bodies - are more appropriate.

The key source strength terms tested, the area of contamination, ASC, and the soil loss rate from the site of contamination, SL_s, both have a direct linear impact on the both sediment and surface water concentrations. The other soil loss term, the erosion rate for the watershed, SL_w, also has a direct linear impact. Somewhat less critical in this algorithm is the size of the watershed. The reduction of watershed size by about an order of magnitude increased water concentrations by about a factor of 2, and an increase in size by an order of magnitude reduced impacts by about 70%.

The algorithm seemed fairly insensitive to the remaining five parameters tested. The average watershed concentration, initialized at 0.0 in order to just show the incremental impact from the contaminated site, was increased to 1 ppt. This approximates a background concentration of 2,3,7,8-TCDD and was an order of magnitude lower than the contaminated site

concentration of 1 ppb. It is seen in Figure 6-4 that background soils have a marginal impact on a water body which is impacted from a site of elevated soil concentrations located near the water body. The impact of the organic carbon partition coefficient, Koc, on bottom sediments appears small despite the fact that the Koc range spans two orders of magnitude. This is an indication that it is so high for the dioxin-like compounds, that (at least in the algorithm of this assessment), its assignment is not critical for sediment concentration estimations. The same lack of impact appears to be the case for the organic carbon content of water body sediments, and the level of suspended solids in the water column. The range of enrichment ratios tested, 1 to 5, represents the appropriate high and low value this parameter would take, based on literature studies of this phenemona. As will be discussed in Chapter 7, a site in Connecticut had sediment concentrations in background settings about 2.8 times higher than surface soil concentrations. In this tested range, only a small impact to surface water is noted.

6.3.3.4. Vapor-Phase Transfers and Particle-Phase Depositions to Above Ground Vegetation

Concentrations in above ground vegetation are a function of vapor-phase transfers and particle phase depositions. Vapor and particle reservoirs originate from contaminated soils as volatilization and wind erosion, respectively. Atmospheric dispersion and deposition modeling delivers concentrations and depositions, respectively, from a stack to a site of exposure. The principal difference in the soil and stack emission source categories is in the relative proportions of the contaminant which are in the vapor and particle phases. As discussed below, more contaminant is delivered via particle depositions for the stack emission source category as compared to the soil contamination source category.

Vapor transfers and particle depositions for the soil contamination source category are evaluated in Figures 6-5 and 6-6. The same general trends shown in these figures also occurs in the stack emission source category. Three types of vegetation are modeled for this assessment, including vegetables/fruit, grass, and animal feeds. The latter two are for the terrestrial animal bioconcentration algorithms, the first for human exposure via consumption of unprotected fruits or vegetables.

For vapor-phase impacts shown in Figure 6-5, it would appear that changes to total vegetation concentrations are critically a function of parameters specific to the vapor transfer algorithm. There is between one and two orders of magnitude range of plant concentrations predicted over the range of the vapor phase transfer coefficient, B_{vpa}, tested. This parameter is uncertain as well as very influential in this methodology. There is about a one order of magnitude range for the vegetable/fruit category and a two order of magnitude range for the grass

and feed categories. The reason there is a difference in the influence of B_{vpa} in the vegetative categories has to do with the use of a second and also influential and uncertain parameter, the VG parameter. This parameter was introduced to model the difference between the leaves of the experiment for which B_{vpa} was developed an the bulky vegetation to which the B_{vpa} is applied, the VG parameters (VG_{veg}, VG_{gr}, and VG_{fod}). The need for such a correction factor is justified given the evidence that dioxin-like compounds to do not translocate into vegetation. The grass leaf concentrations in the experiments for which B_{vpa} was derived are likely to be analogous only to the outer layer concentrations in bulky vegetation, not the whole plant (or whole fruit/vegetable) concentrations. This empirical parameter was set to 0.01 for bulky fruits/vegetables, but was set at 1.00 for grass, under the assumption that grass is similar to leaves, and 0.50 for cattle fodder, which is assumed to contain some bulky (grains) and leafy (hay) vegetation. Relatively speaking, therefore, the impact of grass concentrations to vapor phase concentrations are 100 times higher than the impact of vegetable/fruit concentrations to vapor phase concentrations because of this VG parameter. There is a linear impact for grass and feed to changes in VG - halving VG for grass halves the grass concentration, for example. The impact of changes to VG is less for vegetables/fruits, again because its influence is minimized due to its low initial value of 0.01.

A dry weight to fresh weight conversion factor, FDW, is required for estimating above ground concentrations of vegetable/fruits. This is because the algorithms estimate above ground vegetative concentrations on a dry weight basis, and the concentrations need to be diluted since fruit and vegetable consumption are given in this assessment on a fresh weight basis. The impact to concentrations is direct and linear, and since the range of likely FDW is small, the impact is small as well. This parameter is also required for the particle deposition algorithm, but is. left out of Figure 6-6 for clarity. In fact, FDW is applied once vapor phase and particulate phase contributions to vegetable/fruit concentrations are already summed; in other words, it is not tied to either the vapor or particle phase algorithms.

The impact of all the particle phase parameters to overall plant concentrations is less than that of vapor transfers, as seen in a comparison between Figures 6-5 and 6-6. For the parameters including rainfall amount (R), washout factor (W_p), denseness of vegetation (as modeled by yield, Y, and intercept fraction, INT), velocity of particle deposition (V_p), and plant weather dissipation rate, kw, results in Figure 6-6 are for vegetable/fruits and not grass or fodder. Vegetables/fruits are more impacted by particle depositions than grass/fodder, and as seen, there is less than half an order of magnitude impact from the range of values for these parameters tested. As noted above, the impact of depositions on vegetable/fruit concentrations occurs because the correction factor for vegetables, VG_{veg}, is equal to 0.01, which minimizes the vapor-

phase contributions to vegetable concentrations in comparison to the contributions of the vapor phase concentrations for grass and fodder concentrations, which have correction factors of 1.00 (for grass) and 0.50 (for fodder).

This trend is quantified in Table 6-2. Model results on the proportion of above ground plant concentrations that are due to air-to-leaf transfer and particulate deposition were examined for the soil contamination and stack emission source categories for 2,3,7,8-TCDD, and results are summarized in Table 6-2. Results show that vapor phase transfers tend to dominate vegetative concentrations, although particle phase concentrations are important for bulky fruits and vegetables. Results also show that the relative impact of vapors and particles is a function of distance for the stack emission source category. For the central stack emission Scenario, #4, where the site of exposure is 5000 meters from the stack, vapor transfers generally have more of an impact to vegetation as compared to the high end Scenario, #5, where the site of exposure is 500 meters away.

It is possible that the impact of particle depositions is being underestimated, for at least four reasons:

- The wind erosion algorithm estimating air-borne contaminant concentrations for the soil contamination source category only estimates concentrations of PM-10, or inhalable size particulates, those 1 0 μm size diameter and less, while the ISCST3 model considers all size particulates emitted from stacks. Larger size air-borne particulates, while not inhalable, would deposit onto vegetation.
- For the demonstration of the soil contamination source category which involves soil contamination distant from the site of exposure, only the off-site locations provide the source of air-borne particulates. Meanwhile, algorithms are in place estimating exposure site contamination, albeit to thin surface levels. Certainly, the reservoir of air-borne particulates depositing onto vegetation would also include contributions from where the vegetation is located and the surrounding land, not only from the area of soil contamination.
- For the stack emission source category, resuspension of deposited particles and deposition onto plants is not considered. This omission is similar to the omission noted in the bullet above.
- The modeling does not consider the splash effect of rainfall, which would deposit soil onto the lower parts of plants. This would make the most impact for grass and for vegetables near the ground surface such as lettuce.

- For the soil contamination source category, an additional factor is on the way the model does not reapportion volatilized residues onto airborne particles. As was discussed in Chapter 5, the 2,3,7,8-TCDD vapor phase dominates the total air concentration and is about 95% of the total concentration. Residues which volatilize from the soil are assumed to remain in the vapor phase. In contrast, the 2,3,7,8-TCDD vapor phase is 51% of total air concentrations in the stack emission source category, because this is the fraction developed from the equilibrium vapor/particle partitioning algorithm. If dioxins were reapportioned after volatilizing, the vapor/particle partitioning for the soil contamination source category would shift over to the particle phase and the particle phase impacts to vegetation would be increased.

The precise impact of these factors might be investigated more fully in a later assessment with additional models. Tests were run for this sensitivity analysis by increasing the amount of particulate phase contaminants depositing onto vegetation by an order of magnitude to the soil contamination demonstration scenario, without changing the vapor phase contributions. The vapor phase/particulate phase contributions to above ground fruits and vegetables, originally 56%/44% (from Table 6-2), changed to 11%/89% with an order of magnitude increase in particulate phase contributions. Vegetable concentrations increased by a factor of 6. The impact was less for grass and fodder, with concentrations increasing by a factor of 1.7.

The impact of partitioning of airborne dioxins between a vapor and a particle phase was more fully investigated using results from the high end demonstration of the stack emission source, Scenario 5. The results from this analysis are shown in Figure 6-7. For this test, the partitioning of 2,3,7,8-TCDD was altered from the originally assigned values of 51% vapor/ 49% particle. The vegetation examined include above and below ground vegetable concentrations, and above ground grass and cattle feed.

The obvious trend to note from this figure is that the impact of this repartitioning is the opposite for vegetables/fruits, both above and below ground, as compared to grass and cattle feed. For above ground vegetation, this is the result of the use of the empirical correction factor, VG. As discussed above, assignment of the value of 0.01 for vegetable/fruit VG minimizes the impact of vapors on above ground vegetables/fruits. Therefore, when particle phase depositions are increased, as in the right-hand side of Figure 6-7, vegetable/fruit concentrations increase, and likewise, decreases in particle phase depositions decrease the concentrations. The reason that the trend is the same for below ground vegetables is that changes in particle depositions lead to concurrent changes in soil concentrations. Since the leafy vegetation of grass and cattle feed are

dominated by vapor phase transfers, reductions and increases in the vapor phase concentration lead to reductions and increases in the concentrations of these vegetation. Even at the lower vapor fraction, 20% in the right-hand side of Figure 6-7, vapor impacts still dominate the predicted concentrations for these vegetation.

6.3.3.5. *Estimation of Below Ground Vegetation Concentrations*

One important factor to note up front about below ground vegetable concentrations as compared to above ground vegetable concentrations (no underground fruits are assumed in this assessment) is that below ground vegetable concentrations of 2,3,7,8-TCDD are about four orders of magnitude higher than above ground vegetable concentrations for the soil contamination demonstration scenario. For the stack emission scenario, above and below ground concentrations of 2,3,7,8-TCDD are comparable. Also, the below ground vegetable ingestion rate of 1.16 g/kg-day is quite comparable to the above ground vegetable ingestion rate of 1.52 g/kg-day. Given the difference in concentration estimations in the soil contamination demonstration, below ground vegetables explain over 99% of the total exposure via ingestion of impacted vegetables in that demonstration. Again, they are about half the total vegetable exposure for the stack emission source category. Sensitivity of underground vegetable concentrations to parameter changes for the soil contamination source category becomes important from this perspective.

The reason for this dichotomy in performance between the soil contamination and stack emission source categories has been examined in other parts of this document, including the examination of vegetable results in Chapter 5, and the soil-to-air model testing in Chapter 7. To review these discussions, it was found that when soil is assumed to be source for air concentrations, as in the soil contamination source category, then a ratio of air to soil concentrations will be very low compared to an air to soil concentration ratio when the air is assumed to be source for soil concentrations, as in the stack emission source category. This air to soil ratio does not have any important meaning except in the context of this discussion. Two possible explanations were offered for this trend: 1) the models predicting volatilization and dispersion were underpredicting air concentrations, and/or 2) the soil to air models are not unpredicting air concentrations - the tendency for dioxins to escape soil (i.e., the fugacity of dioxins in soil to air transfers) is very low compared to the tendency for dioxins to move towards soil.

This question now is whether this dichotomy in performance is reasonable. A model exercise in Chapter 7 evaluated the air-to-soil algorithm and the soil-to-air algorithm using air

and soil data from the same rural site. It was shown that the air to soil model very reasonably was able to duplicate the soil concentrations, but that the predictions of air concentrations above the soil were much lower than observed, by about an order of magnitude. Again, this could be due to the fact that the models may be underpredicting air concentrations above them. Also, it could be due to the fact that air concentrations measured in the rural setting are due to long range transport from distant sources and not the soil concentrations. Given that the model appeared to perform well in air-to-soil modeling, it is expected that the observation that above, and below ground vegetable concentrations in the stack emission are comparable, is supportable. The same confidence cannot immediately be placed on the difference in modeling between above and below ground vegetables for the soil contamination source category.

In any case, the impacts of parameter changes for the algorithm predicting concentrations in underground vegetables are shown in Figure 6-8. These results were generated by the soil contamination source category, although analogous results would result for the stack emission, source category. All results are essentially linear, which is not surprising since below ground vegetable concentrations are a linear function of all the parameters tested: $C_{veg} = (C_{soil} * RCF * VG_{bg}) / (Koc * OC_{sl})$. The two orders of magnitude range for the root concentration factor, RCF, translates to a two order of magnitude range of concentration estimation. The same is true for the empirical correction factor applied to below ground vegetables, VG_{bg} , and the organic carbon partition coefficient, Koc. A smaller impact is noted for the organic carbon fraction of soil, OC_{sl}. Koc and OC_{sl} are required for this algorithm because vegetable concentrations are a function of soluble phase concentrations, not soil concentrations. Increasing Koc and/or increasing OC_{sl} results in decreasing the water concentrations, explaining why the high values for these parameters reduce vegetable concentrations. The smallest range in Figure 6-8 is the depth of tillage parameter, which directly influences the soil concentration, C_{soil}. Reducing the depth of tillage by 2 increases the soil concentration by about this same amount, as seen in Figure 6-8.

One final note is that the dry to fresh weight ratio, FDW, is not on this figure, while it does appear on Figure 6-7. This is because the RCF was developed on a fresh weight basis already, so no conversion to a fresh weight is required.

6.3.3.6. *Beef Fat Concentration Estimation in the Soil Contamination and Stack Emission Source Categories*

The impacts of parameter changes to beef fat concentration estimation for the soil contamination and stack emission source categories are shown in Figures 6-9 and 6-1 0. These sensitivity runs were both run on 2,3,7,8-TCDD, the only dioxin congener demonstrated for the

soil source category in Chapter 5, but 1 of the 17 dioxin-like congeners evaluated in the demonstration of the stack emission source in Chapter 5.

The overriding difference in the way the two source categories predict beef fat concentrations is that, in the soil contamination source category, the soil-to-cattle pathway dominates the prediction of beef fat concentration, whereas in the stack emission source category, the air-to-plant-to-cattle dominates. In Figure 6-9 showing results for the soil contamination source, there is essentially a linear relationship between changes in soil concentration and the beef impact, whereas in Figure 6-10 showing the stack emission relationships, a nearly linear impact is noted instead for changes in the grass and fodder concentrations. This overall trend is principally due to trends that have previously been discussed - that is, when soil is the source of contamination, the impact to air and above ground vegetation is proportionally smaller as compared to when air is the source of contamination.

This trend is further elucidated in the impact of two other soil related tests - one on the soil bioavailability factor, Bs, and one on the proportion of soil ingested in the cattle diet. In both cases, changes to these parameters have a significant impact in the soil source category but a minor impact in the stack emission category. Actually, the importance of soil exposure in the soil source category and the importance of vegetation in the stack ,emission category influences most of the other results on Figures 6-9 and 6-10. In the "low" exposure conditions, the reduction in soil intake from 4% of the diet to 1% of the diet influenced the results for the soil source category, but the influence was minor for the stack emission category because intake of contaminated grass was essentially unchanged and the "lower" exposure was mainly reflected in a reduction of intake of contaminated cattle feed. In the "extent of pasturing" test, the increase in soil intake from 4% to 8% resulted in a significant impact for the "high" condition in the soil source category, but less of an impact in the stack emission category, because again the vegetative intakes were not significantly changed for this test.

In addition to the sensitivity analysis shown in Figures 6-10 and 6-1 1, this trend can be described simply by displaying the following results from the demonstration of the soil source and stack emission source categories from Chapter 5:

	Percent impact due to ingestion of:		
Description	Soil	Grass	Feed
Soil contamination, beef	98	< 1	> 1
Soil contamination, milk	97	< 1	> 2
Stack emission, beef	11	61	28
Stack emission, milk	7	14	79

As seen here, soil only accounts for 11 and 7% of beef and milk concentration impacts from stack emissions in the example scenario, but overwhelms the soil source category.

The only parameter which was equally influential for both categories, was the bioconcentration factor, BCF. To estimate beef fat concentrations, the concentrations in the soil and vegetation of the cattle diet are multiplied by this factor, so logically, its influence is separate from the modeling of concentrations in soil or vegetation. Also, the response to changes in this parameter are linear.

As seen in the above results, the relative impacts of soil and vegetation to milk fat is similar to that of beef fat in the two source categories. The baseline scenario for a dairy cow's exposure has a significantly greater amount in cattle feed, 90%, as compared to the beef cattle, 45%. That is why the percent of impact for milk is more driven by feed than grass as compared to beef in the stack omission source.

The free range chicken scenario is driven by soil in both the stack emission and the soil contamination scenario. The following results display this trend:

	Percent impact due to ingestion of:		
Description	Soil	Grass	Feed
Soil contamination, chicken and eggs	> 99.9	< 0. 1	0
Stack emission, chicken and eggs	79	21	0

The reason for this trend is that the free range chicken exposure scenario has the chicken diet comprised of 10% soil, 5% incidental leafy vegetation while scavenging, and 85% residue free chicken feed. The justification for assuming that 85% of the chicken diet was residue free came

from Stephens, et al. (1995), who did not detect dioxins in the analysis of a standard chicken feed. They also developed the chicken/egg bioconcentration factors used in this assessment and assumed a 10% soil percent in the diet of the free range chicken. Further detail on the use of the Stephens, et al. (1995) data can be found in Chapter 4. In any case, it is expected that the chicken and egg models will respond to parameter changes in the same manner as the beef fat sensitivities as displayed in Figure 6-9, showing sensitivities in the soil contamination source category, rather than Figure 6-10, which shows the stack emission source sensitivities.

6.3.3.7. *Impact of Distance from the Stack Emission Source on Concentrations in Soil, Vegetables, and Beef Fat*

For this test, the high end scenario for the stack emission demonstration, Scenario 5, was used as the baseline. The exposure site was located 500 meters from the stack in the downwind direction. Two other locations, 200 and 5000 meters, were, evaluated, and predictions for soil, below and above ground vegetables, and beef fat were examined. The results of this examination are shown in Figure 6-11.

In the high end stack emission demonstration scenario, the farm was assumed to be 500 meters from the stack. Nearer to the stack at 200 meters, ambient air concentrations and dry deposition amounts were lower, but wet deposition was at its maximum. One effect of this was that vegetable concentrations increased. Below ground vegetables increased by about a factor of about 4, due to the same increase in soil concentration as a result of much higher wet deposition. Above ground vegetation increased by about 50%. As was described earlier, particle depositions dominated above ground vegetable/fruit concentrations. Therefore, an increase in overall particle depositions due to an increase in wet depositions led to increased above ground vegetable/fruit concentrations. However, the trend was not the same for beef fat. As discussed in earlier sections, vapor contributions dominated grass and feed concentrations for the stack emission source category. Therefore, a drop in ambient air vapor phase concentrations at 200 meters as compared to 500 meters dominated the result, and the net impact was to reduce beef fat concentrations. From Figure 6-11, it is seen that beef fat concentrations were reduced by about 30% when using ISCST3 output from 200 m instead of 500 m. Further from the stack at 5000 meters, all biota concentrations were lower. Vapor phase air concentrations were roughly halved as compared to what they were at 500 m, and dry and wet deposition were lower by 60 and 80% respectively compared to levels at 500 m. This led to substantial reductions in vegetable concentrations. Beef fat concentrations were also lower at 5000 meters as compared to 200 m

and the baseline distance of 500 m. Overall, beef fat concentrations were about 70% less at 5000 meters as compared to 500 m.

Trends for milk fat concentration are not exactly the same, but very similar to those of beef fat. Trends for chicken and egg are similar to that of soil and below ground vegetables, because these tissues are modeled primarily as a function of the free-range chicken exposure to soil - this was discussed in the previous section to this one.

6.3.3.8. *Water and Fish Concentrations Resulting from Effluent Discharges*

The impacts of parameter changes for algorithms estimating water and fish concentrations are shown in Figure 6-12. First, it should be noted that fish and water impacts are included in the same graph because the impacts to both concentrations are exactly the same with the noted changes in parameters, with one exception. This exception is the partition coefficient, Koc. Increases in Koc result in higher suspended sediment concentrations, which lead to higher fish tissue concentration estimations, but lower water concentration estimations. Increasing Koc by an order of magnitude actually decreases water concentrations to 14% of its baseline value, or 0.14 on the y-axis of Figure 6-12. Decreasing Koc by an order of magnitude increases water concentrations by a factor of 2.4. Roughly, the location of the high and low Koc points on Figure 6-12 should be reversed for water concentration impacts. Also, the biota to suspended solids accumulation factor, BSSAF, and the fish lipid content, f_{lipid}, are specific to fish tissue estimations.

Clearly, both concentrations are mostly impacted by the loading rate - the impact is linear and direct. Of all the parameters describing the effluent stream and the receiving water body, only the two order of magnitude change in receiving water body flow rate seems to have about an order of magnitude range of predictions. The effluent flow rate is ultimately low in comparison to the receiving water body, so its impact is limited. The range of organic carbon contents of the effluent and of the suspended solids in the receiving water are reasonably assigned and appear to have a small impact.

Higher suspended solids content in the receiving water body can result in lower fish and water concentrations. This might be termed a "solids dilution effect". Few studies are available in the literature which support this result, but two studies were found which are consistent with a solids dilution effect. One “simulated field experiment" conducted by Isensee and Jones (1975) maintained a constant water concentration of 239 ppb, but reported a decrease in 2,3,7,8-TCDD concentrations in both mosquite fish (2200 ppb to 90 ppb) and catfish (720 to 90 ppb) as the amount of sediment increased from 20 to 440 g. Sherman (1992), in a review of this and other

simulated field experiments and laboratory flow through experiments, points out that a bioconcentration factor for these simulated field experiments would decrease as the sediment increases. He speculates that, in comparing water flow through experiments with field simulated data, the bioconcentration factors tend to be less in field simulated experiments because 2,3,7,8-TCDD may sorb to sediments and be less bioavailable. A second study supporting a solids dilution effect was conducted by Larsson, et al. (1992). They studied uptake of PCBs and p,p'-DDE in 341 northern pike in 61 lakes in southern Scandinavia. They found that the levels of these persistent pollutants in the fish decreased as productivity increased. Productivity was measured by total phosphorus, chlorophyll a, and lake water transparency, which was mainly influenced by phytoplankton biomass. Their hypothesis was that the levels decreased because humus adsorbs persistent pollutants, rendering them less available for uptake in fish.

The two order of magnitude range in Koc translates to about a one order of magnitude range in estimated fish and water concentration estimations. Fish tissue concentrations are linearly and directly related to the BSSAF and f_{lipid}. About an order of magnitude of concentration estimation is noted with about the same order of magnitude in likely values.

6.3.3.9. *Water and Fish Concentrations Resulting from Stack Emissions*

Results of sensitivity analysis of algorithms estimating surface water and fish concentrations resulting from stack emissions are shown in Figure 6-13. First, it is noted that the impact to both these media is the same with impacts to all parameters. The impact with changes in the deposition of particles onto the water body, $RDEP_p$, and with the fraction of deposited particles remaining in suspension, f_{sd}, is negligible. The assigned values to these parameters for the demonstration are, therefore, sufficient for any purpose. It is importantly noted the ISCST3 model or other atmospheric transport models do not need to estimate the concentration of contaminants on emitted particles - all that is required are mass emissions of contaminants (in g/sec units) and the delineation of size fractions of particles emitted. The ISCST3 model does not require a particle emission rate. An assumption of a greater deposition of particles directly into surface waters might translate back to an assumption of particle emissions. The $RDEP_p$ is only required to maintain a mass balance of solids entering the surface water body, and as it turns out, particles entering surface waters by this route are only a miniscule part of the total solids entering the body. There are no impacts to water or fish concentration estimations with reasonable values for this parameter. The same appears true for f_{sd}, which determines the extent to which directly depositing contaminants remain in suspension. The assigned value of 1.00 (meaning that all directly depositing contaminants remain in suspension), based on the argument

that particles emitted from stack are likely to be lighter than eroding soil particles, appears sufficient for general purposes.

Water body impacts are essentially linearly related to the average watershed depth of mixing. The value assigned for the demonstration scenario was 0.1 m, which is midway between the value assumed for non-tilled conditions, 0.02 m, and tilled conditions, 0.20. The value of 0.10 m suggests that half the watershed is tilled. The linear relationship underscores the importance of this uncertain parameter, and also suggests that erosion drives water body impacts rather than direct deposition. This trend is also apparent for the tests on depositions to the watershed, the RDEPwat, input, versus depositions directly onto the surface of the water body, the $RDEP_{sw}$ input. The impact to changes in $RDEP_{wat}$ are roughly linear - an increase in watershed depositions (but not depositions directly onto the water body) by about a factor of 13 leads to an increase in the water body impacts by a factor of 11 . There was less but still a noteworthy change when depositions directly onto the water body increased or decreased - a 13-f old increase led to a 2.5 fold increase in water body impacts.

Changing the size of the watershed did not have much of an impact to water body impacts. In changing the size, the four parameters as noted on Figure 6-13 were changed simultaneously. Intuitively, increasing the size of watershed should increase water body impacts, since more land impacted by depositions would be draining into the water body. However, two factors counter this intuition: 1) the water body volume also changes concurrently, tending to dilute any additional soil inputs, and 2) soil inputs are not proportionally increased because the sediment delivery ratio decreases as the size of the watershed increases - from 0.06 in the baseline setting to 0.01 in the test for the large watershed. In fact, water body impacts dropped slightly for the large watershed and increased only very slightly for the smaller watershed. This increase was due also to the change in the sediment delivery ratio, which increased from 0.06 to 0.25.

6.3.4. Key Trends from the Sensitivity Analysis Testing

These are as follows:

1) Source terms are the most critical for exposure media impacts. Source terms include soil concentrations, stack emissions, and effluent discharges. In nearly all cases, the impact to exposure media is linear with changes to source terms. Proximity to the source term can be important as well, as demonstrated with differences in distance from the stack emission source.

2) Chemical-specific parameters, particularly the bioconcentration/biotransfer parameters, are the second most critical model inputs. Some of these have lesser impacts,

such as the organic carbon partition coefficient, Koc, for surface water impacts. Generally, at least an order of magnitude in range in possible media concentrations is noted with the range of chemical-specific parameter ranges tested. The impact of changes to bioconcentration/biotransfer parameters is mostly linear. This is because these transfer factors estimate media concentrations as a linear transfer from one media to another - fish lipid concentrations are a linear function of the concentration of contaminants in sediments. These transfer parameters are also identified as uncertain parameters. Tested ranges sometimes spanned over an order of magnitude for 2,3,7,8-TCDD.

3) All other parameters had less of an impact as compared to source strength and chemical specific parameters; nearly all impacts were within an order of magnitude for the range of tested values. Part of the reason for this trend is that there is a reasonably narrow range for many of the parameters in this range - soil properties, wind speeds, vegetation yields, and others. It is important, nonetheless, to carefully consider all the model parameters. While impacts were generally within an order of magnitude of the values selected for the demonstration scenarios, there was often an order of magnitude or more difference between plausible high and low values for individual parameters.

4) A principle trend of note concerns the air to soil algorithm for the stack emission source category compared to the soil to air algorithm of the soil source category. Several tests in this chapter demonstrated the difference in model performance when soil is the source of contamination compared to when air is the source of contamination. The relationship between air and soil concentrations is distinctly different for the soil contamination source category as compared to the stack emission source category. It is found that the "air/soil" concentration ratio is much smaller in the soil source category as compared to that same ratio in the stack emission source category. This air to soil ratio does not have any important meaning except in the context of this discussion. An air-to-soil model validation exercise in Chapter 7 showed that the deposition modeling appeared to very reasonably predict soil concentrations. This exercise relied on concurrent measurements of air concentrations and soil concentrations in an actual rural background setting. The air concentrations became the independent variable used to model soil concentrations. The reasonable validation was the result of predicted soil concentrations matching observed soil concentrations. However, when the same exercise was turned around - i.e., the observed soil concentration was used to predict air concentration, it was found that the predicted air concentration was much lower than the observed air concentration. Two possible explanations were offered for this trend: 1) the models predicting volatilization and dispersion were underpredicting air concentrations, and/or 2) the soil to air models are not underpredicting

air concentrations - air concentrations over a soil are perhaps more a function of atmospheric transport from distant sources than volatilization or wind erosion from soils. In any case, this dichotomy in air/soil model performance had several cascading impacts as were found in this chapter as well as Chapter 5 demonstrating the methodologies. Results include, for example: 1) soil concentrations drive terrestrial animal food concentrations for the soil source category, since vegetation concentrations are so low as not to be a large influence in comparison to soil. On the other hand, the vegetation concentrations drive the terrestrial animal food concentrations in the stack emission source category - the air-to-plant pathway is most important here, and 2) below ground vegetable concentrations are four orders of magnitude higher than above ground vegetables for the soil contamination source category while they are roughly comparable for the stack emission source category.

6.4. MASS BALANCE CONSIDERATIONS

As has been discussed in this document more than once is the characterization of this methodology as a screening level methodology. Steady state, equilibrium partitioning, and assumptions of nondegradation of source strengths are key assumptions which lead to this qualification. Stacks are assumed to emit a constant amount of contaminant over a duration of exposure for the stack emission source category. Effluent discharges are assumed to continue unabated over a duration of exposure. These are both reasonable assumptions for evaluating the long-term impacts of these sources where no change in practices occur. Any violation of mass balance principals will, therefore, not be examined for these sources. The same assumption of unabated and c6nstant releases might be questioned, however, for the soil contamination source category. Soil concentrations are assumed to remain constant, despite mechanisms which would dissipate concentrations over time. Volatilization and transport off-site, and wind erosion and transport off-site, are two mechanisms which dissipate residues into the air and deplete the source strength. Soil erosion off the site to a nearby exposure site and to nearby water bodies also is a mechanism of release. A key dissipation mechanism is soil degradation. There is evidence that photolysis is a mechanism of degradation of dioxin-like compounds, as discussed in Chapter 2 of Volume 11 of this assessment. However, this would only apply to those residues directly on the soil surface and, as such, it may be reasonable to make an assumption of nondegradation if a concurrent assumption is that residues exist below the soil surface. In any case, releases for a bounded area of soil contamination including volatilization, wind erosion, and soil erosion, which are estimated for purposes of estimating off-site impacts, are not also used to

estimate dissipation of the reservoir of contaminant in the soil. Said another way, the amount lost via these pathways is not a function of a soil reservoir which decreases over time.

The purpose of this section is to examine this assumption for the case of a bounded area of hig.h soil concentration. The demonstration of the soil contamination source category will be the focus of discussions below. First, an estimate of the "reservoir" of 2,3,7,8-TCDD that is implied with the default parameters will be made. Then, an estimate of the rate at which this reservoir dissipates using the solution algorithms for dissipation: volatilization and wind erosion flux from soils, and soil erosion, will be made. Other routes of dissipation that will be examined are the soil ingestion by cattle and children, the loss via dermal contact, and the removal via harvest of below ground vegetation. These will be shown to be minuscule in comparison to air and soil erosion. The loss of soluble residues via surface runoff or leaching will be evaluated. Surface water bodies and above ground vegetation are sinks for dioxin-like compounds and therefore are not mechanisms of soil dissipation. If it can be shown, for example, that it takes several hundred years to dissipate a given reservoir, then it may be fair to conclude that exposures assuming non-dissipation over a 20 or even a 70 year exposure period are not significant overestimates. On the other hand, complete dissipation within a time period less than or even near to the period of exposure would mean that exposures and risks are being overestimated.

As will be shown, the rates of reservoir dissipation are very important considerations for soil contamination. Users of this-methodology should consider dissipation of available residues and the discussions below when determining the duration of exposure for site-specific assessments. A recommended rule of thumb for users of this methodology is to evaluate the time to dissipation using the methodology below, and if it is less than or even near the assumed period of exposure (2 years to dissipate versus 20 years of assumed exposure, e.g.), then it may be appropriate to assign a duration of exposure equal or less than the calculated time to residue dissipation.

One of the key parameters in determining how rapidly residues will dissipate is one which is not required for this methodology. This is the depth of contamination. This depth, plus the initial concentration and the areal extent of contamination, describe the full extent of the source strength. The exercises below have assumed a shallow depth of 0.15 meters, or 6 inches, in soil. The impact of this assumption is demonstrated below. Also, the exercises below are specific to 2,3,7,8-TCDD.

The demonstration of the off-site soil contamination source category. were as follows: 40,000 m2 soil contaminated with an initial concentration of 1 ug/kg (ppb). It is assumed that the contamination extends to 0. 1 5 meters (6 inches).

Step 1. Estimate the amount bound to soil:

(total volume of contaminated site = 40,000 m^2 * 10,000 cm^2/m^2 * 15 cm =		6×10^9 cm^3
(soil bulk density)	x	1.5 gm/cm^3
(unitless 2,3,7,8-TCDD soil con., g/g)	x	$(1/10^9)$
= grams 2,3,7,8-TCDD in soil		9 gms

Note: at a soil concentration of 1 µg/kg, there will also be some 2,3,7,8-TCDD in soil pore water. This amount is insignificant in comparison to the amount bound to soil, and will be neglected.

Step 2. Now estimate the amounts lost by various routes of dissipation

- Volatilization -Volatilization flux is a function of exposure duration, with less average flux calculated over longer durations - this is, in fact, the only model algorithm which accounts for reservoir depletion over time. The durations of exposure for the high end scenarios was 20 years. The release rate via volatilization is given as the term FLUX and is shown in Equation (4-22) in Chapter 4. Plugging in baseline parameter values for 2,3,7,8-TCDD and a duration of 20 years results in a calculated flux of 1.06×10^{-18} g/cm^2-sec. Over a year and over the 40,000 m^2 contaminated area, this translates to an annual dissipation rate of 0.013 g/yr of 2,3,7,8-TCDD.

- Wind erosion: Unlike the volatilization algorithm, the flux due to wind erosion is not dependent on the duration of exposure. The wind erosion algorithm is described in Section 4.3.3 in Chapter 4. Plugging in baseline parameter values results in a flux of 2,3,7,8-TCDD of 5.74×10^{-20} g/cm^2-sec, or an annual flux over the 40,000 m^2 contaminated area of 0.0007 g/yr.

- Soil erosion: The annual erosion rate off the contaminated site was 21515 kg/hayr. This rate was assumed to erode towards the exposure site as well as towards the impacted surface water body. However, it would not be appropriate to double that quantity since it is used in two

different algorithms - the exposure site could be in the direction of the water body, for example. Or, if applied to a specific site, one could ascertain that the exposure site is upgradient from the contaminated site, and so on. In any case, 21515 kg/ha-yr can be translated to a cm/yr of soil erosion as follows:

volume per 1-cm hectare slice = 10,000 m^2/ha * 10,000 cm^2/m^2 * 1 cm =
$1x10^8$ cm^3
X 0.015 kg/cm^3 (soil bulk density)
kilograms per 1-cm hectare slice = 150,000 kg/cm-hectare

Therefore, 21515 kg/ha-yr translates to a loss of soil equal to 0.14 cm/yr. Given that 9 g 2,3,7,8-TCDD are estimated to occur in 15 cm, the annual loss of 2,3,7,8-TCDD is 0.084 g/yr.

- Runoff and Leaching: Transport via water is not considered in this methodology since the dioxin-like compounds are so tightly sorbed that these are expected io be negligible. An estimate of loss via water will nonetheless be made for this exercise. Surface water body volume was estimated assuming a runoff rate of 15 in/yr, which was defined as all surface water contributions (surface runoff, interflow, and ground water recharge). This is a reasonable estimate for water-borne losses for this exercise. The annual amount of 2,3,7,8-TCDD lost in this water can be estimated using the soil partition coefficient, Kd_s, relationship, which is C_s/C_w. Kd_s is equal to 39,800 for 2,3,7,8-TCDD (organic carbon partition coefficient, Koc of $3.98x10^6$ * soil organic carbon, OC_{sl} of 0.01), so the concentration in water, C_w, given a soil concentration, C_s, of 1 µg/kg, is $2.5x10^{-5}$ µg/L, or $2.5xl0^{-11}$ g/L. Translated to a 40,000 m^2 area, 15 in/yr equals $1.524xl0^7$ L, so the total annual loss in water equals 0.00038 g/yr 2,3,7,8-TCDD.

Except for soil degradation, these are the dissipation routes that would be considered for a site of soil contamination that is not used for any purpose - residence, agriculture, and so on. For the sake of completeness, other routes that will be looked at now include soil ingestion, soil dermal contact, and harvesting of underground vegetation.

- Soil Ingestion: Soil ingestion by children in the high end scenario is 600 mg/day, or 0.22 kg/yr. Soil ingestion by cattle will also be considered. First, an assumption of how many cattle would be feeding on a 40,000 m^2 area should be made. A daily cattle dry matter ingestion rate is 19 kg/day. For beef cattle that are assumed to principally graze, for 90% of their dry matter intake, the daily ingestion of grass would be 17.1 kg/day, and their daily intake of soil

while grazing, 8% of total dry matter intake, is 1.52 kg/day. With this daily ingestion of grass, their annual need for grass would be 6200+ kg/yr. The yield of grass assumed for other purposes in this assessment was 0.15 kg/m^2-yr dry weight, or 6000 kg/40,000 m^2-yr. Therefore, it appears that one grazing cow requires the 40,000 m^2 to himself (as a rough approximation). The annual intake of soil by this cow equals 555 kg/yr, which as expected, is much higher than child soil ingestion. The annual removal of 2,3,7,8-TCDD by cattle soil ingestion is 555 µg/yr, or 0.0006 g/yr.

- Dermal Contact: The dissipation of 2,3,7,8-TCDD residues via dermal contact is estimated as, EV*CA*CR*C_s, where EV = event frequency in terms of number of dermal contact events per year, which equals 365 in the high end scenario, CA = contact area, which ranges from 1000-10,000 cm^2, CR = contact rate, which ranges from 0.005-0.1 mg/cm^2-event, and Cs = 2,3,7,8-TCDD concentration, which is 1 µg/kg, or in more convenient units, 10^{-12} g/mg. Using the higher values, the annual loss via dermal contact is negligible at $3.7xl0^{-7}$ g/yr.

- Underground Vegetation Harvests: The yield of vegetables required for other algorithms of this assessment, is 7.8 kg/m^2 fresh weight. The vegetable concentration/soil concentration ratio for tilled soils is about 0.033 (from results of the demonstration scenario). Therefore, for a 1 µg/kg soil concentration, the fresh weight vegetable concentration would be 0.033 µg/kg fresh weight. Therefore, the removal per m^2 is 0.26 µg/m^2, and the removal over 40,000 m^2 in g/yr is 0.01 g/yr if all the 40,000 m^2 were devoted to underground vegetables.

This exercise has shown that the principal mechanism of removal is soil erosion at 0.084 g/yr 2,3,7,8-TCDD, with volatilization explaining 0.013 g/yr removal. The sum of these two routes is 0.097 g/yr, and the sum of all the other routes examined briefly above is 0.01 g/yr, leading to a round total estimate of 0.11 g/yr. With an initial reservoir of 9 gr, it would take 82 years to dissipate the available reservoir, not including degradation and assuming that surface concentrations remain constant. The limited field data that is available on the loss of dioxins from surface soils suggested anywhere from 10 to 100 years for surface and subsurface residues. These losses would include degradation and transport. This assessment assumes a 25-year half-life for residues arriving at exposure sites from distant sources of contamination such as soils or stack emissions. As a rough estimate, half of the 9 gram reservoir would be dissipated at 25 years; 4.5 grams loss per 25 years translates to 0.18 g/yr lost. The algorithms of this assessment already lead to 0.11 g/yr lost, and therefore the observation that it would take about 80 years to

dissipate the reservoir appears sound. In other words, this simple exercise suggests that transport from a site, rather than degradation, could dominate the dissipation rates of 10 to 100 years that have been observed in the field.

This was not a definitive exercise, by any means, but it does lend some confidence that a principal of mass balance may not have been violated for the soil source categories, and for the assumption of 30 years exposure duration. As this section began, the algorithms of this assessment are characterized as screening level methodologies. Users of this methodology should be cognizant, nonetheless, of the possibility of depleting a reservoir of soil contamination prior to an assumed duration of exposure.

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Table 6-1. Parameters used to estimate exposure media concentrations for this assessment.

Parameter Name and Definition	Low[1]	Selected[1]	High[1]	Rating[2]
1. Contaminated and Exposure Site Characteristics				
A. Site of Exposure				
AES Area of exposure site, m^2	4,000	40,000	400,000	SS
E_{slp} Soil porosity, unitless	0.35	0.50	0.60	SS
P_{soil} Particle bulk density, g/cm^3	2.55	2.65	2.75	FOD
B_{soil} Soil bulk density, g/cm^3	1.20	1.50	2.00	SS
OC_{sl} Soil organic carbon fraction	0.005	0.01	0.05	SS
d_t Depth of tillage, m	0.10	0.20	0.30	SOD
d_{not} No-till depth, m	0.01	0.02	0.10	SOD
B. Contaminated Site for Soil Contamination Source Demonstration				
C_s Soil concentration of 2,3,7,8-TCDD, µg/kg (ppb)	0.01	1.00	100.0	SS
ASC Area of contamination, ha	4,000	40,000	400,000	SS
E_{slp} Soil porosity, unitless	0.35	0.50	0.60	SS
P_{soil} Particle bulk density, g/cm^3	2.55	2.65	2.75	FOD
OC_{sl} Soil organic carbon fraction	0.001	0.01	0.05	SS

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Table 6-1. (cont'd)

Parameter Name and Definition		Low	Selected	High	Rating
2. Soil and Sediment Delivery Parameters					
SL_s	Contaminated site soil loss, kg/ha-yr	2,100	21,520	42,000	SS
SL_{ec}	Soil loss between cont. and exposure site, kg/ha-yr	0	2,150	21,000	SS
SL_w	Watershed soil loss, kg/ha-yr	2,100	6,455	21,500	SS
ER	Enrichment ratio	1	3.0	5.0	SOD
C_w	Watershed 2,3,7,8-TCDD concentration for contaminated soil source demonstration, pg/g (ppt)	0	0	1.00	SS
OC_{ssed}	Suspended sediment organic carbon fraction	0.02	0.05	0.10	SS
OC_{sed}	Bottom sediment organic carbon fraction	0.01	0.03	0.05	SS
A_w	Watershed drainage area, ha	10,000	100,000	1,000,000	SS
SD_w	Watershed sediment delivery ratio, unitless	0.25	0.06	0.01	SS
TSS	Total suspended sediment, mg/L	2	10	70	SS
DL_e	Distance from contaminated to exposure site, m	50	150	1,000	SS
DL_w	Distance from contaminated site to water body, m	50	150	1,000	SS
V_{wat}	Volume of water body, L/yr	$5*10^{10}$	$4.8*10^{11}$	$5*10^{12}$	SS

$AREA_w$ Surface area of water body, m^2	$4*10^5$	$4*10^6$	$4*10^7$	SS

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Table 6-1. (cont'd)

Parameter Name and Definition	Low	Selected	High	Rating
3. Volatilization and Dust Suspension Parameters				
ED Exposure duration, yrs	1	30	70	SS
V Fraction of vegetative cover at contaminated site	0	0	0.9	SS
U_m Average windspeed, m/sec	2.8	4.0	6.3	SS
U_t Threshold wind speed, m/sec	2.5	8.25	11.3	SS
F(x) Model-specific parameter, unitless	0.87	0.50	0.05	SS
FREQ Frequency wind blows to site, unitless	0.05	0.15	0.50	SS
4. Bioconcentration and Biotransfer Parameters				
Fish: f_{lipid} Fish lipid fraction	---	0.07	---	SS
Vegetation, FDW Dry to fresh weight conversion	0.05	0.15	0.30	SS
Particle V_p Particle deposition velocity, m/yr	$1.5*10^5$	$3.2*10^5$	$7.0*10^5$	SOD
Impacts: R Annual rainfall, m/yr	0.30	1.00	2.00	SS
W_p Washout factor, unitless	2,000	50,000	1,000,000	SOD

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Table 6-1 (cont'd)

Parameter Name and Definition			Low	Selected	High	Rating
	R_w	Fraction of wet deposition retained	0	0.30	1.00	SOD
	Y_{gr}	Grass yield, kg/m^2 dry	0.15	0.15	0.35	SS
	INT_{gr}	Grass interception fraction	0.13	0.35	0.64	SS
	Y_{ctfd}	Cattle feed yield, kg/m^2 dry	0.25	0.63	1.30	SS
	INT_{ctfd}	Cattle field interception fraction	0.20	0.62	0.93	SS
	Y_{chfd}	Chicken feed yield, kg/m^2 dry	---	0.63	---	SS
	INT_{chfd}	Chicken feed interception fraction	---	0.62	---	SS
	Y_{veg}	Above ground veg. yield, kg/m^2 fresh	2.7	7.8	8.6	SS
	INT_{veg}	Vegetable interception fraction	0.18	0.48	0.72	SS
	Y_{frt}	Fruit yield, kg/m^2 fresh	---	7.8	---	SS
	INT_{frt}	Fruit interception fraction	---	0.48	---	SS
Vegetation,	VG_{vg}	Vegetable/fruit correction factor	0.001	0.01	0.10	SOD
Vapor	VG_{gr}	Grass correction factor	0.50	1.00	1.00	SOD
Impacts:	VG_{ctfd}	Cattle feed correction factor	0.25	0.50	0.75	SOD
	VG_{chfd}	Chicken feed correction factor	---	0.00	---	SOD

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Table 6-1. (cont'd)

Parameter Name and Definition			Low	Selected	High	Rating
Below Gr. Veg:	VG_{bg}	Below ground veg. correction factor	0.01	0.25	1.00	SOD
Beef:	BCSDF	Beef cattle soil diet fraction	0.01	0.04	0.15	SOD
	BCGDF	Beef cattle grass diet fraction	0.02	0.48	0.90	SOD
	BCFDF	Beef cattle feed diet fraction	0.02	0.48	0.90	SOD
	BCGRA	Beef cattle fraction of cont. grazing land	0.25	1.00	1.00	SOD
	BCFOD	Beef cattle fraction of cont. feed	0.25	1.00	1.00	SOD
	b_{fat}	Beef fat fraction	---	0.19	---	SS
Dairy:	DCSDF	Dairy cow soil diet fraction	---	0.02	---	SOD
	DCGDF	Dairy cow grass diet fraction	---	0.08	---	SOD
	DCFDF	Dairy cow feed diet fraction	---	0.90	---	SOD
	DCGRA	Dairy cow fraction of cont. grazing land	---	1.00	---	SOD
	DCFOD	Dairy cow fraction of cont. feed	---	1.00	---	SOD
	d_{fat}	Dairy fat fraction	---	0.035	---	SS
Chicken/Egg:	CSDF	Chicken soil diet fraction	---	0.10	---	SOD
	CGDF	Chicken grass diet fraction	---	0.00	---	SOD

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Table 6-1. (cont'd)

Parameter Name and Definition		Low	Selected	High	Rating
CFDF	Chicken feed diet fraction	---	0.90	---	SS
CGRA	Chicken fraction of cont. grazing land	---	1.00	---	SS
CFOD	Chicken fraction of cont. feed	---	1.00	---	SS
All animals: B_s	Bioavailibity of dioxin in soil relative to vegetative feeds	0.30	0.65	0.90	SOD
5. Effluent Discharge Source Category					
LD	Loading to surface water body, mg/hr	0.00315	0.0315	0.315	SS
Q_e	Effluent flow rate, L/hr	$1*10^5$	$4.1*10^6$	$1*10^7$	SS
Q_u	Upstream receiving water flow, L/hr	$1*10^7$	$4.7*10^8$	$1*10^9$	SS
OC_e	Effluent organic carbon content, fraction	0.15	0.36	0.50	SS
OC_u	Upstream organic carbon content, fraction	0.02	0.05	0.10	SS
TSS_e	Effluent total suspended solids, mg/L	10	70	250	SS
TSSu	Upstream total suspended solids, mg/L	2.0	9.5	50	SS

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Table 6-1. (cont'd)

Parameter Name and Definition	Low	Selected	High	Rating
6. Stack Emission Source Category				
$RDEP_e$ Wet+dry deposition at high end exposure site, $\mu g/m^2$-yr	$1.82*10^{-6}$	$1.13*10^{-6}$	$1.43*10^{-7}$	SS
$RDEP_{wat}$ Wet+dry deposition onto watershed, $\mu g/m^2$-yr	$1.82*10^{-6}$	$1.43*10^{-7}$	$5.20*10^{-8}$	SS
$RDEP_{sw}$ Wet+dry deposition onto surface water, $\mu g/m^2$-yr	$1.82*10^{-6}$	$1.43*10^{-7}$	$5.20*10^{-8}$	SS
C_{va} Vapor phase concentration at high end exp. site, $\mu g/m^3$	$4.34*10^{-13}$	$6.99*10^{-12}$	$2.49*10^{-12}$	SS
$RDEP_p$ Deposition of particles onto water body, g/m^2-yr	0.003	0.03	3.00	FOD
d_{wmx} Average mixing depth of deposition over watershed, m	0.01	0.10	0.20	SOD
f_{sd} Fraction of particles depositing onto water body from the atmosphere which remain in suspension	0	1.00	1.00	FOD
7. 2,3,7,8-TCDD Physical, Chemical, and Bioconcentration/Biotransfer Parameters				
H Henry's Constant, atm-m^3/mole	$3.29*10^{-6}$	$3.29*10^{-5}$	$3.29*10^{-4}$	FOD
D_a Molecular diffusivity in air, cm^2/s	0.005	0.047	0.10	FOD
Koc Organic carbon partition coefficient, L/kg	$4*10^5$	$3.98*10^6$	$4*10^7$	FOD
ϕ Fraction of airborne reservoir sorbed	0.80	0.49	0.20	SOD/SS

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Table 6-1. (cont'd)

Parameter Name and Definition	Low	Selected	High	Rating
B_{vpa} Air-to-leaf vapor phase transfer factor, unitless	$6.55*10^{3}$	$6.55*10^{4}$	$6.55*10^{5}$	SOD
BCF Beef/milk fat bioconcentration factor, unitless	1.00	5.76	10.00	SOD
CCF Chicken fat bioconcentration factor, unitless	---	8.80	---	SOD
ECF Egg fat bioconcentration factor, unitless	---	7.80	---	SOD
BSAF Biota sediment accumulation factor, unitless	0.03	0.09	0.30	SOD/SS
BSSAF Biota suspended sediment accumulation factor, unitless	0.03	0.09	0.30	SOD/SS
k Soil dissipation rate for eroding/depositing dioxins, yr^{-1}	0.0028	0.0277	0.28	SOD
kw Plant weathering rate constant, yr^{-1}	51.0	18.1	8.4	SOD
RCF Root bioconcentration factor, unitless	1,600	5,200	100,000	SOD

Notes:

[1] "Selected" is the value chosen for the demonstration scenarios. The "Low" and "High" values were selected for the sensitivity analysis.

[2] "Ratings" are qualitative judgements pertaining to the use of the selected values for use in other assessments - see text for more detail.

[3] "----" means that low and high values were not selected because these parameters were not tested in the sensitivity analysis exercises. Trends with these parameters were demonstrated with related parameters.

Table 6-2. Contribution of above ground vegetation concentrations of 2,3,7,8-TCDD from air-to-leaf transfers and particulate depositions.[1]

Description[2]	Air-to-leaf vapor transfers	Particle depositions
Scenario 3: Soil contamination		
vegetables/fruit	56	44
grass	96	4
feed	97	3
Scenario 4: Stack emissions, central		
vegetables/fruit	35	65
grass	91	9
feed	92	8
Scenario 5: Stack emissions, high		
vegetables/fruit	20	80
grass	82	18
feed	87	13

[1] Results are in percent of total contribution.

[2] Scenario 3 demonstrated the soil contamination source category, where soil at a contaminated site 150meters away was initialized at 1 μg/kg (ppb) 2,3,7,8-TCDD; Scenarios 4 and 5 demonstrated the stack emission source category - in Scenario 4, the exposure site was 5000 meters from the emitting stack, and in Scenario 5, the exposure site was 500 meters from the stack.

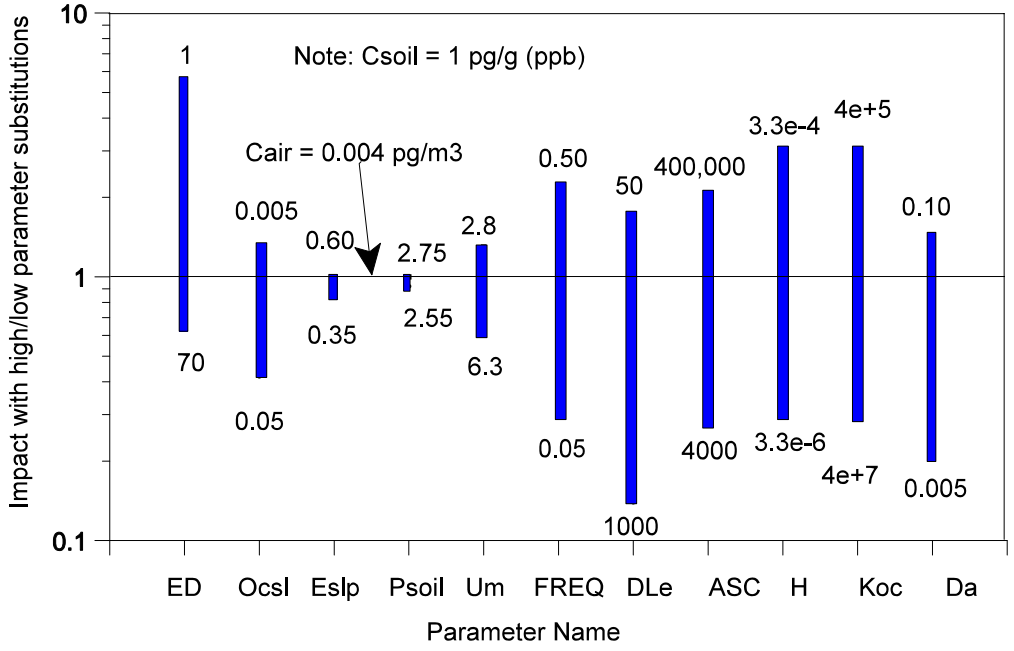

Figure 6-1. Results of sensitivity analysis of algorithms estimating exposure site vapor phase air concentrations resulting from a distant contaminated soil site.

Parameter Name	Definition	Selected
C_{soil}	soil concentration at contaminated area, ng/g (ppb)	1.00
C_{air}	air concentration at exposure site, pg/m^3	0.004
ED	exposure duration, yrs	30
OC_{sl}	soil organic carbon fraction	0.01
E_{slp}	soil porosity, unitless	0.50
P_{soil}	particle bulk den, g/cm^3	2.65
U_m	average windspeed, m/sec	4.0
FREQ	frequency wind blows to site, unitless	0.15
DL_e	distance to exposure site, m	150
ASC	area of off-site contamination, m^2	40,000
H	Henry's Constant, atm-m^3/mole	$3.29*10^{-5}$
Koc	organic carbon partition coefficient, L/kg	$3.98*10^6$
D_a	molecular diffusivity in air, cm^2/s	0.047

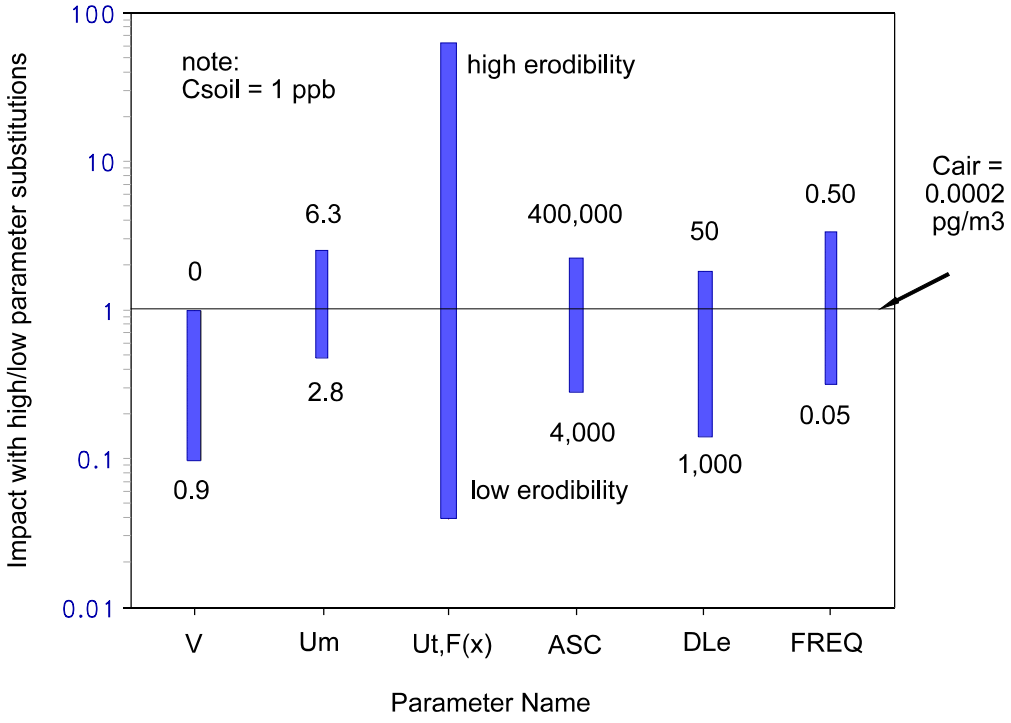

Figure 6-2. Results of sensitivity analysis of algorithms estimating exposure site particle phase air concentrations resulting from a distant contaminated soil site.

Parameter Name	Definition	Selected
C_{soil}	contaminated site soil concentration, ng/g (ppb)	1.00
C_{air}	exposure site air concentration, pg/m^3	0.0002
V	fraction of vegetative cover, unitless	0.0
U_m	average windspeed, m/sec	4.0
U_t	threshold wind speed, m/sec	8.25
F(x)	model-specific parameter	0.50
ASC	area of soil contamination, m^2	40,000
DL_e	distance to exposure site, m	150
FREQ	frequency wind blows to exposure site, unitless	0.15

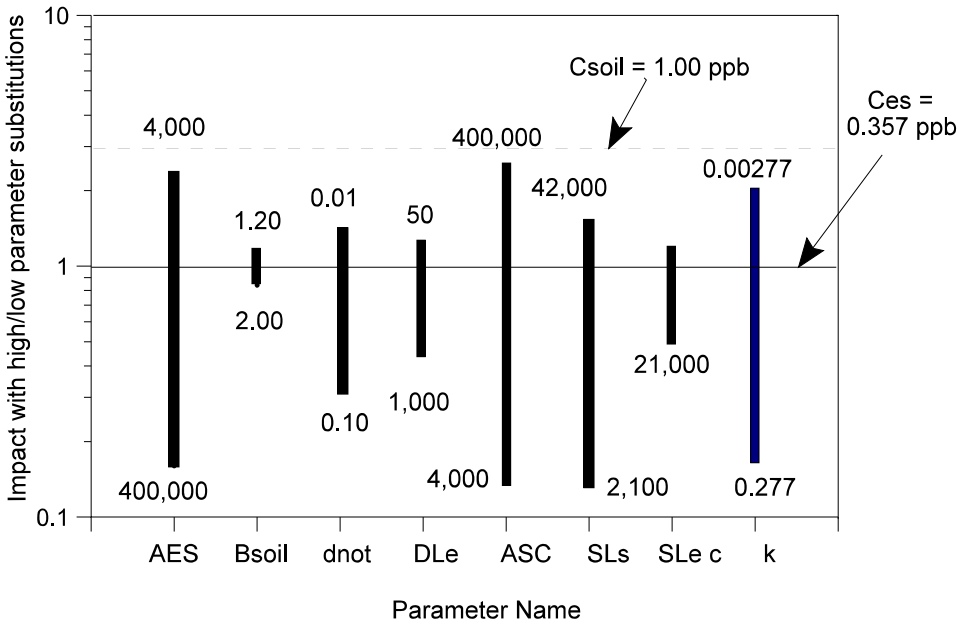

Figure 6-3. Results of sensitivity analysis of algorithms estimating exposure site soil concentrations resulting from erosion from a site of soil contamination.

Parameter Name	Definition	Selected
C_{soil}	contaminated site soil concentration, ng/g (ppb)	1.00
C_{es}	exposure site soil concentration, ng/g (ppb)	0.357
AES	area of exposure site, m^2	40,000
B_{soil}	soil bulk density, g/cm^3	1.50
d_{not}	no-till mixing depth, m	0.02
DL_e	distance to exposure site, m	150
ASC	area of off-site contamination, m^2	40,000
SL_s	contaminated site soil loss, kg/ha-yr	21520
SL_{ec}	soil loss between exp. and cont. site, kg/ha-yr	2152
k	dissipation rate for eroding/depositing cont., yr^{-1}	0.0277

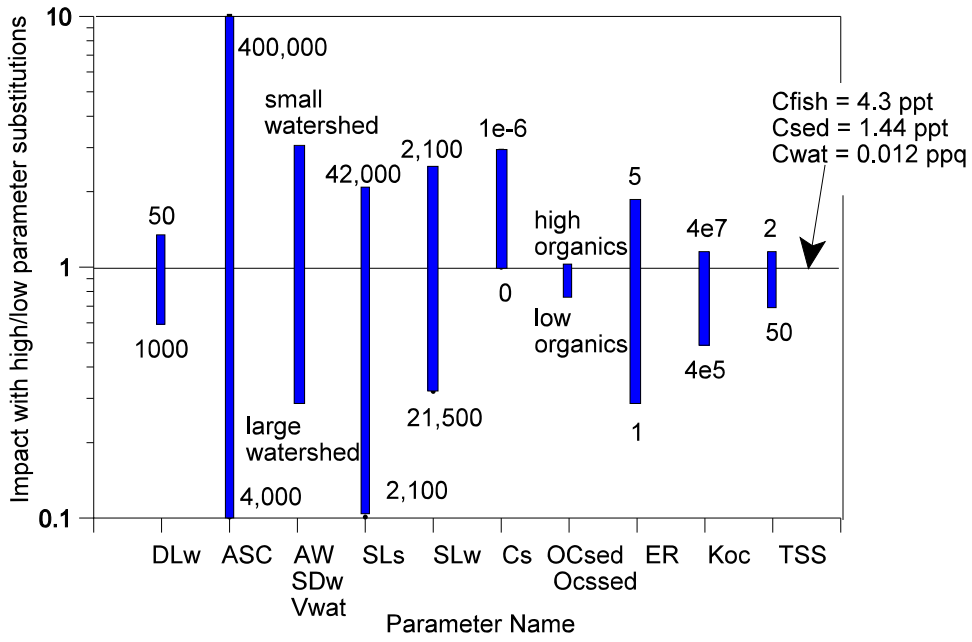

Figure 6-4. Results of sensitivity analysis of algorithms estimating surface water impacts, including sediment, water, and fish concentrations, resulting from a site of soil contamination.

Parameter Name	Definition	Selected
C_{soil}	concentration in contaminated soil area, ng/g (ppb)	1.00
C_{sed}	concentration in bottom sediment, pg/g (ppt)	1.44
C_{fish}	concentration in fish lipid, pg/g	4.3
C_{wat}	concentration in water, pg/L (ppq)	0.012
DL_w	distance to water body, m	150
ASC	area of off-site contamination, m^2	40,000
A_w	watershed drainage area, ha	100,000
SD_w	watershed sediment delivery ratio, unitless	0.06
V_{wat}	volume of water body, L/yr	$4.8x10^{11}$
SL_s	contaminated site soil loss, kg/ha-yr	21,520
SL_w	watershed soil loss, kg/ha-yr	6,455
C_w	watershed contaminant conc, mg/kg	0
OC_{sed}	bottom sediment organic carbon fraction	0.03
OC_{ssed}	suspended sediment organic carbon fraction	0.05
ER	enrichment ratio, unitless	3
Koc	organic carbon partition coefficient, L/kg	$3.98x10^6$
TSS	total suspended sediment, mg/L	10

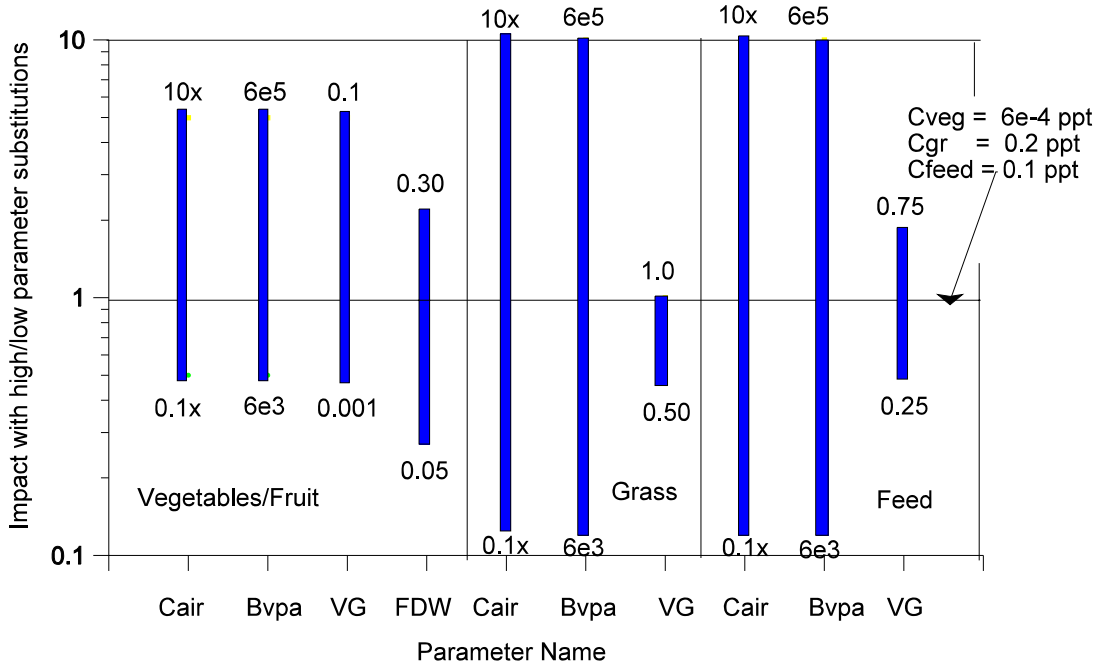

Figure 6-5. Results of sensitivity analysis of algorithms estimating above ground vegetation concentrations due to vapor phase transfers.

Parameter Name	Definition	Selected
Cveg	vegetable concentration, pg/g (ppt) fresh	6e(-4)
Cgr	grass concentration, pg/g (ppt) dry	0.2
Cfeed	cattle feed concentration, pg/g (ppt) dry	0.1
Cair	vapor-phase air concentration, pg/m^3	0.004
Bvpa	air-to-leaf transfer factor, unitless	6.55e(-4)
VG	Vegetable correction factor, unitless	
	vegetables/fruit	0.01
	grass	1.00
	feed	0.50
FDW	fresh to dry weight ratio	0.15
FREQ	frequency wind blows to site, unitless	0.15

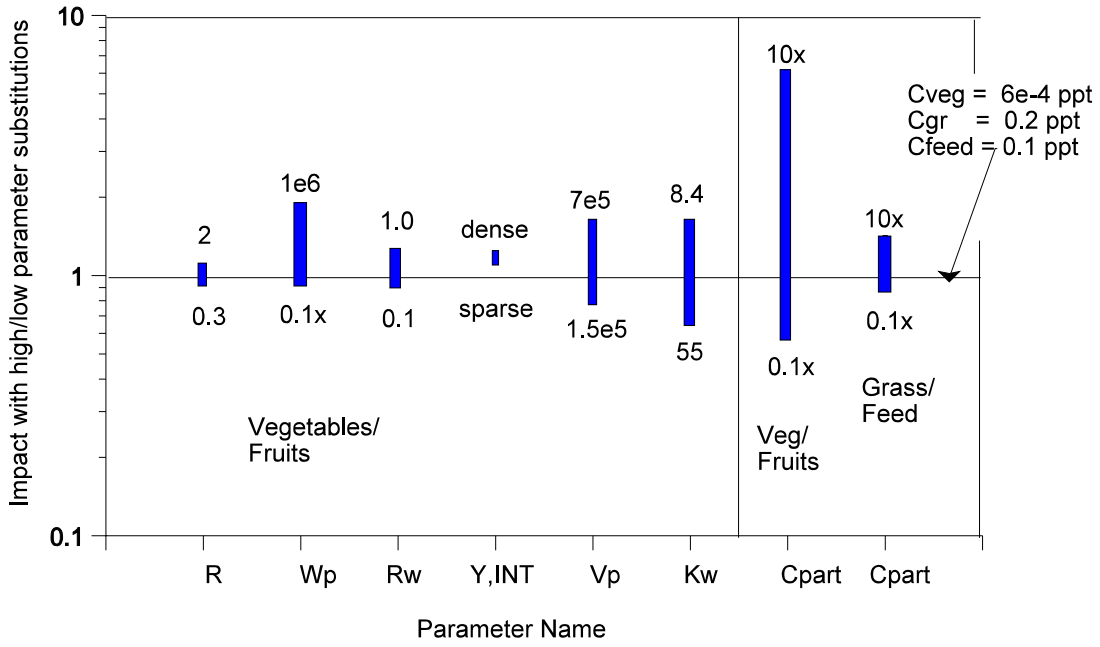

Figure 6-6. Results of sensitivity of algorithms estimating above ground vegetation concentrations from deposition of particle-bound dioxins.

Parameter Name	Definition	Selected
Cveg	vegetable concentration, pg/g (ppt) fresh	6e(-4)
Cgr	grass concentration, pg/g (ppt) dry	0.2
Cfeed	cattle feed concentration, pg/g (ppt) dry	0.1
Cair	vapor-phase air concentration, pg/m^3	0.0002
Wp	washout factor, unitless	1.0
Rw	rainfall retention factor, unitless	0.3
Y	vegetable yield, kg/m^2 fresh	7.8
INT	vegetable interception fraction, unitless	0.48
Vp	particle deposition velocity, m/yr	3.2e(-5)
kw	plant wash-off rate constant, yr^{-1}	18.01

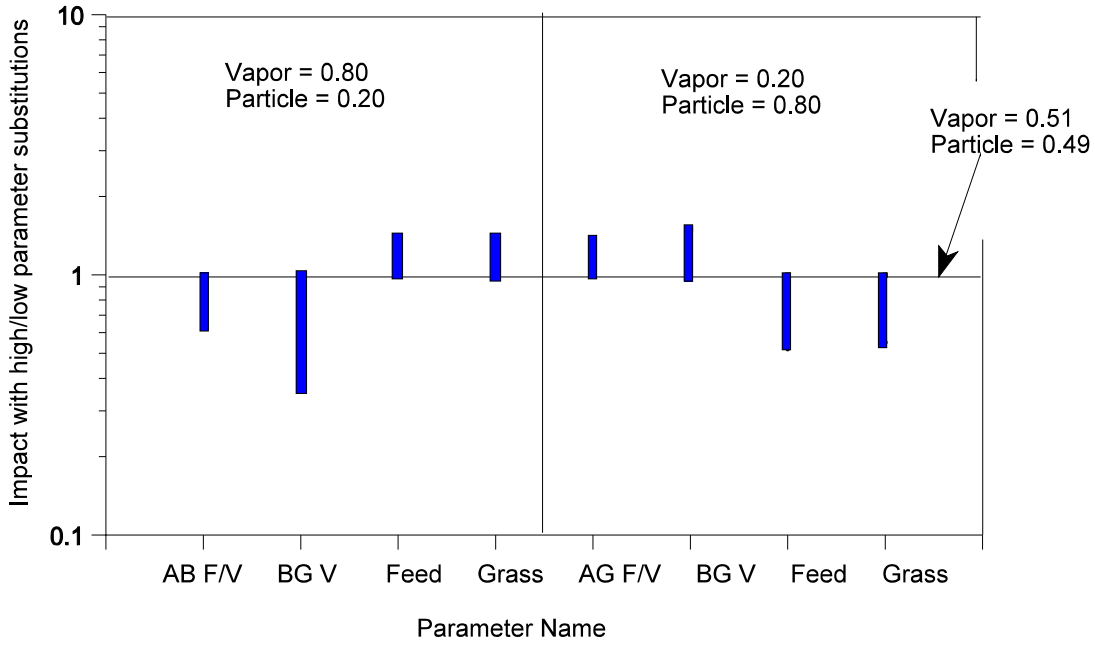

Figure 6-7. Impact of vapor/particle partitioning on vegetation concentrations in the stack emission source category.

Parameter Name	Definition	Selected
AG F/V	above ground fruit/vegetable conc., pg/g (ppt) fresh	3e(-6)
BG V	below ground vegetable conc, pg/g (ppt) fresh	4e(-6)
Feed	cattle feed concentration, pg/g (ppt) dry	2e(-4)
Grass	grass concentration, pg/g (ppt) dry	5e(-4)
Vapor	vapor fraction, unitless	0.51
Particle	particle fraction, unitless	0.49

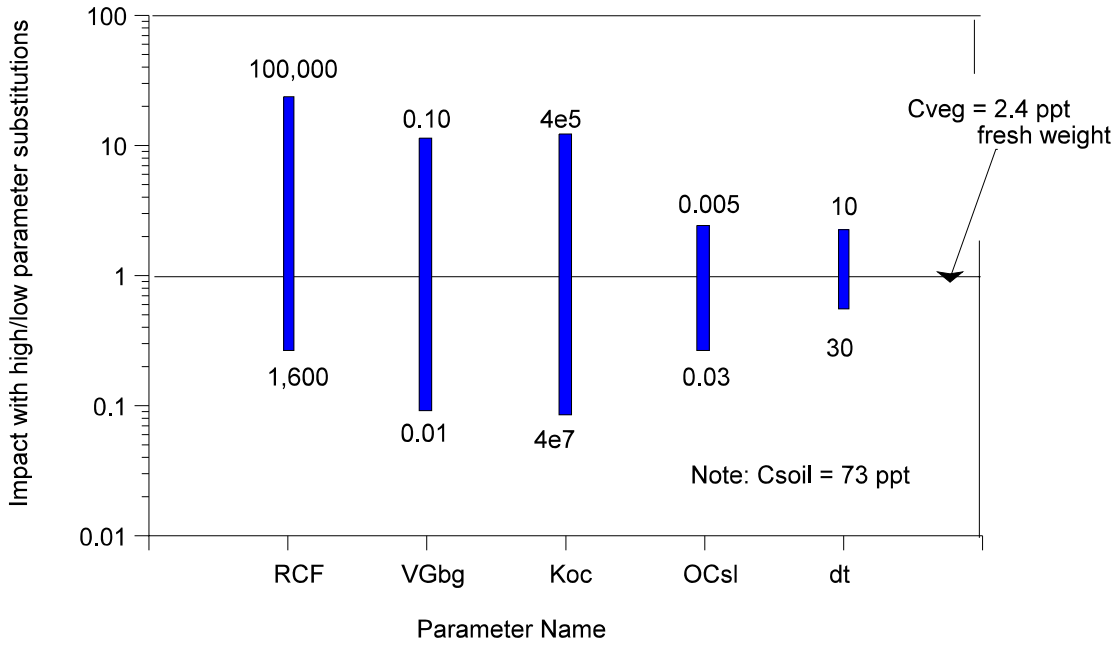

Figure 6-8. Results of sensitivity analysis of algorithms estimating below ground vegetable concentrations in the soil contamination source category.

Parameter Name	Definition	Selected
Cveg	vegetable concentration, pg/g (ppt) fresh	2.4
Csoil	tilled soil concentration, pg/g (ppt)	61.0
VGbg	below ground vegetation correction factor, unitless	0.01
OCsl	soil organic carbon fraction	0.01
RCF	root bioconcentration factor, unitless	5,200
Koc	organic carbon partition coefficient, L/kg	3.98e6
dt	depth of tillage, cm	20

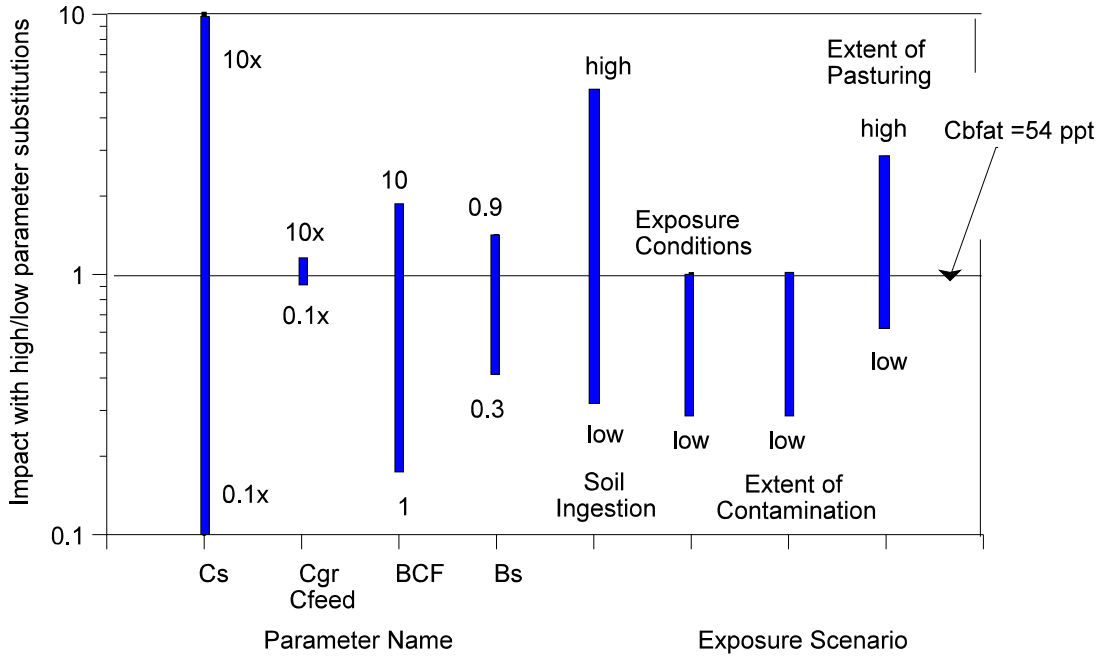

Figure 6-9. Results of sensitivity analysis of algorithms estimating beef fat concentrations in the soil contamination source category.

Parameter Name	Definition		Selected
Cs	2,3,7,8-TCDD soil concentration, pg/g		1000
Cgr	2,3,7,8-TCDD grass concentration, pg/g dry wt.		0.2
Cfeed	2,3,7,8-TCDD feed concentration, pg/g dry wt.		0.1
Cbfat	2,3,7,8-TCDD beef fat concentration, pg/g		54
BCF	beef/milk bioconcentration factor, unitless		5.76
Bs	bioavailability of contaminant on soil relative to vegetation		0.65
<u>Exposure Scenario Parameters:</u>			
BCSDF	beef cattle soil diet fraction		0.04
BCFDF	beef cattle feed diet fraction		0.48
BCGDF	beef cattle grass diet fraction	0.48	
BCGRA	beef cattle fraction of contaminated grazing land		1.00
BCFOD	beef cattle fraction of contaminated feed		1.00

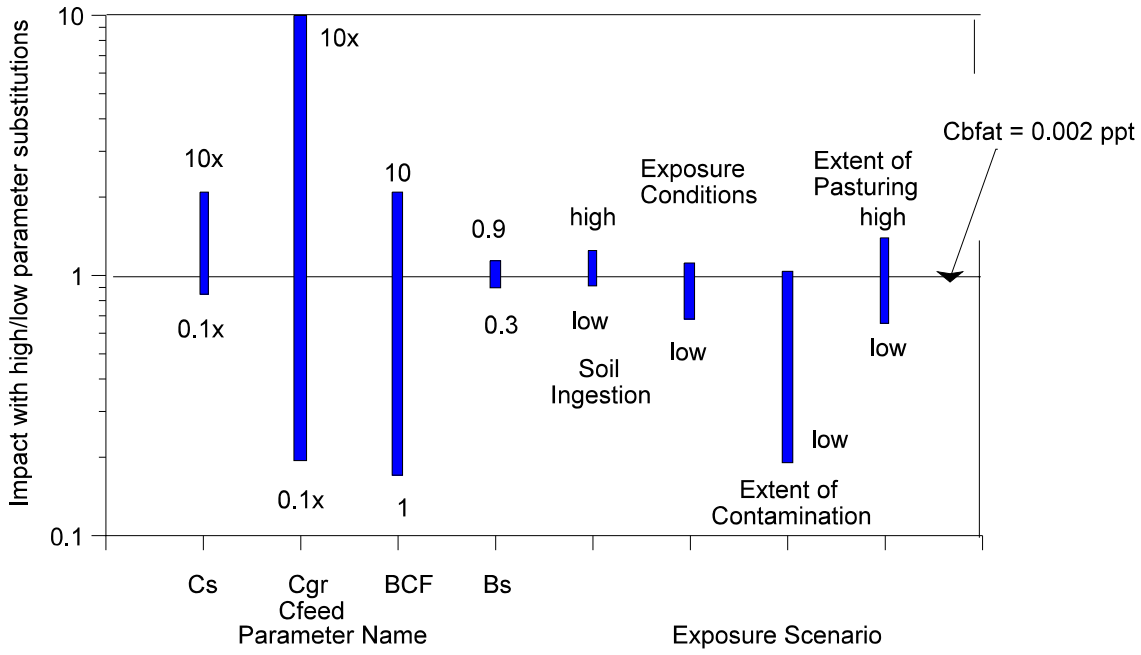

Figure 6-10. Results of sensitivity analysis of algorithms estimating beef fat concentrations in the stack emission source category.

Parameter Name	Definition		Selected
Cs	2,3,7,8-TCDD soil concentration, pg/g		0.001
Cgr	2,3,7,8-TCDD grass concentration, pg/g dry wt.		0.0004
Cfeed	2,3,7,8-TCDD feed concentration, pg/g dry wt.		0.0002
Cbfat	2,3,7,8-TCDD beef fat concentration, pg/g		0.002
BCF	beef/milk bioconcentration factor, unitless		5.76
Bs	bioavailability of contaminant on soil relative to vegetation		0.65
<u>Exposure Scenario Parameters:</u>			
BCSDF	beef cattle soil diet fraction		0.04
BCFDF	beef cattle feed diet fraction		0.48
BCGDF	beef cattle grass diet fraction	0.48	
BCGRA	beef cattle fraction of contaminated grazing land		1.00
BCFOD	beef cattle fraction of contaminated feed		1.00

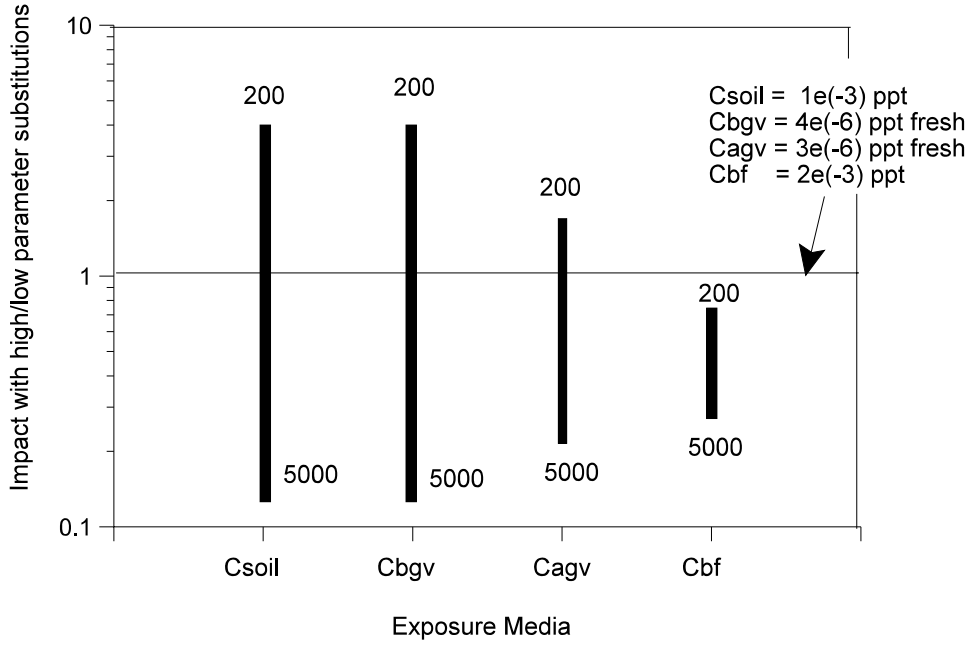

Figure 6-11. Impact of distance from the stack emission source to soil, vegetable, and beef fat concentrations.

Parameter Name	Definition	Selected
Csoil	2,3,7,8-TCDD soil concentration, ng/g	$1*10^{-3}$
Cbgv	2,3,7,8-TCDD below grd. veg. conc., fresh wt, pg/g (ppt)	$4*10^{-6}$
Cagv	2,3,7,8-TCDD above grd. veg. conc., fresh wt, pg/g (ppt)	$3*10^{-6}$
Cbf	2,3,7,8-TCDD beef fat concentration, pg/g (ppt)	$2*10^{-3}$

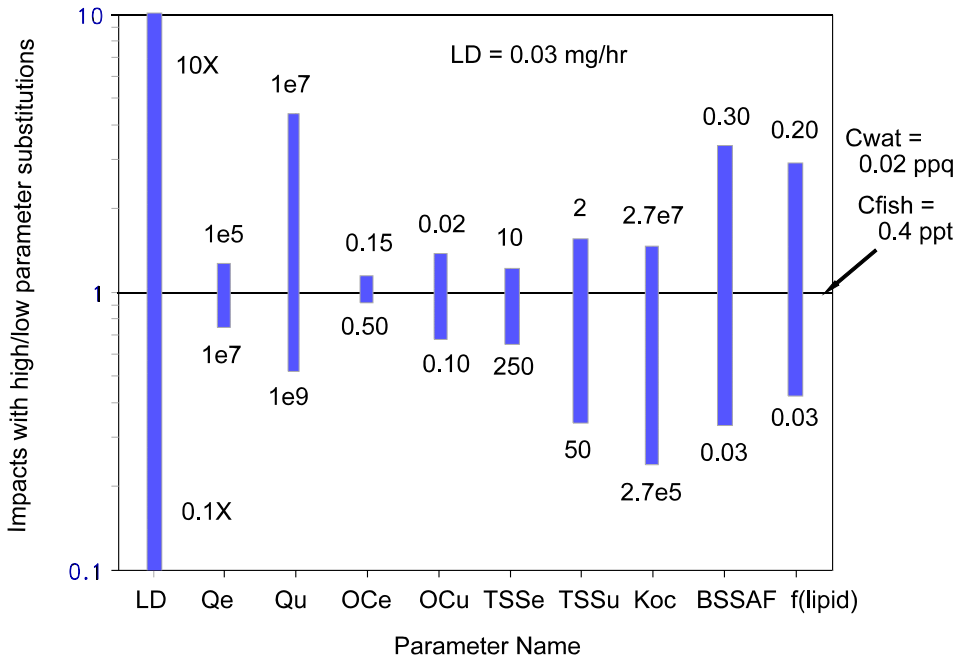

Figure 6-12. Results of sensitivity analysis of algorithms estimating surface water and fish concentrations resulting from effluent discharges.

Parameter Name	Definition	Selected
Cwat	water concentration, pg/L (ppq)	0.02
Cfish	whole fish concentration, pg/g (ppt)	0.4
LD	loading to surface water body, mg/hr	0.0315
Qe	effluent flow rate, L/hr	4.1×10^6
Qu	upstream receiving water flow, L/hr	4.7×10^8
OCe	effluent organic carbon content, unitless	0.36
OCu	upstream organic carbon content, unitless	0.05
TSSe	effluent total suspended solids, mg/L	70
TSSu	upstream total suspended solids, mg/L	9.5
Koc	organic carbon partition coefficient, L/kg	2.69×10^6
BSSAF	biota suspended solids acc. factor, unitless	0.09
flipid	fish lipid fraction	0.07

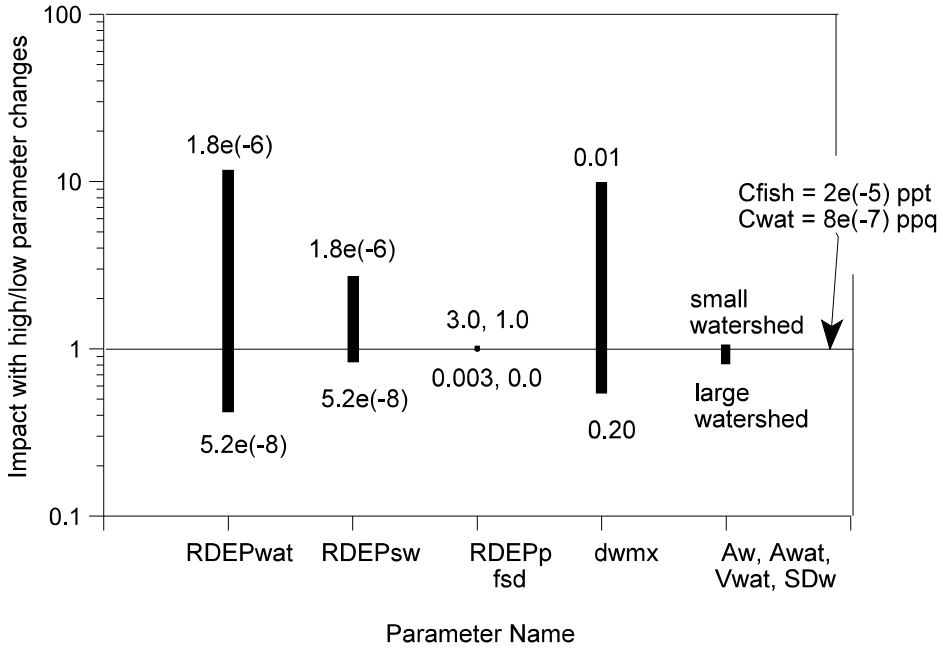

Figure 6-13. Results of sensitivity analysis of algorithms estimating surface water and fish concentrations resulting from stack emissions.

Parameter Name	` Definition	Selected
Cfish	2,3,7,8-TCDD whole fish concentration, pg/g (ppt)	$2*10^{-5}$
Cwat	2,3,7,8-TCDD surface water concentration, pg/L (ppq)	$8*10^{-7}$
RDEPwat	2,3,7,8-TCDD dep. rate on watershed, µg/m^2-yr	$1.4*10^{-7}$
RDEPsw	2,3,7,8-TCDD dep. rate on surface water, µg/m^2-yr	$1.4*10^{-7}$
RDEPp	particle dep. onto surface water, g/m^2-yr	0.03
dwmx	watershed soil mixing depth, m	0.10
fsd	fraction of deposited particles remaining in suspension	1.00
Aw	area of watershed, ha	100,000
Awat	surface area of water body, m^2	$4*10^6$
Vwat	water body annual volume, L/yr	$4.8*10^{11}$
SDw	watershed sediment delivery ratio	0.06

7. MODEL COMPARISONS AND MODEL VALIDATIONS

7.1. INTRODUCTION

This chapter is comprised of two principle sets of exercises aimed at lending credibility to the models selected for use in this site-specific methodology. One set compares alternate approaches to modeling the fate and transport of dioxins, which users can consider in place of the models selected. The comparisons involve generating results with both sets of models, and then seeing how the results compare. Assuming the models selected in this document and the alternates have some inherent credibility, the model results should compare favorably. In most cases, they do compare well, but there are a few where model comparisons are not satisfactory. If the two sets of models compare favorably, one would expect that this lends credibility to both sets of models, and hopefully some confidence in the use of the models selected for this document.

The fate, transport, and transfer models presented in this document can also attain a measure of credibility if it can be shown that estimations of environmental and exposure media concentrations are consistent with those found in the literature. Some of those comparisons can use the exposure media concentrations generated in the demonstration scenarios because the source strength terms of the demonstrations were crafted to be meaningful. Specifically, the background scenario was demonstrated with both air concentrations and soil concentrations that are from an actual rural background setting that is justified as being generally typical for rural settings. The soil contamination source category was demonstrated with a bounded area of high soil concentrations of 1 ppb. This was also supported by literature showing this that sites of high soil contamination contained dioxin-like compounds in the ppb range. Other comparisons are more site-specific: for a specific site, the source strength is known and input into the model, and the model predictions of environmental media concentrations are compared with site-specific measurements of these concentrations.

Tests of this latter case can be termed “validation” exercises. In this document, the word “validation” refers to an exercise in which the following holds true:

1. An impacted media concentration is known. A concentration of a contaminant in a media that can be predicted by the fate models, such as a concentration in soil, vegetation, water, sediment, biota, or ambient air, is known through a site-specific monitoring program. Model predictions of these concentrations have often been termed the “dependent” model results in a validation exercise.

2. The source causing this impact is known. The source term information has often been called the "independent" model input in a validation exercise. For example, if the concentration of a contaminant in ambient air represents the known dependent quantity, than the independent, or source, term could be the emissions from one or more tall stacks nearby. Specifically, source term information would translate to the level of emissions (in units of mass/time such as g/sec) of the particular contaminant from the identified stacks. The model validation exercise would take these known emissions, put them into an air dispersion model along with other parameters (i.e., stack heights, exit velocities, site-specific meteorological data, etc.), and predict ambient air concentrations. In other model validation exercises, however, the source is likely not going to be the incinerator emissions. For example, if underground vegetables were the impacted media, than the independent source term could be the concentration in the soil in which the vegetables were growing. One could also start with ambient air concentrations in a model validation exercise involving underground vegetables. In this case, the air concentrations would be used to predict the soil concentrations, and these soil concentrations would be used to predict the vegetable concentrations. In any case, the source term needs to be known and the model user needs to be reasonably certain, or at the very least, the model user needs to assume, that the source directly impacts the effected media.

3. All other model parameters are assigned values using the best available information. Site-specific information is the most appropriate to use, if it is available. Chemical-specific parameters, such as the bioconcentration/biotransfer parameters, can either rely on site-specific information or are inherent properties of the chemical. An example of the former are the soil (or sediment)/water partition coefficients: Kd, Kdsed, and Kdssed. These parameters are calculated as the product of the organic carbon partition, Koc, which is an inherent chemical property, and the organic carbon content of the sorbing media (soil, sediment, or suspended sediment), which is site-specific. Examples of inherent properties are the bioconcentration parameters which are used to predict, for example, biota concentrations (vegetation, animal fat) as a function of the concentration in the contacting media (soil, vegetation).

4. Model predictions of the impacted media are compared with observations. Once all the parameters are assigned values, the model is run and model predictions of the dependent media concentration are compared to the real world observations of this concentration. This is the final step in a model validation exercise.

Model validation needs to be distinguished from model "calibration". Calibration exercises require real world measurements of independent source terms and dependent media impacts, as do validation exercises. What distinguishes the two exercises is that a calibration exercise is conducted in order to determine values for one or more key model input parameters by "forcing" the model to duplicate the observed data by adjusting the value of this key input parameter until this duplication is reached. As described in step 3 above, all model parameters are assigned values in a validation exercise; none are adjusted in order for model predictions to fit the observed data. An example of a model calibration exercise is the calibration of the air-to-leaf transfer factor for the vapor phase, B_{vpa}. The exercise is described in detail in Chapter 4. Briefly, air concentrations of these compounds in experimental conditions were known, as were the final concentrations in grass harvested after three weeks of growth. All other model parameters necessary for the prediction of the concentration of the dioxins and furans in the grass, including the physical parameters (mass of grass harvested, fresh to dry weight conversion, etc.), vapor/particle partitioning in the air, and particle deposition algorithm parameters, were assigned values based on site-specific measurements or the literature. The B_{vpa} was then adjusted until the model predictions of grass concentrations matched the observed grass concentrations.

Finally, it should be understood that model testing is an ongoing process. The model comparisons and validations described in this chapter are, by no means, expected to establish model validity beyond any doubt. Users of this methodology are encouraged to subject the models to any number of tests, validation or otherwise, as they use the models described in this document to conduct site-specific assessments for dioxin-like compounds

7.2. MODEL COMPARISON EXERCISES

7.2.1. Evaluation of Alternative Air-to-Leaf Modeling Approaches

The first section below describes the field data that was used in this model testing exercise. The second section describes the two alternative empirical models of air-to-plant impacts of the dioxin-like compounds. One was developed only for the impact of vapor phase dioxins, and does not have an explicit particle phase impact model. It will be compared to the vapor transfer model of this methodology. The other model assumes that plants "scavange" a fixed volume of air of dioxins; grass concentrations are very simply modeled as the total (vapor+particle) air concentration times a "scavenging" coefficient. The third section presents the results of this exercise. These first three section are paraphrased from Lorber and Pinsky (1999), where further details on this exercise can be found. Finally, the fourth section reviews a

very similar model comparison exercise published in the literature in which the model of this methodology, along with these same two alternative models, are applied to different field data.

7.2.1.1. The Field Data

Jones and Duarte-Davidson (1997) present the results of an extensive monitoring study of dioxin concentrations in air and grass, as well as deposition fluxes, from three sites over three time periods between 1992 and 1993 in the United Kingdom. The three sites include a rural background site, an urban site, and an industrial site. The study was originally funded as a monitoring program to evaluate the environmental levels of dioxin-like compounds in a contaminated industrial area in Bolsover, UK (Sandalls, et al, 1996). By also including an urban site and a rural background site in their study, the authors were able to use the data to better understand the processes of air-to-plant transfer of the dioxins. The regional background site was located about 6 km upwind of the industrial complex in Bolsover, the urban site was about 2 km in the town of Bolsover, and the industrial sampling location was located just outside the industrial complex, about 100 m away.

Jones and Duarte-Davidson (1997) present two sets of data which are appropriate for air-to-plant model validation and model comparison purposes. Specifically, they presented concurrently measured concentrations of dioxin and furan congeners, and homologue groups, for air and grass sampled for two of the sites, the industrial and rural background site, for one of the sampling periods, Sep. 14 - Oct. 30, 1993. They also presented the results of their deposition collection for those two sites/sampling periods. Although other data sets of this kind were collected during the program, only these two sets were presented. Specifically, the following observed data were available for one sampling period each at the rural background and industrial sites: 1) average total air concentrations of 17 dioxin congeners and 8 homologue groups for a 6+-week period (9/14/93-10/30/93), 2) average concentrations of these compounds in grass grown during this period, 3) average deposition rates, in units of pg/m^2-day for these compounds, and 4) grass yields, in g/m^2. The air, grass, and deposition data are provided in Table 7-1. Further details on the sampling design, monitoring program, analytical methods, and other aspects of the study can be found in Jones and Duarte-Davidson (1997).

7.2.1.2. Model Descriptions and Application to the Field Data

The vapor transfer approach was parameterized and applied to 2,3,7,8-TCDD by Smith, et al. (1995a) and Trapp and Matthies (1995). The steady state solution for their vapor transfer velocity approach is given as:

$$C_{vpa} = \frac{F_v}{k_v \; Y_j} \qquad (7\text{-}1)$$

where:

C_{vpa} = plant concentration due to vapor-phase transfer, pg/g dry weight
F_v = deposition of vapor-phase congener, pg/m^2-day
k_v = first-order dissipation constant, day^{-1}
Y_j = yield of crop j, g/m^2

The non-steady state solution has an additional term in the numerator, $1\text{-}e^{(-kv\ t)}$, where t is the time to harvest. This non-steady state term was used for the particle phase solution in the model validation exercise. However, given that the k_v was assigned a relatively large value by both researchers for 2,3,7,8-TCDD vapors depositing onto plants (a large k_v corresponds to a short half-life), and the growing period for grasses is 45+ days in the field data set applied, this additional term approaches 1.0, and it can therefore be neglected in the vapor phase solution.

The two articles evaluated diverge at this point. The Trapp and Matthies (1995) approach is actually a comprehensive approach involving root uptake impacts. They summarize the literature to conclude that vapor phase impacts for lipophilic compound such as dioxin dominate the plant contamination and hence, they do not model particle phase impacts. They also present their solution in a more generalized fashion by having a volume term in the denominator of Equation (7-1) above instead of a plant yield term; the volume term is easily converted to a mass (or yield) term with a plant density factor. Their solution for F_v is:

$$F_v = A \; g \; C_{va} \; 86400 \qquad (7\text{-}2)$$

where:

F_v = deposition of vapor-phase congener, pg/m^2-day
A = leaf area index, m^2 leaf area/m^2 ground area
g = conductance, m/sec
C_{va} = vapor phase air concentration, pg/m^3
86400 = converts sec to days

Trapp and Matthies (1995) state that g has a range of 0.0001 m/sec to 0.005 m/sec, where the upper boundary conductance is appropriate for a plant species with relatively permeable cuticles and the compounds are very lipophilic, and the lower boundary conductance is where uptake is mainly via stomata and the compounds are less lipophilic. For 2,3,7,8-TCDD, Trapp and Matthies (1995) assume a g of 0.001 m/sec. For the leaf area term, they have assumed a value of 5 for the condition they describe as "meadow". Without further information on refinement of these terms for the experimental conditions of the Jones and Duarte-Davidson (1997) settings, a g of 0.001 m/sec and an A of 5 will be assumed for this exercise.

Smith, et al. (1995a) estimate the F_v as a multiplication of the vapor phase air concentration, C_{va} (pg/m^3), the transfer velocity, V_t, (cm/sec), and the plant interception (fraction, unitless). They state that the transfer velocity is represented as the inverse of the sum of the resistances to transfer to the plant surface as:

$$V_t = \frac{1}{R_a + R_b + R_c} \qquad (7\text{-}3)$$

where:

V_t = transfer velocity, cm/sec

R_a = atmospheric resistance, sec/cm, a function of vertical turbulent transport

R_b = surface boundary layer resistance, sec/cm, a function of molecular diffusivity

R_c = plant canopy/leaf resistance, sec/cm, a function of vegetative density, stomatal uptake, surface effects, humidity, and so on

They have assigned values of R_a = 0.4 sec/cm, R_b = 0.38 sec/cm, and R_c = 0.5 sec/cm, leading to an overall V_t of 0.78 cm/sec. They assumed a crop interception fraction of 1.00.

Both research efforts have, therefore, arrived at fairly similar quantities in front of the air concentration term (C_{va}), despite having slightly different theoretical frameworks. Trapp and Matthies (1995) arrive at the quantity of 0.005 m/sec (A g = 5 * 0.001 m/sec), and Smith, et al. (1995a) arrive at 0.0078 m/sec (INT * V_t = 1 * 0.0078 m/sec).

Both also have used the same experimental work of McCrady and Maggard (1993) as part of their derivation of the k_v. Trapp and Matthies (1995) assumed that the overall k term was a function of losses by photodegradation, volatilization, and dilution from plant growth. They used the photodegradation k term of 0.3744 day^{-1} taken from McCrady and Maggard (1993), but then multiplied it by 0.30 assuming that the plant was in full sunlight only 30% of the time. They

calculated a volatilization rate term of 0.012 day^{-1}, and assumed a dilution term of 0.035 day^{-1}, leading to an overall k_v term of 0.159 day^{-1}. Smith, et al. (1995a) took the full photodegradation plus volatilization rates determined by McCrady and Maggard (1993), without any correction for time in sunlight, to arrive at a k of 0.495 day^{-1}. They did not consider dilution by plant growth.

McLachlan (1995) developed a simple "scavenging" approach to predict grass concentrations of dioxins from air concentrations of dioxins. He suggests that grass scavenges the equivalent of 9 m^3 or air per gram of grass, and that corn scavenges 4.5 m^3 of air. The important assumption in this approach is that plants can scavenge vapors and particles equivalently; therefore, vapor/particle partitioning is unnecessary, and grass concentrations are very simply modeled as:

$$C_{gi} = SC\ C_{ai} \qquad (7\text{-}4)$$

where:

C_{gi} = grass concentration of congener i, pg/g dry weight basis
SC = scavenging coefficient, m^3/g
C_{ai} = total (vapor + particle) phase air concentration of congener i, pg/m^3

With this as background, it is now possible to describe how the three models will be applied to the field data. For simplicity, the three models will be referred to as the EPA model, the scavenging model, and the vapor deposition model. In applying the EPA model, total dioxin concentrations were first partitioned into a vapor and a particle phase following the procedures outlined in Chapter 3. In that chapter, particle fractions, ϕ (the vapor fractions are solved as, 1 - ϕ), are developed for an ambient air temperature of 20 °C for airsheds described as, "clean continental", "background", "background plus local conditions", and "urban". For this application, these ϕ were rederived for 10 °C, the air temperature more typical of September and October in the UK, and the "average background" and "urban" ϕ were used for the rural and industrial sites, respectively. According to the modeling procedures of this assessment, described in detail in Chapter 4, vapor dioxins "transfer" to the grass; grass concentrations due to air-borne vapors are modeled simply as the air concentration times an air-to-leaf transfer factor, B_{vpa}. Chapter 4 describes the derivation of this empirical transfer factor. Particle-phase dioxins deposit onto grass, under both wet and dry conditions. Jones and Duarte-Davidson (1997) do not provide the rainfall data for the sampling period necessary to estimate wet deposition. For

simplicity, wet deposition will not be modeled. Dry deposition, as outlined in Chapter 4, Section 4.3.4, will be modeled as a function of the particle phase concentration times a deposition velocity, which will be assumed to be 0.20 cm/sec. This deposition mixes in a reservoir of grass, described by the grass yields, which were provided in Jones and Duarte-Davidson (1997) as 89 and 42 g dry weight/m^2 for the rural and industrial sites, respectively. As outlined in Chapter 4, Section 4.3.4, interception fractions for grasses corresponding to these yields are solved for as 0.23 (for 89 g/m^2) and 0.11 (42 g/m^2). The first-order weathering constant will be assigned a value of 0.0495 day^{-1}, corresponding to a half-life of 14 days. This value has also been used in the literature and otherwise in this document.

For testing of the scavenging model, the measured air concentrations in the rural and industrial site will be multiplied by the scavenging coefficient of 9.0. For testing of the vapor deposition model, the total air concentration of 2,3,7,8-TCDD will be partitioned into the particle and vapor phase for these field data, again assuming "average background" for the rural site and "urban" for the industrial site. The vapor portion of the air concentration will be used in the vapor deposition model. The model predictions of the vapor component of the grass concentration will be compared against the vapor component of grass concentration as predicted by the models of this assessment and the measured grass concentration.

There were 25 modeled/measured concentration pairs in the rural site data set, including the 17 individual congeners and the 8 homologue groups. In order to obtain independent data points for model testing, the measured air and grass concentrations of the individual congeners were subtracted from the homologue group concentrations; individual congener concentrations are, by definition, contained within the homologue group concentrations. Doing this subtraction should have resulted in 25 independent measured/modeled pairs for model testing. However, it was found that, for HpCDD, HxCDF, and HpCDF, subtraction of the congener air concentrations from these homologue group air concentrations resulted in negative concentrations. There was obviously some measurement error in this data set. The air:grass pairs for these three homologue groups were, therefore, not considered for further model testing. Without these three readings, the air and grass data at the rural site were quite correlated; the correlation coefficient of the remaining 22 data pairs was 0.92.

Similar measurement error resulted in the deletion of 4 air:grass pairs in the industrial data set. The air concentrations of the homologue groups HpCDD and HpCDF also were lower than the sum of the individual congener concentrations. The grass concentrations of 1,2,3,7,8-PCDD and 1,2,3,7,8-PCDF were given as non-detected, but the air concentrations of these

congeners in the urban settings were similar to the air concentrations in the rural settings, and significant grass concentrations were noted in the rural setting.

Even with these four pairs deleted, the industrial site data was not as consistent as the rural data. The correlation coefficient for the remaining 21 data pairs was 0.66. An examination of the data highlights some of the differences between the two data sets. In some instances, air concentrations that were similar in the rural and industrial sites led to grass concentrations that were more impacted in the industrial site. For example, the air concentration of 2,3,7,8-TCDD in the rural setting was 0.01 pg/m^3, while it was 70% higher than that in the industrial setting at 0.017 pg/m^3. However, the grass concentration in the industrial site was about 4 times as high as in the rural setting, 2.8 pg/g in the industrial site versus 0.72 pg/g in the rural site. Similar observations can be made for 4 other congeners. On the other hand, there were several instances where similar rural and industrial air concentrations resulted in lower grass concentrations in the industrial as compared to the rural setting. Similar OCDD concentrations of 2.5 pg/m^3 in the two settings resulted in a grass concentration of 94 pg/g in the rural setting but only 43 pg/g in the industrial site setting. This trend can be found in 13 other instances. Also, the industrial data contained three data points that appeared to be flawed.

In summary, then, 22 air:grass pairs for the rural data set and 21 air:grass pairs for the industrial site were retained for model testing

Model goodness-of-fit tests were run for the rural site only, not on the industrial site, simply because the rural site data was better correlated. The absolute and signed difference between the natural logs of the measured and modeled grass concentrations provided the goodness-of-fit measure. The signed error, or bias, measures the systematic tendency of the model to under or overpredict; a bias near 0 suggests that the model underpredicts and overpredicts by about the same amount. The absolute error calculation describes model variation; how close the model predictions come to the observations, regardless of whether the model over or underpredicted. A value close to 0 suggests a very good match between predictions and observations. Log concentrations were used because there were a wide range in grass concentrations, from sub-ppt concentrations for the lower chlorinated dioxins to concentrations near 100 ppt for the homologue groups.

7.2.1.3. Results and Discussion of the Air-to-Leaf Model Comparison Exercise

Results of this model comparison are shown in Figures 7-1 through 7-4, and Table 7-2.

Figures 7-1 and 7-2 compare the measured grass concentrations with the EPA and the Scavenging Model for the rural and urban site, respectively. The natural log of the observed

concentrations are shown on the x-axis and the predicted concentrations on the y-axis. The dashed line shows where predicted equals observed; points above the line show overpredictions by the models while points below the line show model underpredictions. As seen in Figure 7-1, model predictions of rural grass concentrations using the EPA Model matched the observed concentrations better than the Scavenging model, but both models underpredicted concentrations. The predicted total toxic equivalent (I-TEQ) concentration of the EPA model was 3.7 pg/g, compared to the observed I-TEQ concentration of 6.0 pg/g. The bias was -0.66, giving a bias factor of exp [-0.66] = 0.51 and suggesting that the EPA model underpredicted by about a factor of 2.0. The absolute error was close to the bias at 0.68, again indicating that the EPA model mostly underpredicted plant concentrations; of 22 observation:prediction pairs, the EPA model underpredicted concentrations 21 times.

Figure 7-1 shows that the Scavenging Model underpredicted grass concentration at the rural site more than the EPA model. The modeled I-TEQ concentration was 1.85 pg/g, less than one-third the measured I-TEQ concentration of 6.0 pg/g. The absolute error was 1.325, and the bias was its negative counterpart, -1.325. This means that the model underpredicted concentrations in all instances, and that this underprediction was by an average factor of 3.8 ($e^{1.325}$) .

Figure 7-2 shows the EPA and the Scavenging Model predicting essentially the same concentration for nearly every data point, and both underpredicted grass concentrations significantly. The TEQ concentrations predicted by the EPA and the Scavenging Models were 3.26 and 2.94 pg/g, respectively, while the observed TEQ concentration was 7.35 pg/g. The bias and absolute differences for both models on this data set also mirrored each other. For the EPA Model, the bias and absolute differences were -1.01 and 1.09, and for the Scavenging Model, the bias and absolute difference were nearly the same at -1.07 and 1.15. These results indicate that both models underpredicted by about the same factor of 3.

One reason for this similarity in performance is that the EPA model reduced to principally a particle-phase deposition model; nearly all the dioxin was in the particle phase for the “urban” setting at 10 °C. Like the Scavenging Model, therefore, plant concentrations were mostly a linear function of total air concentrations for the application of the EPA Model at the industrial site.

As described earlier, the data at the industrial site was not nearly as well correlated as the data at the rural site - the correlation between air and grass data at the industrial site was 0.66 compared to 0.92 at the rural site. One factor likely to have influenced this is the fact that the soil at the industrial site was much higher for some of the dioxins as compared to the rural site. While the soil concentrations were not reported by Jones and Duarte-Davidson (1997), Sandalls

(1996) reported exceedingly high concentrations of TCDD (up to 9400 ppt, and several hundred ppt even 4-5 km from the major air source identified in the Bolsover area), and elevations in 2,3,7,8-TCDD, PCDD and TCDF in soils near the industrial site. Not ironically, these same four compounds, along with 1,2,3,6,7,8-HxCDD, were identified earlier as the compounds which had high grass concentrations at the industrial site despite air concentrations that were comparable to air concentrations of the same compounds at the rural site. If these five air:grass pairs are subtracted from the industrial site data set, the correlation between air and grass data now is much improved: it is at 0.80, up from 0.66. Also, the absolute error for both the Scavenging and the EPA Model for this smaller observed:predicted test improve to 0.61, indicating that modeled grass concentrations are now within exp [0.61] = 1.85 of measurements concentrations, rather than within a factor of 3.0. Obviously, the grass concentrations of these five compounds appear to have been influenced by high soil concentrations, and the ability of the models to reproduce these concentrations is limited because they are air-to-grass models and not air/soil-to-grass models. While it has been demonstrated that there is essentially no translocation from soil to above-ground plants (although pumpkins, cucumbers, squash, and other members of the cucumber family have been shown to translocate dioxins for an unknown reason (Hulster, et al., 1994)), there may have been some rainsplash impact or soil-to-air-to-plant impacts such as from wind erosion or soil volatilization for these compounds at the industrial site.

On the other hand, it was also true that air concentrations reasonably similar at the industrial and rural site led to lower grass concentrations at the industrial site for all the other dioxin and furan compounds. This is a trend that can possibly be explained and modeled by the EPA Model of this evaluation. For an urban setting, more of the dioxins are modeled to partition into the particle phase. As will be described below when discussing the calibration of the Scavenging Model, vapor phase dioxins have been shown to have a greater impact to plants compared to particle phase dioxins. Therefore, equivalent total air concentrations in a rural and an urban setting would lead to higher vegetation concentrations in the rural setting, because dioxins partition more into the vapor phase in such a setting, both in reality and as modeled by the EPA Model.

Table 7-2 shows the comparison of the measured grass concentration of 2,3,7,8-TCDD with the modeled vapor transfer concentration using the EPA vapor transfer model and the two Vapor Deposition Models. It is clear from this table that the vapor deposition algorithm, as parameterized by Smith et al. (1995) and Trapp and Mattheis (1995), predicts concentrations that are 2 to 4 times lower than predictions made by the vapor transfer algorithms of the EPA Model, and even lower still than observed grass concentrations. As will be described below, vapor phase

deposition velocity and the decay rate of the dioxins on the plant are two parameters likely to have been assigned inappropriate values for this exercise, and also likely to be difficult to assign in any application of the vapor deposition approach.

Whereas the scavenging ratio of 9.0 may have been appropriate for the field data used by McLachlan (1995) in the development of this approach, it is by far too low for this particular data set. A calibration exercise was performed on the 22 rural air/grass data points. In this exercise, the least squares fit of the difference between predicted and measured log grass concentrations was sought. The best fit was found at the constant scavenging coefficient of 36.4. With this value, the goodness-of-fit measures improve substantially: the bias goes to 0 (by definition of the least squares fit) from -1.325, and an absolute error goes to 0.417 (predictions are within a factor of 1.5, sometimes higher, sometimes lower) from 1.325 (predictions are always lower by about a factor of 4.0).

A critical assumption of the scavenging approach is that vapor and particle-phase dioxins are scavenged equivalently from the air. Therefore, a constant scavenging coefficient can be applied to total air concentration to predict total grass concentration. The error terms for the best-fit scavenging ratio suggest this might be reasonable. However, this assumption is not supported by the data in this field site. Figure 7-3 shows the scavenging ratios calculated for the 22 air:grass data points of the rural field site graphed as a function of the degree of chlorination. For example, there are four data points plotted for 4 on the x-axis: 2,3,7,8-TCDD, 2,3,7,8-TCDF, the TCDD homologue group, and the TCDF homologue group. The scavenging ratios are simply calculated as the grass concentration (in pg/g dry weight) divided by the air concentration (in pg/m^3) at the rural field site (with subtractions of congener concentrations from homologue group concentrations). As seen in the figure, there is a clear trend in that the scavenging ratio appears to generally decrease from the tetra to the hepta degrees of chlorination, with perhaps an increase at the octa degree of chlorination. It also suggests more of a trend for the dioxins as compared to the furans: there may be a higher scavenging ratio, in general, for the dioxins.

The experiments on Welsh Ray Grass (Welsch-Pausch, et al., 1995) used to calibrate the EPA's air-to-leaf transfer factor (Lorber, 1995) provided a reason for this trend: when blocking out the particle deposition impacts to potted grass, the authors found that the grass concentrations of the tetra through hexa chlorinated dioxins and furans were similar to concentrations in potted grass where particle depositions were not blocked out. The authors concluded that the plant concentrations for these dioxin/furan homologue groups were dominated by vapor-phase dioxins, even though the total air concentration itself was not necessarily dominated by the vapor phase. Therefore, given these experimental results, it follows that the lower chlorinated congeners

would have a larger overall scavenging coefficient. The field data certainly shows that trend; Figure 7-3 shows larger scavenging coefficients for the lower chlorinated dioxins and furans.

Figure 7-4 compares measured and modeled deposition amounts for the rural and industrial site combined. It is clear that the modeled rates of deposition were consistently higher than the measured rates. There was a high degree of correlation between measured and modeled rates, however, with a correlation coefficient of 0.99. The absolute error and bias were 1.16 and 1.11, respectively, suggesting that the model predictions were about 3.2 times higher than observed. This would indicate a systematic bias, either that the model tended to overpredict depositions or that the measurements tended to under-represent depositions.

If the model tended to overpredict deposition, this may have been due to inappropriate parameter assignment: too rapid a velocity of deposition, or too much dioxins assumed to be in particle phase. Measured deposition velocities can be calculated from the data of Jones and Duarte-Davidson (1997) in Table 7-1 simply as the deposition flux divided by the air concentration (with proper conversions). Average velocities calculated this way were 0.06 cm/s for the rural site and 0.08 cm/s for the industrial site and only one calculated deposition velocity was greater than the 0.20 cm/s velocity assigned for this modeling exercise. The predicted depositions would be lower still if measured particle phase fractions were used instead of modeled fractions since, measured particle-particle fractions of dioxins tend to be lower than modeled using the Junge model for vapor/particle partitioning. For this particular field site, measured vapor/particle fractions were not available to evaluate this possibility.

On the other hand, it could be the case that the deposition collectors are underestimating depositions. Jones and Duarte-Davidson (1997) suggest two possible causes for the upturned frisbees to be underestimating deposition: 1) they are smooth and therefore less efficient at capturing particles as compared to leafy vegetation or ground surfaces, and 2) dioxins in wet deposition can be adsorbed onto the sampler surface and presumably, not be available to be measured.

In any case, it can be concluded that the deposition model, which was the simple product of the particle-phase reservoir times a deposition velocity of 0.20 cm/s, resulted in the deposition amounts that about 3 times higher than were measured in the rural and industrial sites of this data set.

In the introduction to Section 7.2.1, this exercise was described as both a model validation and model comparison exercise. It can be concluded that the EPA model was reasonably successful in this validation with the rural site field data, but less successful on the industrial site data. On the other hand, both the vapor transfer and scavenging models could not

be successfully validated on this field data. In the case of the vapor transfer model, the likely shortcoming was in the assignment of the parameters, vapor deposition velocity and degradation of vapor phase 2,3,7,8-TCDD deposited on the grass. In the case of the scavenging coefficient, the value of 9.0 suggested in its development (McLachlan, 1995) was too low. One can calibrate both models such that the fit between observed and predicted grass concentrations is favorable. These calibrated models can then be applied to other field data sets in order to see if the calibrated values are "valid". The deposition portion of the EPA model was found to consistently overpredict deposition, which could be due to either inappropriate parameter assignments, or the tendency of the upturned frisbee to underestimate deposition amounts.

7.2.1.4. Literature Comparisons of Air-to-Plant Modeling Approaches

Douben, et al. (1997) presents an exercise comparing the three air-to-plant approaches that were compared in the previous section: the approach in this document, the scavenging approach, and the vapor deposition approach. Their exercise used, as observed air data, concentrations from a semi-rural site in the United Kingdom (UK). This was not the same as the rural site in the Jones and Duarte-Davidson (1977) study. Since this data set had several non-detects, the authors supplemented it with data from a rural site showing similar detected concentrations in Germany; the final observed air concentrations were crafted from these two data sets. The observed grass data came from a different site in the UK. Comparing model performance on a set of data from a single site, as was done in the previous section, is preferable to "crafting" observed air and grass data. Still, if the data can be considered representative, than using data from different sites may not be invalid; developing representative air and beef profiles was done for the air-to-plant-to-beef model validation described in Section 7.3.11 below. The application of the approach of this document used an earlier vapor transfer factor, from Lorber (1995), which also had an earlier vapor/particle partitioning scheme. They used the vapor deposition approach described and parameterized by Smith, et al. (1995) for all dioxin congeners, not just 2,3,7,8-TCDD - the vapor deposition velocity (0.78 cm/sec) and plant degradation (0.495 day^{-1}, corresponding to a half-life of 1.4 days) parameters were assigned the same the same for all congeners. For the vapor deposition algorithm, they used measured vapor fractions (from the site in Germany) as compared to use of the modeled vapor fractions in the exercise above. Finally, they used the scavenging approach promoted by McLachlan (1995) including the assignment of a scavenging coefficient of 9 for all congeners.

In general, they showed some of the similar trends that were described above. The models of this assessment had the highest predicted grass concentration; this was also the trend

in the exercise described above. However, these predictions were higher than the grass observations of the crafted air/grass data set in Douben, et al. (1997), sometimes by upwards of a factor of 10. The vapor transfer approach was the lowest predictor, but in their case, predictions were usually within an order of magnitude, sometimes within a factor of 2. The scavenging approach performed the best on their data set. Similar to the conclusion in Jones and Duarte-Davidson (1997), Douben, et al. (1997) concludes the following regarding vapor and particle atmospheric scavenging (p. 342 in Douben, et al. (1997)): "However, an implication of the good predictions obtained across the range of PCDD/Fs with the scavenging model is that airborne PCDD/Fs which may be present either in the vapour- or particulate-phase appear to transfer with similar efficiencies to pasture grass and may remain associated with the grass after deposition." However, even in the crafted air and grass profile, there is similar evidence as described above in that the scavenging coefficient increases as the degree of chlorination decreases, at least clearly so for the tetra congeners. From their data, calculated scavenging coefficients are: 57 for TCDD/Fs (n=2), 9 for PCDD/Fs (n=3), 5 for HxCDD/Fs (n=7), 11 for HpCDD (n=3), and 11 for OCDD/Fs (n=2).

Currado and Harrad (1998) evaluated two of the three modeling approaches described in the previous section to a data set including air concentrations, deposition amounts, and grass concentrations of 20 individual PCB congeners from an urban site in Birmingham, UK. The two models they tested were the EPA air-to-leaf model (which they further developed for CDD/Fs to include a soil-to-plant algorithm as described in Harrad and Smith (1997), although they only used the air-to-plant algorithm for this application to PCBs), and the Scavenging Model. For the EPA model, they partitioned the PCBs into particle and vapor phases using the Junge-Pankow model advocated in this assessment, corrected for air temperature, and then transferred the vapor-phase and deposited the particle-phase PCBs onto the grass. The vapor phase transfer factors were determined as a function of the PCB log Kow and H, as described in Lorber, et al. (1994), including an empirical reduction factor of 40. For the test of the Scavenging Model, they simply plotted total (vapor + particle) air concentrations against measured air concentrations, and investigated the correlation between the two. According to the Scavenging Model approach, the total air concentration times a constant (equal to the volume of air being "scavenged" of PCB to produce the grass concentration), which is the same constant for all PCBs, should equal the grass concentration.

Using the EPA framework, they found very good agreement between predicted and measured grass concentration for the PCBs: observed/predicted ratios ranged from 0.34 to 1.97, with a mean of 0.93 and a correlation coefficient of 0.46. They also found good agreement

observed and predicted vapor/particle partitioning (observed/predicted particle fraction ratios ranged from 0.17 to 2.15, mean of 0.89 and correlation coefficient of 0.59) and observed and predicted particle deposition fluxes (observed/predicted ratios from 0.33 to 4.19, mean of 1.33, and correlation coefficient of 1.09).

On the other hand, they did not get as good results with the Scavenging Coefficient model. They did find that this would work for the penta- and hexachlorobiphenyls - their grass scavenged the PeCBs and HxCBs present in 22 m^3 of air, but there was not a similar relationship found for tri- and tetrachlorobiphenyls. Although the authors didn't investigate further, there may be a relationship between portion of the PCBs in the particle-phase, there would be more in the particle phase as the degree of chlorination increases (as it is with CDD/Fs), and the capabilities of the Scavenging Approach.

7.2.2. An Alternate Modeling Approach for Estimating Water Concentrations Given a Steady Input Load from Overland Sources

A study to evaluate the bioaccumulation of 2,3,7,8-TCDD in fish in Lake Ontario included an extensive modeling exercise (EPA, 1990a). The model used was WASP4 (Ambrose, et al., 1988). This is a substantially more complicated model than used in this assessment. The underlying principal for the WASP4 model is a conservation of mass. Contaminant source terms, described in mass/time units, enter what are termed control volumes, or segments. The contaminant partitions between sorbed, bound, and dissolved phases; it is not required to specify whether the contaminant enters via soil erosion, water runoff, surface deposition, or otherwise. Contaminants are, however, assumed to enter via the surface or as part of inflows to the water body, in contrast to ground water recharge. The mass transported into a segment is either transported out of the segment, accumulates in the segment, or is transformed by chemical or biological reactions.

As noted, 2,3,7,8-TCDD input into the Lake Ontario application partitions within the water column into a sorbed compartment, a dissolved compartment, and a bound compartment. This bound compartment is further described as non-settling organic matter. Three analogous compartments receive 2,3,7,8-TCDD in the bottom sediment layer. Several exchanges between the six compartments and contaminant losses within each compartment are modeled. For example, losses from water column compartments include downstream transport, volatilization and photolysis; the loss mechanism from the bottom sediment layer is sedimentation. Exchanges between compartments consider partitioning, diffusion, and sediment settling and resuspension.

This model requires substantial parameterization. Once values were selected for the Lake Ontario application, an evaluation was made on the impact of different levels of 2,3,7,8-TCDD input. Dynamic and steady state results were discussed. Principally examined for the steady state results were the concentrations of bottom sediment sorbed 2,3,7,8-TCDD and water column dissolved (soluble) phase 2,3,7,8-TCDD. A given level of steady 2,3,7,8-TCDD input, in kg/yr, resulted in a steady state concentration sorbed to bottom sediment and dissolved in the water column.

The premise in both the Lake Ontario steady state application of WASP4 and the water concentration algorithms in this assessment is that contaminants continue to enter water bodies over time unabated. Ground water entry of contaminants is not considered in either approach. Although a direct modeling comparison cannot be done, it is possible to slightly adjust the algorithms of this assessment to evaluate how results from a simple partitioning approach would compare with results from the complex fate and transport approach of the WASP4 steady state application.

Assume a surface water body is initially free of contaminant and at time t equals 1 day, a strongly hydrophobic contaminant, such as the dioxin-like compounds of this assessment, begins to enter a lake. Assuming the contaminant enters via soil particles, as in the approach of this assessment, it will then partition between those soil particles and surrounding water. The soil particles will slowly move toward the bottom of the lake at a rate described by a particle settling velocity. A settling velocity of 1 m/day is assumed in the Lake Ontario simulations. The amount of time it takes to settle to the bottom once entering from the surface equals the lake depth divided by this settling time. The Lake Ontario depth was 86 m. Therefore, it might take 86 days to settle. This, of course, neglects resuspension of settled particulates. With this simplistic framework, a steady state amount coming into the lake after 86 days is matched by an amount depositing onto the lake bottom; the amount of contaminant within the water column has reached steady state. Water concentrations can then be estimated assuming equilibrium partitioning.

Results of sediment and water column steady state concentrations are described for any loading of 2,3,7,8-TCDD in the WASP4 steady state application; those loadings are described in kg/yr. Loadings in kg/yr are easily correlated to a steady state water column amount, given the above analysis. For example, a loading of 1.0 kg/yr could translate to a within water column steady state amount of 0.24 kg (1.0 kg/yr * (86 d)/(365 d/yr)).

This steady water column amount partitions between suspended sediment and surrounding water. First, the total concentration (sorbed + soluble) simply equals:

$$C_{tot} = 1000 \frac{LD}{VOL} \quad (7\text{-}5)$$

where:

C_{tot} = total concentration, mg/L
LD = water column steady state amount of contaminant, kg
VOL = lake volume, m^3
1000 = converts kg to mg and m^3 to L

The dissolved phase portion of total is given by:

$$C_{wat} = \frac{C_{tot}}{1 + (Kd_{ssed}\ TSS\ 10^{-6})} \quad (7\text{-}6)$$

where:

C_{wat} = soluble phase water concentration, mg/L
C_{tot} = total concentration, mg/L
Kd_{ssed} = partition coefficient between suspended sediment and surrounding water, L/kg
= $Koc*OC_{ssed}$
Koc = organic carbon partition coefficient, L/kg
OC_{ssed} = fraction organic carbon of suspended sediments
TSS = total suspended sediments, mg/L
10^{-6} = converts mg/kg to mg/mg

Parameters in this equation for the Lake Ontario WASP4 application include VOL, Koc, OC_{ssed}, and TSS. Lake Ontario volume was given as 1.68×10^{12} m^3, Koc was estimated for the WASP4 application as 3,162,000, OC_{ssed} was estimated at 0.03, and TSS was estimated 1.2 mg/L. For a steady load of 1 kg/yr and a resulting LD of 0.24 kg, the steady state water column 2,3,7,8-TCDD concentration, using the simplistic approach described above, is estimated as 0.13 pg/L (ppq). The steady state water column concentration estimated by WASP4 given the same parameters and a load of 1 kg/yr is roughly 0.20 pg/L. An uncertainty analysis done with these WASP4 results concluded that 95% confidence limits around this prediction are 0.03 and 0.40 pg/L.

This would seem to imply that the simple partitioning approach used in this assessment compares favorably with the more complex fate and transport modeling assessment using WASP4, for Lake Ontario.

7.2.3. Estimating Fish Tissue Concentrations Based on Water Column Concentrations Rather than Bottom Sediment Concentrations

EPA prepared a document titled, "Interim Report on Data and Methods for Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin Risks to Aquatic Life and Associated Wildlife" (EPA, 1993). That document provides details on the two key bioaccumulation parameters used for the methodologies of this document, the Biota Sediment Accumulation Factor, BSAF, used for the soil and stack emission source categories, and the Biota Suspended Solids Accumulation Factor, BSSAF, used for the effluent discharge source category. That document also discussed several water column based bioaccumulation factors, which are the focus of this section. A later publication prepared by the same group at EPA titled, “Great Lakes Water Quality Initiative Technical Support Document for the Procedure to Determine Bioaccumulation Factors” (EPA, 1995a), also describes water and sediment based bioaccumulation factors.

Before discussing these factors, it is noted that food chain modeling is a well developed alternate approach for estimating fish tissue concentrations of bioaccumulating contaminants (Thomann, 1989), which has also been applied to 2,3,7,8-TCDD (Parkerton, 1991). This approach is significantly more complex than the bioaccumulation/biotransfer approach of this methodology. It involves detailed site-specific characterizations, specifically the identification and transfer modeling between trophic levels of a food chain in a water body. Food chain modeling is a mechanistic approach, while the transfer approaches of this methodology are empirical. No judgement is rendered as to the relative merit of food chain models versus use of bioaccumulation coefficients. If detailed site-specific data is available, and given time and resources, assessors should consider food chain modeling for estimating fish tissue concentrations.

One water column measure which has been classically used is termed the Bioconcentration Factor, or BCF. Bioconcentration refers to the net accumulation of a chemical from exposure via water only, and BCFs are most often obtained in laboratory conditions. BCFs are defined as the ratio of the chemical concentration in organism (mass of chemical divided by wet weight of organism tissue) to that in water.

Another water column measure of the potential for a contaminant to accumulate in fish tissue is termed the Bioaccumulation Factor, or BAF. Bioaccumulation refers to the net

accumulation of a chemical from exposure via food and sediments as well as water. Similar to the BCF, BAFs are defined as the ratio of the chemical concentration in the organism to that in the water.

For chemicals that are not strongly hydrophobic (unlike the dioxin-like compounds), the distinction between bioconcentration and bioaccumulation is small. Whereas food intake is generally a few percent of body weight per day, water passing over gills will equal hundreds to thousands times the organism weight per day, depending on species, activity, temperature, and other factors. Given this, the concentration of chemical in food must be 3 or more orders of magnitude greater than that in water before food can substantially contribute to uptake. EPA (1993) estimates that food intake becomes a critical contributor to the accumulation of contaminants in fish tissue for contaminants with log Kow of 5 and greater.

Since the dioxin-like compounds fall into this category, the remainder of this section will focus on the Bioaccumulation Factor. EPA (1993) defines steady-state lipid-based BAFs for total chemical in water and freely dissolved chemical in water (i.e., chemical which is truly in a dissolved phase and not bound to dissolved or suspended particulate organic materials) as:

$$ssBAF_l^t = \frac{C_{lipid}}{C_w^t} \quad (7\text{-}7a)$$

$$ssBAF_l^d = \frac{C_{lipid}}{C_w^d} \quad (7\text{-}7b)$$

where:

$ssBAF_l^t$ = steady-state lipid-based BAF for total chemical in water, unitless

C_{lipid} = the mass of contaminant in fish lipid tissue divided by the mass of fish lipid tissue, mg/kg

C_w^t = the mass of total contaminant in water divided by the mass of water in the water body, mg/kg (note: 1 L water nearly equals 1 kg, therefore, 1 mg/L can be assumed to equal 1 mg/kg)

$ssBAF_l^d$ = steady-state lipid-based BAF for freely dissolved chemical in water, unitless

C_w^d = the mass of freely dissolved contaminant in water divided by the mass of water in the water body, mg/kg

EPA (1993) then develops relationships between $ssBAF_l^d$ and $ssBAF_l^t$, based on dissolved and particulate organic carbon reservoirs in the water column, and partition coefficients for these reservoirs. This is meaningful in complex modeling where these two reservoirs of organic carbon can be accounted for, such as in the WASP4 model. Alternately, EPA (1993) defines the TBF_{oc}, a total binding factor to organic carbon, which empirically considers the reservoir of dissolved organic material (i.e., increases total binding and reduces truly dissolved phase concentrations) when such a reservoir is not explicitly modeled. The modeling frameworks in this assessment have only one compartment of suspended material to which contaminants sorb, with one associated organic carbon content. A second reservoir to which contaminants bind, the reservoir of dissolved organic material, is not modeled.

EPA (1993) developed a $ssBAF_l^t$ and a $ssBAF_l^d$ for lake trout, 2,3,7,8-TCDD, and for Lake Ontario 1987 contamination conditions. The WASP4 model was used to model three hypothetical loading conditions that might have resulted in fish tissue concentrations observed in 1987: steady state loading, a steady state loading followed by a 90% reduction in annual loads for 20 years (i.e., 1968-1987), a steady state loading followed by a 100% reduction (i.e., no loading) for 20 years. The BSAF for lake trout estimated for 1987 data is given in EPA (1990a) as 0.07. The BSAF is determined from measured bottom sediment concentrations and fish tissue concentrations; an assumption of historical loading is not necessary for BSAF development. Details of the Lake Ontario study, including initial modeling efforts with the WASP4 model can be found in EPA (1990a). Slight refinements to the WASP4 runs were later made (cited in EPA, 1993 as an unpublished report: Endicott, D.D., W.L. Richardson, T.F. Parkerton, and D.M. DiToro. 1990. A steady-state mass balance and bioaccumulation model for toxic chemicals in Lake Ontario: Report to the Lake Ontario Fate of Toxics Committee. U.S. EPA, Environmental Research Laboratory, Duluth, MN: 121 pp). The BAFs determined in these later runs will be tested using the models of this assessment.

In order to do this exercise, all critical model parameters used to develop the BAFs for this WASP4 modeling exercise will be used in the model framework of this assessment. The most critical parameter is the organic carbon partition coefficients, Koc, assumed for 2,3,7,8-TCDD. BAFs were determined assuming Koc of 10^7 and 10^8. Since the models of this assessment assume steady loading into water bodies, only the BAFs developed under "steady state" loading conditions will be used. As noted, the WASP4 model considers binding to more than one suspended compartment. The increased binding can be modeled using a TBF_{oc}, which was assumed to be 1.5 for Lake Ontario by Cook. For the models of this assessment, this factor will be applied to Koc - it effectively increases Koc by 50%. The concentration of suspended

solids in Lake Ontario and used in the WASP4 modeling exercise was 1.2 mg/L. The other critical parameters are the fraction organic carbon contents of the suspended solids and the bottom sediments, OC_{ssed} and OC_{sed}, respectively. Assigned values to these parameters, based on Lake Ontario data, in the WASP4 exercise and in this exercise were 0.15 (15%) and 0.03 (3%), respectively.

Since the purpose of this exercise is to evaluate how the modeling approaches of this document perform using the BSAF or the alternate BAF approach, duplicating the source strength terms used in the WASP4 modeling exercise is not necessary. The pertinent question is, with a given source strength, how would both approaches predict fish tissue concentrations. For simplicity, the background demonstration scenario described in Chapter 5 will be adopted for use here. In this scenario, the soil within the watershed is assumed to at a uniform concentration. For the exercise here, a uniform concentration of 1.0 ppt for 2,3,7,8-TCDD will be assumed.

In summary, the parameters for this exercise including the steady state BAFs are:

Test 1: Koc = $1.5*10^7$; $ssBAF_l^d = 1.9x10^6$; $ssBAF_l^t = 5.16x10^5$; BSAF = 0.07

Test 2: Koc = $1.5*10^8$; $ssBAF_l^d = 1.9x10^7$; $ssBAF_l^t = 6.78x10^5$; BSAF = 0.07

The 1.5 in the Kocs was the TBF_{oc} noted above. The BAFs specific to each Koc were the ones developed also specific to those Koc in the WASP4 modeling exercises. For both tests: soil concentration of 2,3,7,8-TCDD = 1.0 ng/kg (ppt), total suspended solids (TSS) = 1.2 mg/L, the organic carbon content of suspended sediments (OC_{ssed}) = 0.15, and the organic carbon content of bottom sediments (OC_{sed}) = 0.03. Whole fish tissue concentrations are estimated as $C_{lipid} * f_{lipid}$, where f_{lipid} is 0.07.

The whole fish tissue concentration for the BSAF approach in Test 1 was estimated to be 0.61 ppt. Using the $ssBAF_l^t$ and $ssBAF_l^d$, the whole fish tissue concentrations were estimated very nearly to be the same at 0.867 ppt for $ssBAF_l^t$ and 0.863 ppt for $ssBAF_l^d$. The test results did not change substantially for Test 2. The BSAF approach led to a fish tissue concentration of 0.62 ppt, and the concentration was identical for BAFs at 0.869 ppt.

While it appears that the water column based approaches estimate fish tissue concentrations identical to each other and very close to estimates made based on bottom sediment concentrations, in fact the performance of the models differ when parameters are changed in these tests. More incoming 2,3,7,8-TCDD can be modeled to remain in the water column with an increase in the reservoir of total suspended solids, the TSS parameter initialized in above tests at 1.2 mg/L. Continuing with Test 1 parameters above, increasing TSS from 1.2 mg/L to 10 mg/L has the following changes to fish tissue concentrations: 0.54 ppt for the BSAF test, 4.85 ppt for the $ssBAF_{lt}$ test and 0.76 ppt for the $ssBAF_l^d$ test. Decreasing the organic

carbon content of the suspended solids will have the effect of reducing the amount of incoming 2,3,7,8-TCDD simulated to remain in the water column, while increasing the amount modeled to reside in bottom sediments (because a mass balance of 2,3,7,8-TCDD is maintained), and also increases the dissolved phase concentration. Changing the TSS back to 1.2 mg/L and reducing the organic carbon content of suspended solids from 0.15 to 0.05 results in the following changes to fish concentrations: 0.62 ppt for the BSAF test, 0.45 ppt for the $ssBAF_l^t$ test and 0.88 ppt for the $ssBAF_l^d$ test. These two tests have demonstrated the variability in fish tissue concentrations when key water column parameters are altered. Fish concentrations would also differ if the key bottom sediment parameter, the organic carbon content of bottom sediments, was different. Returning to original Test 1 parameters and reducing the organic carbon content of bottom sediments from 0.03 to 0.01 results in the following changes to fish concentrations: 1.73 ppt for the BSAF test, 2.45 ppt for the $ssBAF_l^t$ test and 2.44 ppt for the $ssBAF_l^d$ test.

The predictions for all tests might be considered reasonably close, given the uncertainties in the bioaccumulation and water modeling parameters. The one test described above where the BSAF and BAF approaches led to the most differences was the one which increased suspended material contents from 1.2 mg/L to 10 mg/L. In that case, nearly a ten-fold difference was noted in fish concentrations with the $ssBAF_l^t$ as compared to the BSAF or the $ssBAF_l^d$.

An important consideration in using the water column based approaches is that the BAFs developed by Cook (or that could be developed otherwise) are based on modeled rather than measured water column concentrations, and measured lake trout tissue concentrations. In that sense, the BAFs were calibrated for Lake Ontario conditions and specific to the WASP4 modeling exercise. Therefore, using these BAFs in the modeling framework of this assessment is, strictly speaking, invalid. Further, the values of the BAFs varied depending on the assumptions on historical loadings into Lake Ontario. As noted above, three loading conditions were tested. The steady state BAFs were given above. For the 20 year - 90% reduction tests, the following BAFs were determined: BAF_l^d was 3.03×10^6 for Koc = 10^7 and 2.86×10^7 for Koc = 10^8, and BAF_l^t was 8.26×10^5 for Koc = 10^7 and 1.02×10^6 for Koc = 10^8. For the 20 year - 100% reduction tests, the following BAFs were determined: BAF_l^d was 3.86×10^6 for Koc = 10^7 and 3.40×10^7 for Koc = 10^8, and BAF_l^t was 1.05×10^6 for Koc = 10^7 and 1.21×10^6 for Koc = 10^8. The BSAF developed for lake trout for Lake Ontario was developed using measurements of both fish tissue and bottom sediment concentrations.

Both the BSAF and BAF are most appropriately developed using site specific data (coupled with a modeling exercise for BAF). Inasmuch as that can be impractical or difficult for many sites, efforts are underway to determine the general applicability of BSAFs and BAFs

determined for one site to other sites. EPA (1993) proposes that BAF_ls for different congeners can be roughly estimated as the BAF_l for 2,3,7,8-TCDD multiplied by the ratio of the BSAF for the congener and the BSAF for 2,3,7,8-TCDD. Such an estimate will incorporate differences in uptake, metabolism and chemical partitioning but not differences caused by chemical loss processes such as volatilization and photolysis. This approach for estimating BAF_ls for other congeners does allow for some generality since sediment and fish tissue data for other congeners and water bodies is available.

Another bioaccumulation term discussed in one literature article for dioxin is termed the Regulatory Bioaccumulation Multiplier, or RBM (Sherman, et al., 1992). Multiplication of this term and a "nominal water concentration" estimates a 3% lipid fish concentration. A nominal water concentration equals an amount of a contaminant, 2,3,7,8-TCDD in this application, added or entering a water body over time, divided by a flow volume over that same time. Assuming a fish lipid content of 3%, an RBM of 5000 was recommended based on examination of laboratory flow through data, simulated field data, and actual field data (EPA's Lake Ontario study and data downstream of pulp and paper mills). Dividing the 5000 by 0.03 gives $1.67*10^5$, and this number is now analogous to the $ssBAF_l^t$ developed by EPA (1993) described above, and in the same range as the $5.2\text{-}6.8*10^5$ range for $ssBAF_l^t$.

7.2.4. Other Modeling Approaches and Considerations for Air Concentrations Resulting from Soil Volatilization

Volatilization was modeled for the soil contamination source category, using an approach given in Hwang, et al. (1986), developed for PCB flux from soils. Another model often used to estimate volatilization from soil was presented by Jury and coworkers in a series of papers in the early 1980s (Jury, et al., 1983, 1984a,b). The full solution to Jury's model is complex and not amenable to spreadsheet programming structure. It was available for use in this exercise in an EPA model known as EMSOFT (EPA, 1997a). There is a steady state, simplified solution to the Jury model which is used in EPA's Superfund Soil Screening Methodology (EPA, 1996). Both of these Jury approaches account for movement of the organic contaminant in the vapor phase via diffusion and the dissolved phase via solute movement, and they also account for changes in volatilization rate over time: volatilization decreases with time after an initially assumed soil concentration in the surface soil depletes and deeper residues volatilize to a lesser extent (the Hwang model also accounts for a decrease in the volatilization rate over time).

If one assumes that the contaminant moves through the soil column in only the vapor phase, a simplification of the fundamental equations used by Jury offers another option for

modeling soil volatilization. The steady-state vapor diffusion equation was used by Farmer, et al. (1980a) in modeling hexachlorobenzene vapor diffusion in a laboratory soil column, and also by Johnson and Lindberg (1995) in modeling mercury volatilization from soil. It will be applied here to 2,3,7,8-TCDD.

The two Jury models and the vapor phase diffusion model are compared with the Hwang approach, as applied in this document for 2,3,7,8-TCDD. Following now are more complete descriptions of the Hwang model, the Jury models and the vapor diffusion model. The parameters used for all models are shown in Table 1.

I. Hwang Model: Farmer, et al. (1980b) applied a basic diffusion equation to the problem of soil volatilization of pesticides. This diffusion equation does not consider movement of the contaminant with soil water or degradation in the soil column:

$$\frac{\partial^2 C_T}{\partial z^2} - \frac{1}{D}\frac{\partial C_T}{\partial t} = 0 \qquad (7\text{-}8)$$

where:

C_T = mass of chemical per unit soil volume, g/cm^3
z = soil depth, cm
D = apparent diffusion coefficient for contaminant in soil, cm^2/sec
t = time, sec

Hwang, et al. (1986) redefined this basic equation to consider instead the gas phase, C_G, which they assumed was in local equilibrium with soil concentration, Cs. Their steady state equation was:

$$\frac{\partial^2 C_G}{\partial z^2} - \left[1 + \frac{BD\ Kd}{\Phi\ K_H}\right]\frac{1}{Dei}\frac{\partial C_G}{\partial t} = 0 \qquad (7\text{-}9)$$

where:

C_G = concentration of chemical in the gas phase, g/cm^3
BD = soil bulk density, g/cm^3

Kd	=	soil/water partition coefficient, cm^3/g
	=	Koc * foc
Koc	=	organic carbon partition coefficient, cm^3/g
foc	=	fraction organic carbon in soil, unitless
ϕ	=	soil porosity, cm^3/cm^3, or unitless
K_H	=	dimensionless Henry's Constant
	=	H/RT (= 41 H, substituting R and T below)
H	=	Henry's Constant, atm-m^3/mol
R	=	universal gas constant, $8.21*10^{-5}$ atm-m^3/mol-°K
T	=	standard temperature, 20 °K
Dei	=	effective diffusivity of contaminant in soil, cm^2/sec
z	=	distance from surface soil, cm
t	=	time, sec

Hwang, et al.(1986) assumed that PCBs in soil were in equilibrium between the sorbed and the gaseous phase as follows:

$$C_G = \frac{K_H \, Cs}{Kd} \qquad (7\text{-}10)$$

where:

C_G	=	concentration of chemical in the gas phase, g/cm^3
K_H	=	dimensionless Henry's Constant (= 41H, as defined above)
Cs	=	soil concentration, g/g (unitless form here for units consistency)
Kd	=	soil/water partition coefficient, cm^3/g (= foc*Koc, as defined above)

They also assumed that the effective diffusion was related to the diffusion coefficient of the contaminant in air as:

$$Dei = D_G^{air} \, \Phi^{1/3} \qquad (7\text{-}11)$$

where:

Dei	=	effective diffusion coefficient, cm^2/sec
D_g^{air}	=	diffusion coefficient for contaminant in air, cm^2/sec
ϕ	=	soil porosity, cm^3/cm^3, or unitless

Hwang, et al. (1986) solved this equation for two cases: when the contaminated soil was bare to the atmosphere and where the contaminated soil was covered with a layer of clean soil. Obviously, the option chosen for this methodology, and for this examination of alternate volatilization methods, was the bare soil contamination. Their initial and boundary conditions were: 1) the concentration of the contaminant in the air at the soil surface is 0 continually, and 2) the concentration in the soil air just below the surface and at an infinite depth remains constant and is a function of the soil concentration and contaminant properties - this function is given as Equation (7-10) above.

The flux rate that occurs after a time period t is given as:

$$J_s\ (t) \;=\; \frac{(\Phi)\ (D_{ei})\ (Cs)\ (H)\ (41)\ (10^{-6})}{Kds\ [\ (\pi)\ (I)\ (t)\ ]^{0.5}} \qquad (7\text{-}12)$$

where:

J_s	=	average volatilization flux rate of contaminant from soil, g/cm^2-s
ϕ	=	soil porosity, cm^3/cm^3, unitless
D_{ei}	=	effective diffusivity of contaminant in air, cm^2/s
Cs	=	contaminant concentration in soil, ppm or mg/kg
H	=	Henry's Constant of contaminant, atm-m^3/mol
Kds	=	soil/water partition coefficient, cm^3/g
t	=	time, sec
I	=	interim undefined term for calculation, cm^2/s
	=	$[\ D_{ei}\ \phi\ ]\ /\ [\ \phi + P_{soil}\ (1\text{-}\phi)\ [Kds/(41\ H)]\ ]$
P_{soil}	=	particle bulk density of soil, g/cm^3

The average flux rate during the exposure period is given as $2 * J_s(ED)$, where ED is the exposure duration in seconds.

It is noted in Hwang, et al. (1986) that this procedure would tend to overestimate emissions and resulting exposures in situations involving small spills which would not involve deep contamination. It is also noted that the average flux rate is inversely proportional to the square root of the duration of exposure - the longer the duration of exposure, the lower will be the average flux rate. Whereas this solution assumes an unlimited reservoir of contaminant, it is an unsteady state solution (unlike most other solution strategies) and is essentially an average flux rate over an amount of time defined by the exposure duration. Inherent in the solution was the consideration that residues dissipate by volatilization at the surface layers, resulting in contaminants diffusing upwards from deeper soil layers over time. With this longer path of diffusion, volatilized amounts decrease, and hence the average flux over time also decreases.

The parameters required for the Hwang model are provided in Table 7-3, and these include the initial soil concentration of 2,3,7,8-TCDD, C_0, the soil parameters P_{soil}, foc, ϕ, and BD, the exposure duration (or total time during which volatilization occurs starting from time t = 0 at the initial soil concentration, C_0), and the chemical-specific parameters D_g^{air}, Koc, and H.

II. Jury Model: This model assumes: 1) uniform soil properties throughout the soil column to an infinite depth, 2) there is a stagnant air boundary layer at the soil surface across which diffusion occurs and the chemical concentration at the top of this boundary layer is zero, 3) linear equilibrium liquid-solid and liquid-air partitioning is valid, and 4) degradation follows first-order kinetics. With these conditions, the mass conservation equation is:

$$\frac{\partial C_T}{\partial t} + \frac{\partial J_s}{\partial z} + \mu C_T = 0 \qquad (7\text{-}13)$$

where:

C_T	=	mass of chemical per unit soil volume, g/cm^3
J_s	=	chemical mass flux per unit soil are per unit time, g/cm^2-sec
μ	=	net degradation rate, 1/sec
t	=	time, sec
z	=	soil depth, cm

The volumetric total soil concentration, C_T, is given as:

$$C_T = BD\ Cs + \theta\ C_L + a\ C_G \quad (7\text{-}14)$$

where:

C_T	=	mass of chemical per unit soil volume, g/cm^3
Cs	=	concentration of chemical on soil, g/g (expressed in unitless form here for units consistency)
BD	=	soil bulk density, g/cm^3
C_L	=	concentration of chemical in the liquid phase, g/cm^3
θ	=	volumetric soil water content, cm^3/cm^3, or unitless
C_G	=	concentration of chemical in the gas phase, g/cm^3
a	=	volumetric soil air content, cm^3/cm^3, or unitless

The terms BD, θ, and a are in front of the concentration terms to convert them to volumetric units, to be consistent with the volumetric definition of C_T. It should be noted that for 2,3,7,8-TCDD, which is very tightly sorbed to soil, C_G and C_L become very small and C_T can be calculated as Cs BD. The mass flux, J_s, can be written as:

$$J_s = -D_G \frac{\partial C_G}{\partial z} - D_L \frac{\partial C_L}{\partial z} + J_w C_L \quad (7\text{-}15)$$

where:

J_s	=	chemical mass flux per unit soil are per unit time, g/cm^2-sec
D_G	=	soil-gas diffusion coefficient, cm^2/sec
C_G	=	concentration of chemical in the gas phase, g/cm^3
D_L	=	soil-liquid diffusion coefficient, cm^2/sec
C_L	=	concentration of chemical in the liquid phase, g/cm^3
J_w	=	water flux, cm/sec
z	=	soil depth, cm

D_G and D_L are given by appropriate forms of the Millington-Quirk equations:

$$D_G = \frac{a^{10/3}}{\Phi^2} D_G^{air} \quad (7\text{-}16a)$$

$$D_L = \frac{\theta^{10/3}}{\Phi^2} D_L^{water} \quad (7\text{-}16b)$$

where:

D_G	=	soil-gas diffusion coefficient, cm^2/sec
a	=	volumetric soil air content, cm^3/cm^3, or unitless
ϕ	=	soil porosity, cm^3/cm^3, or unitless
D_g^{air}	=	chemical gaseous diffusion coefficient in air, cm^2/sec
D_L	=	soil-liquid diffusion coefficient, cm^2/sec
D_L^{water}	=	chemical liquid diffusion coefficient in water, cm^2/sec
θ	=	volumetric soil water content, cm^3/cm^3, or unitless

Soil porosity is defined as the amount of void space in the soil, and can be calculated as, 1 - (soil bulk density)/(soil particle density). A common value used for soil bulk density, in the absence of site-specific data, is 1.5 g/cm^3. Soil particle density is not site-specific, rather it is an inherent soil property. It has been estimated to be between 2.6 and 2.7 g/cm^3, and is often assigned a value of 2.65 g/cm^3. Therefore, soil porosity is calculated at 0.434 (ie., 1 - 1.5/2.65). This porosity is comprised of air and water; that is, soil porosity, ϕ = volumetric soil water content, θ + volumetric soil air content, a, using the terms defined above. For a soil that is sometimes wet and sometimes dry, an average soil water content would range between field capacity, around 0.30 for typical soils, and wilting point, around 0.15. This exercise will assume a water content of 0.23 and a porosity of 0.43, leaving air content to be calculated at 0.20.

This solution requires the partitioning of the chemical into sorbed (Cs), liquid (Cl) , and gas (Cg) phases. The soil concentration is initially given, and liquid and gas phases are then solved as:

$$C_L = \frac{Cs}{Kds} \quad (7\text{-}17)$$

where:

C_L	=	liquid phase concentration, g/cm^3 soil water
Cs	=	soil concentration, g/g (unitless form here for units consistency)
Kds	=	soil/water partition coefficient, cm^3/g (= Koc*foc, as above)
C_G	=	concentration of chemical in the gas phase, g/cm^3
K_H	=	dimensionless Henry's Constant (= 41 H, as above)

Like the Hwang model, initial and boundary conditions are required for the solution to this model. The key initial condition is that the total concentration is constant to some depth, and that below this depth, the concentration is zero. The upper boundary condition is represented by a stagnant boundary layer condition, and the lower boundary conditions is that the total concentration is 0 at infinite depth. With these initial and boundary conditions, Equation (7-13) is solved using the Laplace transform method. This is not amenable to spreadsheet calculations. The EPA model, EMSOFT, was coded in fortran using original code supplied by Jury for his equations, and it performs this transformation. EMSOFT calculates water flux under user-specified water flux conditions, entering a positive flux amount (meaning a net leaching rate at that amount), 0 (no net leaching or evapotranspiration), or a negative flux amount (meaning a net evapotransiration rate) in units of cm/day. For this exercise, the solution at water flux = 0 will be assumed.

The parameters required for EMSOFT are provided in Table 7-3, and these include the initial soil concentration of 2,3,7,8-TCDD, C_0, the soil parameters foc, θ, ϕ, a, and BD, the water flux assumption, the depth of constant soil concentration, the exposure duration (or total time during which volatilization occurs starting from time t = 0 at the initial soil concentration, C_0), the boundary layer thickness, and the chemical-specific parameters D_g^{air}, D_l^{water}, Koc, H, and the 2,3,7,8-TCDD soil half-life. Of various output options in EMSOFT, average volatilization rate was selected.

$$C_G = K_H C_L \qquad (7\text{-}18)$$

III. Steady-State Solution to the Jury Model: This steady-state, simplified solution to the Jury model was used in Superfund's soil screening model. The simplifying assumptions (in addition to other assumptions of the Jury approach) which allowed for this solution were: 1) there is no stagnant boundary layer, 2) there is no water evapotranspiration or leaching

(equivalent to the selection of 0 water flux in the full Jury model described above), 3) the chemical is at a uniform concentration from the soil surface until depth d_z, and 4) there is no degradation of the chemical over time. The volatilization flux rate, J_s, at any given time after t=0 when the uniform soil concentration is C_{T0}, is given by:

$$J_s(t) = C_{T0} \left(\frac{D_E}{\pi t} \right)^{1/2} \left(1 - \exp \left(\frac{-d_z^2}{4 D_E t} \right) \right) \quad (7\text{-}19)$$

where:

J_s	=	volatilization flux, g/cm^2-sec
C_{T0}	=	initial total concentration on a volumetric basis, g/cm^3
D_E	=	effective soil diffusion coefficient, cm^2/sec
d_z	=	depth of uniform soil concentration at t=0
t	=	time, sec

Equation (7-19) was derived specifically for the case where there is a finite reservoir of contaminant to volatilize; i.e., where the depth of contamination, d_z, is meaningful. At infinite depth, this term drops out. With a combination of large enough d_z and small enough D_E, the exponential term quickly approaches 0, so the parenthetical approaches 1 and can be neglected in the solution. Mayer, et al. (1974) suggests that the infinite reservoir solution is violated for a finite reservoir when t (time) exceeds $(d_z^2)/(14.4*D_E)$. With dioxin parameters, D_E is calculated to be $2*10^{-10}$. Therefore, time t calculates out to over 1000 years with d_z equal to 10 cm before the infinite solution becomes violated. Needless to say, the infinite reservoir steady state solution can be used for dioxin, and the exponential term can be neglected. The total soil concentration, or concentration expressed as mass divided by a volume of (soil+soil pore space), is required for this solution, rather than just the soil concentration expressed as mass of contaminant divided by mass of soil to which it is adsorbed. As discussed above, total soil concentration is the sum of the concentrations in soil, soil air, and soil water, and for 2,3,7,8-TCDD and similarly very tightly sorbed contaminants, the total volumetric soil concentration can be estimated as BD * Cs. The effective soil diffusion is given by:

$$D_E = \frac{D_G^{air} K_H a^{10/3}/\Phi^2 + D_L^{water} \theta^{10/3}/\Phi^2}{BD\ Kds + \theta + aK_H} \quad (7\text{-}20)$$

where:

D_E	=	effective soil diffusion coefficient, cm^2/sec
D_g^{air}	=	chemical air-gas diffusion coefficient, cm^2/sec
D_l^{water}	=	chemical liquid diffusion coefficient in water, cm^2/sec
θ	=	volumetric water content, cm^3/cm^3, or unitless
a	=	soil air content, cm^3/cm^3, or unitless
ϕ	=	soil porosity, cm^3/cm^3, or unitless
BD	=	soil bulk density, g/cm^3
Kd	=	soil/water partition coefficient, cm^3/g (= Koc * foc, as above)
K_H	=	dimensionless form of the Henry's Constant (= 41H, as above)

As can be seen in this formulation, Equation (7-19), the maximum volatilization flux decreases as time increases. Again, the Jury algorithm considers the depletion of the surface residues as a function of time. The Superfund Soil Screening Guidance document (EPA, 1996) suggests that this formulation, Equation (7-19), be run several times over the exposure duration in order to determine the average flux. However, assuming the infinite reservoir solution which neglects the exponential term in Equation (7-19) (and like the Hwang model), the average flux can more easily be calculated as, 2 * J_s (t), where t is the full duration of volatilization flux. That is what is assumed for this exercise.

The parameters required for this simplified solution to the Jury model are provided in Table 7-3, and these include the initial soil concentration of 2,3,7,8-TCDD, C_0 , the soil parameters foc, θ, ϕ, a, and BD, the exposure duration, and the chemical-specific parameters D_g^{air}, D_l^{water}, Koc, and H.

IV. State-State, Infinite Reservoir, Vapor-Phase Diffusion Only: If the liquid phase in the mass flux Equation (7-15) above is neglected, than the flux through soil can be very simply calculated as:

$$J_s = -D_G \frac{C_{G1} - C_{G0}}{d_z} \quad (7\text{-}21)$$

where:

J_s	=	chemical mass flux per unit soil are per unit time, g/cm^2-sec
D_G	=	effective soil diffusion coefficient, cm^2/sec
	=	$(a^{10/3}/\phi^2)\ D_g^{air}$; a, ϕ, and D_g^{air} defined as above
C_{G1}	=	concentration of the contaminant in soil air-filled pore space, g/cm^3
C_{G0}	=	concentration of the contaminant in air at the soil-air interface, g/cm^3
d_z	=	depth over which a constant concentration is assumed, cm

Maximum vapor phase diffusion occurs when C_{G0}, the concentration of the contaminant in air at the soil-air interface (essentially just above the soil surface), is set to 0.0, which is done for this solution. This assumes, essentially, that wind is sufficiently high to cause a 0 concentration directly above the soil. The concentration in air-filled pore space, C_{G1}, is simply solved as, (K_H Cs)/Kds, as described above. The depth of the soil column will be assumed to be 10 cm in this example.

The parameters required for this simplified vapor diffusion solution are provided in Table 1, and these include the initial soil concentration of 2,3,7,8-TCDD, C_0, the soil parameters foc, ϕ, a, and BD, and the chemical-specific parameters D_g^{air}, Koc, and H.

V. Results of Alternate Soil Volatilization Model Testing: The results of this simple test are shown in Table 7-4. This model comparison test showed that the Hwang model predicted an average flux over 30 years roughly four times higher than the average flux predicted by the full Jury model, and about three times higher than the simplified Jury model used in the Superfund Soil Screening methodology. The close match between the full Jury model coded in Fortran in EMSOFT and the simplified Jury solution coded into the spreadsheet was evidence that both models were correctly coded and used (or that they were both incorrect in the same way, which is unlikely). The exact reason for this three- to four-fold difference in the Jury versus the Hwang models was not investigated, and could lie in differences in assumed boundary conditions (Hwang, et al. (1986) discusses differences in boundary conditions between his and Jury's models). In any case, it is judged that both models predict comparable volatilization fluxes. On

the other hand, the vapor diffusion model predicted volatilization rates that were 100 times less than the Jury models and about 250 times lower than the Hwang models. The reason for this discrepancy could not be ascertained.

The Jury model was run altering the boundary layer assumption and the half-life assumption. The simplified Jury solution assumes no boundary layer to offer resistence to volatilization. That was one key reason that the simplified model predicted higher concentrations than the full Jury model. When the boundary layer assumption was reduced from 0.5 cm to 0.01 cm, the volatilization rate predicted by EMSOFT increased slightly from $2.8*10^{-19}$ to $3.0*10^{-19}$ g/cm^2-sec. Another simplification of the Soil Screening Methodology solution was that no soil degradation was assumed. The full Jury model in EMSOFT does allow for consideration of soil degradation. When the half-life was assigned a value of 25 years, which was what has been assumed for dioxins which had deposited in soils from distant sources in this document (depositing by air from incinerators or overland by erosion from contaminated soil sites), the average volatilization dropped slightly from $2.8*10^{-19}$ to $2.2*10^{-19}$ g/cm^2-sec.

These differences between the Hwang and Jury models are insignificant considering that the compounds modeled by this methodology - the dioxins, furans, and PCBs, are all relatively tightly bound and resist degradation in soil, so that losses in the 10^{-19} g/cm^2-sec range represent a minisicule part of the entire soil reservoir.

VI. Alternate Approaches for Dispersion of Soil-Emitted Dioxins: Near-field and far-field dispersion models are used to estimate air concentrations resulting from soil emissions, including volatilization and wind erosion, for the soil contamination source category. The near-field model can be used to estimate concentrations which occur on-site whereas the far-field model can be used to estimate off-site air concentrations. An alternate approach to estimating on-site dispersion given a volatilization flux is the "box-model" approach. This simple approach can be visualized as follows: air above soil is contained within a structure which has two walls, say a north and south wall, and a ceiling - wind blows through the building in an east-west direction mixing the volatilized flux. This is expressed mathematically as:

$$C_{air} = \frac{FLUX\ AREA\ 10^6}{b\ U_{mix}\ Z} \qquad (7\text{-}22)$$

where:

C_{air}	=	total concentration of contaminant in air, $\mu g/m^3$
FLUX	=	average volatilization + wind erosion flux rate of contaminant from soil, g/cm^2-sec
AREA	=	area over which flux occurs, cm^2
b	=	side length perpendicular to wind direction, m
U_{mix}	=	mean annual wind speed corresponding to mixing zone height, m/sec; estimated as ½*Um, where Um is average wind speed
z	=	mixing zone height, m
10^6	=	converts g to µg

Before testing the box-model equation, results for the approach used in this assessment are summarized. The key factors impacting air concentration calculations for the soil contamination source category include characteristics of the contaminant (Henry's Constant, etc.), the duration of exposure, the area over which contamination occurs, and whether the near field or far field dispersion algorithms are used. For the demonstration of the soil contamination scenario, Scenario 3, the contaminated soil area was 40,000 m^2 (10 acres). The exposure duration was 30 years. The flux of 2,3,7,8-TCDD was $1.11x10^{-18}$ g/cm^2-sec. The air concentration estimated for Scenario 3 where the exposure site was 150 meters from the site of soil contamination was 0.0043 pg/m^3. This calculation used the far field dispersion algorithm. When the flux rate is input into the near field algorithms, the air concentrations is a little over ten times higher at 0.045 pg/m^3.

The values used to evaluate the box model approach were the fluxes, as given above, the mixing zone wind speed, 2 m/sec, which is half the average wind speed assumed in this assessment, the areas noted above, the side length, estimated as the square root of the area, and a mixing zone height estimated initially at 2 m. The box-model air concentration is estimated at 0.55 pg/m^3. This is 10 times higher than the near-field dispersion modeling and 100 times higher than the far-field solution.

An uncertain parameter for both modeling approaches is the area of soil contamination. The mixing zone height for the box model is also a parameter of uncertainty. Users of the box model approach have often assumed a conservative 2 m height approximating the height of exposed individuals. However, others have claimed this is far too low a mixing height, suggesting 10 meters or even an atmospheric height closer to 100 meters. Higher mixing zone heights would have brought the box model estimations more in line with estimations made in this

assessment. The closest analogous parameter in the dispersion model to the mixing zone height is the height of exposed individual, which is more unambiguously the breathing zone height of 2 m.

One key assumption concerning the exposure site air concentrations resulting from a distant area of soil contamination should be questioned. The current approach assumes that air-borne contaminates originate at the site of contamination and are transported to the site of exposure. On the other hand, this assessment also assumes that exposure site soil becomes contaminated over time due to erosion. It is at least plausible that volatilization and wind erosion from soils other than the area of elevated contamination would contribute to air-borne contamination, and concentrations to which individuals are exposed to at sites of exposure near sites of contamination.

This was tested by using the near field algorithms and assuming soil concentrations predicted to occur at the exposure site. In more detail, the soil contamination demonstration scenario included a 10 ha field at 1 ppb 150 m from the exposure site, also at 10 ha. The soil concentrations estimated to occur at the exposure site were 0.39 ppb for a 2-cm no-till depth and 0.06 ppb for a 20 cm tilled depth. The near field algorithms for volatilization, wind erosion, and dispersion were run starting with these concentrations, and resulting concentrations were compared with those estimated to occur only from volatilization and wind erosion from the contaminated site followed by transport to the exposure site. The air concentration estimated to occur from untilled soil is about 4.3 times higher than that estimated to occur from the off-site area and transported; the air concentration estimated to occur from tilled soil is 25% less than estimated to occur from volatilization and transport.

This might imply that exposure site air concentrations are being underestimated if air concentrations at the site of exposure are assumed to only originate at the site of contamination, and not also at the site of exposure, or even from other areas. This exercise implies that the underestimation might be less than a factor of 5.0. Of course, this conclusion is contingent on the off-site impact algorithms which have estimated that a 0.39 or a 0.07 ppb soil concentration will result 150 meters from an area whose concentration is 1.00 ppb.

7.2.5. Alternate Models for Estimating Plant Concentrations from Soil Concentrations

The models of this assessment separate above and below ground vegetation for estimating concentrations. Root concentrations (roots are below ground vegetation) are a function of soil water concentrations and a Root Concentration Factor, RCF. Above ground vegetation, which in this assessment include above ground fruits and vegetables, pasture grass, and cattle feed, are

modeled as a function of vapor phase transfers and wet plus dry particle depositions. This section examines one alternate approach for above ground vegetation; alternate approaches for below ground vegetation could not be found.

One approach to modeling plant concentrations would be with passive uptake via evapotranspiration. The assumption here is that soluble phase contaminants move passively with transpiring water. This approach has been applied for contaminants which are soluble in water. However, nearly all the evidence suggests that this would not be appropriate for the dioxin-like compounds. Specifically, the evidence suggests that residues do not translocate to within portions of either above or below ground vegetation. Such would be case for soluble contaminants moving passively with transpiring water. This conventional wisdom was, however, challenged with recent experiments by Hulster, et al. (1994) on vegetation of the cucumber family. Their results were most striking for zucchini, which showed uniform plant concentrations from inner to outer portions of the zucchini fruit, and the highest whole fruit concentrations they had ever measured, despite careful experimental conditions which physically isolated the fruit from the soil. Pumpkins also showed high plant contamination, with more expected plant concentrations measured for the cucumber. Assuming the vegetation of this assessment - fruit/vegetables for human consumption and vegetation of the beef/dairy food chain - do not behave as in the Hulster, et al. (1994) experiments, than translocation to inner plant parts is not expected.

The specific issue of uptake and translocation via transpiration was investigated using soybean and corn plants grown hydroponically in carefully constructed growth chambers (McCrady, et al., 1990). Roots and the hydroponic growth solution were separated from the shoots and leaves of these plants using two separate chambers, one inverted over the other. Separate air-flow systems for each chamber included traps for volatile organics. Mass balance on the tritiated TCDD experiments was able to recover 98% in the soybean experiment and 86% for the corn experiment. Most of the recovered material was found in the roots; 75% for soybeans and 67% for corn, with the second highest recovery was on the inside surface of the root chamber, around 15% for both experiments. Recovered TCDD was also found, in order of decreasing percentage, in the growth solution, root chamber air, shoot chamber air, and shoots. The recovery from the shoots was negligible at 0.004% and 0.001% of the total TCDD for the soybean and corn, respectively. McCrady, et al. (1990) concluded that transpiration stream transport of 2,3,7,8-TCDD to plant shoots is an insignificant mechanism of plant contamination, and that volatilization of TCDD is an important transport mechanism that can result in significant quantities of airborne TCDD being absorbed by plant shoots.

Briggs, et al. (1982) provide another way to evaluate the translocation of contaminants from roots to above ground vegetation. Experiments with barley roots in growth solution led to the development of an empirical parameter describing the efficiency of transport of organic chemicals to plant shoots from root uptake. This parameter is called the Transpiration Stream Concentration Factor (TSCF) and is defined as (concentration in transpiration stream)/(concentration in external solution). The empirical formula presented for this factor is:

$$TSCF = 0.784\ e^{-[\log Kow - 1.78]^2 / 2.44} \quad (7\text{-}23)$$

Given a log Kow for 2,3,7,8-TCDD of 6.8, TSCF is solved for as roughly $2 * 10^{-5}$. Assuming that the concentration of external solution concentration for the experimental conditions of Briggs' experiments is equivalent to the concentration in soil water in a field situation, then the TSCF for 2,3,7,8-TCDD implies that the transpiration stream water of a plant is over 5 orders of magnitude lower than the soil water concentration. Like McCrady's experiments, this also shows the insignificance of translocation of residues from roots to shoots.

The one approach that was found that might have been used in the place of the algorithms for above ground vegetation, is simpler and more general in nature. It was developed from field data on above ground vegetation concentrations correlated to soil concentrations of contaminants and the octanol water partition coefficient (Travis and Arms, 1988). This correlation led to an empirical bioconcentration factor for vegetation, B_v, regressed against the contaminant log Kow, and defined by the authors as the concentration in above ground plant parts divided by the concentration in soil:

$$\log B_v = 1.588 - 0.578 \log K_{ow} \qquad n = 29,\ r = 0.73 \quad (7\text{-}24)$$

With 2,3,7,8-TCDD log Kow equal to 6.8, the B_v translates to a value of 0.0041. Note that this B_v is defined identically to the plant:soil contaminant concentration ratios that are discussed in Section 7.3.10 below which compares the model's estimations of these ratios with those found under experimental conditions. As discussed in that section, plant:soil ratios calculated using the soil contamination algorithms were in the range of 10^{-5} for bulky vegetables and 10^{-3} for leafy vegetation. It is not clear how to compare the B_v of 0.0041 to these ratios without retrieving the studies which Travis and Arms (1988) used, although this value is clearly

higher than the fruit/vegetable ratio and consistent with the grass/feed ratios. The studies used by Travis and Arms were not retrieved. An examination of the chemicals used by Travis and Arms show that 25 of 29 used are pesticides, which suggests that plant concentrations may be those of agricultural crops, which might make it a closer kin to bulky vegetables rather than leafy vegetation. If so, a comparison of the above-ground vegetable 10^{-5} ratio with this 0.0056 ratio would be appropriate. An examination of the chemicals also reveals that 10 of the 29 are moderately to very soluble (log Kow less than 4.00), while others are similarly insoluble as the dioxin-like compounds (including DDT, TCDD, Aroclor 1254, and others; 15 with log Kow greater than 5.0). Developing such an empirical relationship which mixes chemicals whose mode of action is passively with water (which would be the case with aldicarb and simazine, among others on the list) with those whose mode is through vapor transfers or particle depositions (TCDD, and so on) does not appear to be technically valid. Nonetheless, the fact that the Travis and Arms B_v is much higher than the plant:soil ratio for vegetables generated for the soil contamination source category demonstration is noted. Also, there is no provision in the Travis and Arms approach to distinguish between bulky and leafy vegetation, and this appears to be an important consideration for the dioxin-like compounds.

7.2.6. Alternate Modeling Approaches for Estimating Beef and Milk Concentrations

Webster and Connett (1990) compared five models which estimated the 2,3,7,8-TCDD content of cow's milk from 2,3,7,8-TCDD air contamination. The five models were described in Michaels (1989), Connett and Webster (1987), Stevens and Gerbec (1988), Travis and Hattemer-Frey (1987), and McKone and Ryan (1989). Ironically, a sixth model by Fries and Paustenbach (1990), noted by Webster and Connett as available but received too late for inclusion in their article, formed the basis for the approach taken in this assessment.

All five models compared by Webster and Connett have the same basic framework. Particulate-bound 2,3,7,8-TCDD deposits onto the ground and vegetation (cattle feed and pasture grass). Algorithms to estimate resulting vegetation and soil concentrations in these models are the same ones used in this approach, although parameter assignments are different. A daily dosage of 2,3,7,8-TCDD to the cattle is calculated and converted to a concentration in whole milk using a "biotransfer factor". This same structure was used to estimate concentrations in beef, using a beef biotransfer factor different than the milk biotransfer factor. Mathematically, this is expressed as:

$$C_{m,b} = F_{m,b} \; Dose \qquad (7\text{-}25)$$

where:

$C_{m,b}$	=	concentration in whole milk/beef, mg/kg
$F_{m,b}$	=	milk/beef biotransfer factor, day/kg
	=	$(BCF_{mf,bf} * f_{m,b})/Q$
$BCF_{mf,bf}$	=	experimentally-derived unitless bioconcentration factor defined as the concentration in milk fat/beef fat divided by the concentration in the experimental vehicle (cattle feed, e.g.); similar to BCF of this assessment
$f_{m,b}$	=	fat content of milk/beef, unitless
Q	=	daily mass intake of cattle in experiment, kg
Dose	=	total daily dose of 2,3,7,8-TCDD, mg/day
	=	sum $(a_j * c_j * Q_j)$
a_j	=	relative bioavailability on intake vehicle j (soil, air, vegetation, etc)
c_j	=	concentration of 2,3,7,8-TCDD in vehicle j, mg/kg (or equivalent units)
Q_j	=	mass of vehicle j intake, kg (or equivalent units)

Further details on the models can be found in their primary references and in Webster and Connett's comparison. Some highlights, including comparisons of the five approaches to the approach taken in this assessment, are:

1) Two of the approaches, that of Stevens and Gerbec (1988), and McKone and Ryan (1989), consider inhalation of contaminated air by cattle to contribute to their daily dose of 2,3,7,8-TCDD. One of the approaches, that of Travis and Hattemer-Frey (1987), considers ingestion of contaminated water by cattle. A later assessment by Travis and Hattemer-Frey (1991) has all the components of their earlier assessment, and adds cattle inhalation exposures. This assessment does not consider cattle inhalation of contaminated air nor ingestion of contaminated water in estimating beef and milk concentrations. However, these intakes were shown to be insignificant when estimated by these researchers. Stevens and Gerbec estimate inhalation contributions to be less than 0.05% (0.0005 in fractional terms) of total daily dose, or an essentially insignificant amount. Travis and Hattemer-Frey (1991) estimate inhalation to contribute between 0.3 and 1.0% to milk and beef concentrations, respectively. McKone and Ryan (1989) did not provide sufficient information to easily determine the relative contribution

of inhalation on estimation of cattle beef and milk concentrations by their estimations. Travis and Hattemer-Frey (1987, 1991) estimate water contributions to be less than 0.01% (0.0001) of total daily cattle dose of 2,3,7,8-TCDD.

2) None of the approaches considered vapor phase transfers from air to plant, although Webster and Connett recommended its inclusion in their article. The later assessment by Travis and Hattemer-Frey (1991) on 2,3,7,8-TCDD did include vapor phase transfers into vegetation consumed by cattle. According to results of the example scenarios in this assessment, these transfers appear to be particularly critical, and this was also the conclusion of Travis and Hattemer-Frey based on their modeling results.

3) Two of the assessments, that of Stevens and Gerbec (1988) and Fries and Paustenbach (1990) considered a period of residue-free grain only diet for a period of time before slaughter for purposes of fattening the cattle. Stevens and Gerbec (1988) assumed that the residues in cattle would depurate during the last 130 days of their lives on this regime. Assuming a half-life of 2,3,7,8-TCDD in cattle of 115 days, they showed a 54% reduction in beef concentrations due to this practice. Fries and Paustenbach (1990) note that cattle can gain as much as 60-70% in body weight, so dilution can also result in lower beef concentrations at slaughter. Based on these findings, a "feedlot fattening" factor of 0.50 was used in the air-to-beef model validation exercise that is described in Section 7.3.12. The procedures to estimate a reduction in concentration used by these researchers is straightforward. Assuming first order kinetics sufficiently describes reduction in concentrations during a period prior to slaughter, the fractional reduction during such a period is given as, $1 - \exp(-k_d t)$, where k_d is the depuration rate constant, in $days^{-1}$, and t is the depuration period, in days. The rate constant can be estimated from the depuration half-life, HL, as 0.693/HL. The 115 day half-life assumed by Stevens and Gerbec (1988) corresponds to a rate constant of 0.006 day^{-1}, and assuming a 130 day depuration period, the fractional reduction is easily calculated as 0.54 (i.e., $1 - \exp(-k_d t)$). The amount remaining after 130 days is estimated as the initial amount multiplied by 0.46 (i.e., $\exp(-k_d t)$).

4) Two of the assessments did not assume any cattle ingestion of contaminated soil, and two of the assessments estimated the contribution to milk concentrations due to ingestion of contaminated soil was minor at 1 and 2%. Only one of the assessments, Travis and Hattemer-Frey (1987), estimated any significant impact due to soil ingestion, attributing 19% of the concentration due to ingestion of contaminated soil. Their later assessment (Travis and Hattemer-Frey (1991)) estimated soil to contribute 29 and 20% of beef and milk concentration estimations, respectively. They estimated this high a contribution by contaminated soil even though they assumed that contaminated soil comprised 1% of the total dry matter intake by cattle.

Fries and Paustenbach (1990) recognized the importance of cattle soil ingestion, evaluating scenarios where cattle soil ingestion ranged from 1 to 8% of total cattle dry matter intake.

The example scenarios in Chapter 5 assumed that beef cattle ingestion of contaminated soil was 4% of their total dry matter intake, and 2% of a dairy cattle's intake was contaminated soil. The percentage of beef and milk concentrations of 2,3,7,8-TCDD attributed to soil, feed, and pasture grass, when soil contamination is the source and when stack emissions are the source, was examined in Section 6.3.3.6 in Chapter 6. It is noted there that soil ingestion appears significantly more critical for soil contamination as compared to stack emissions. Soil ingestion by beef and dairy cattle explain around 90% of final beef and milk concentration for soil sources. On the other hand, soil ingestion explained only around 5% of final beef and milk concentration for the stack emission source.

The earlier literature noting only 1-2% impact by soil ingestion were more analogous to the stack emission source category than the soil source category, in that impacts were estimated starting from air-borne contaminants depositing onto soils and vegetation. One difference in the assessments estimating the 1-2% impact with this assessment indicating about 5% impact was that the other assessments assumed less soil ingestion, 0.5% in Stevens and Gerbec (1988) and 1-3% in Travis and Hattemer-Frey (1987) and McKone and Ryan (1989).

The critical focus of the Webster and Connett (1990) comparison, is the milk fat bioconcentration factor, BCF_{mf}. As shown in Equation (7-25), the biotransfer factor, F_m, is estimated using experimental data which yields a milk fat bioconcentration factor, BCF_{mf}. Experiments most relied upon by these modelers are those described in Jensen, et al. (1981), and Jensen and Hummel (1982). A key difference in the early modeling approaches is the interpretation of these two and other studies and the resulting assignment of BCF_{mf}, with values ranging from 5 to 25. Webster and Connett (1990) discuss issues of experimental interpretation.

Parameter assignments and assumptions (cattle soil ingestion versus no ingestion, etc.) obviously all impact estimations and can be a critical source of variation and uncertainty in estimates of beef and milk concentrations. The uncertainty associated with the modeling framework described above was explored by McKone and Ryan (1989) using Monte Carlo techniques. They found that the 90% confidence range for human exposure to 2,3,7,8-TCDD, where the source was air contamination and the human exposure route was through milk, spanned two to three orders of magnitude.

The approach taken by all five researchers centers on the milk biotransfer factor, abbreviated F_m in Webster and Connett (1990) and in units of day/kg. Beef bioaccumulation was modeled in the same way using a beef biotransfer factor, F_b. Travis and Arms (1988) developed

this concept to the fullest, taking several data sets from the literature on a variety of contaminants and animals, to derive empirical formulas for F_b and F_m, which they termed B_b and B_m, as a function of contaminant octanol water partition coefficient, Kow:

$$\log B_b = \log Kow - 7.6 \quad (7\text{-}26a)$$

$$\log B_m = \log Kow - 8.1 \quad (7\text{-}26b)$$

Given a log Kow of 6.8 for 2,3,7,8-TCDD (assumed in this assessment), B_b is solved for as 0.16 and B_m is solved for as 0.05. Travis and Hattemer-Frey (1991) used 0.80 and 0.03 for 2,3,7,8-TCDD B_b and B_m.

Simple transformations can show how the earlier approaches, summarized above in Equation (7-25), and the approach of Fries and Paustenbach (1990) (which is the approach used in this assessment), are the same. First, the concentration of dioxin-like compounds in the fat of beef and milk is given in this assessment by (also see Chapter 4):

$$C_{fat} = BCF\ DF_s\ B_s\ AC_s + BCF\ DF_g\ AC_g + BCF\ DF_f\ AC_f \quad (7\text{-}27)$$

where:

C_{fat} = concentration in beef fat or milk fat, mg/kg
BCF = bioconcentration ratio of contaminant as determined from cattle vegetative intake (pasture grass or feed), unitless
DF_s = fraction of cattle diet that is soil, unitless
B_s = bioavailability of contaminant on the soil vehicle relative to the vegetative vehicle, unitless
AC_s = average contaminant soil concentration, mg/kg
DF_g = fraction of cattle diet that is pasture grass, unitless
AC_g = average concentration of contaminant on pasture grass, mg/kg
DF_f = fraction of cattle diet that is feed, unitless
AC_f = average concentration of contaminant in feed, mg/kg.

Transformation steps are: 1) factor out the BCF from Equation (7-27) , 2) multiply Equation (7-27) by unity expressed as Q/Q, where Q equals total dry matter intake by cattle; 3) the multiplication of Q by the diet fraction terms, DF_s, DF_g, and DF_f, gives the values for soil dry matter intake, Q_s, grass - Q_g, and feed - Q_f, 4) with BCF factored out, and Q*DFs replaced by Q_s, etc., the parenthetical now reads, (Qs*Bs*ACs + Qg*ACg + Qf*ACf) - this is the "Dose" term defined earlier in Equation (7-25), 5) finally, multiply the right hand side of Equation (7-27) by fat content, say f_m for milk, which would transform the right and hence left hand side of that equation to whole product concentration. Transformed Equation (7-27) is analogous to Equation (7-25):

$$C = \frac{BCF\ f_m}{Q} \left[Q_s\ B_s\ AC_s + Q_g\ AC_g + Q_f\ AC_f \right] \qquad (7\text{-}28)$$

While this analysis has shown how the biotransfer approach can be transformed into the bioconcentration approach of this methodology, one has to be careful with the assignment of the biotransfer and bioconcentration parameters. The following analysis shows why the Travis and Arms (1988) empirical algorithms shown above in Equations (7-26a) and (7-26b) are not appropriate for dioxin-like compounds.

McLachlan, et al. (1990) kept an inventory of the dioxins ingested by a lactating cow as well as the dioxins being emitted through the milk. This was the data used to develop the bioconcentration factors for the dioxins used in this assessment. The volume of milk generated by the cow was also given, allowing for the calculation of the biotransfer factor. The experimental biotransfer factor for milk derived from McLachlan's data is compared against the factor which can be estimated using the log Kow of the individual dioxin congeners (the congener log Kow are listed below in the issue regarding TEQ parameters) combined with the Travis and Arms (1988) biotransfer equation:

Congener	Travis and Arms B_m	McLachlan B_m
2378-TCDD	0.03	0.01
12378-PCDD	0.03	0.01
123478-HxCDD	0.49	0.006
123678-HxCDD	0.16	0.005
123789-HxCDD	0.16	0.005
1234678-HpCDD	1.26	0.001
OCDD	0.31	0.001

2378-TCDF	0.03	0.003
23478-PCDF	0.07	0.009
12378-PCDF	0.05	0.002
123478-HxCDF	0.16	0.007
123678-HxCDF	0.16	0.006
123789-HxCDF	0.16	0.006
234678-HxCDF	0.16	0.005
1234678-HpCDF	0.63	0.001
1234678-HpCDF	0.63	0.003
OCDF	5.00	0.001

It is clear that the Travis and Arms' biotransfer relationship will greatly overestimate the transfer of dioxins into milk, given the data of McLachlan. It would appear from McLachlan's data that as the log Kow increases, the biotransfer decreases, which is the opposite of the trend implied from the Travis and Arms' relationship.

The Travis and Arms trend is explainable, however, given the data from which Travis and Arms developed their relationship. In their literature article, they supplied the log Kow and the experimentally derived biotransfer factor for all the data points they used to derive their empirical relationship. For determining a milk biotransfer factor, they had 28 data points, and only 6 of them were for chemicals with log Kow greater than 6.00. The range of log Kows for data they had was 2.8 to 6.5. The dioxin-like compounds, on the other hand, have log Kow that range from 6.5 to 8.0. In this 2.8-6.5 log Kow range, it would appear that as log Kow increases, the tendency to bioaccumulate in milk increases. Interestingly, of the 6 data points Travis and Arms had for chemicals with log Kow over 6.00, their actual data point leads to a higher biotransfer point than is calculated with their derived empirical relationships:

Chemical	log Kow[1]	B_m from the data[2]	B_m calculated[3]
Aroclor 1254	6.47	0.01	0.02
Chlordane	6.00	0.0004	0.008
DDD	6.02	0.003	0.008
fenvalerate	6.20	0.0008	0.01
mirex	6.89	0.009	0.06
TCDD	6.15	0.01	0.01

[1] as used by Travis and Arms
[2] the actual data point claimed by Travis and Arms (1988)
[3] as calculated with Equation (7-26b)

As discussed above, it would appear that the trend of higher bioaccumulation with higher log Kow is true for the range of log Kow used by Travis and Arms - 2.8 to 6.5. However, for the dioxin congeners where log Kow is higher at 6.5 to 8.0, the trend is the opposite - the biotransfer decreases as the log Kow increases. This could be due to greater rates of metabolism for organic compounds of higher log Kow, or just for the dioxins, leading to lower concentrations in the animal food products. In any case, it is clear that the Travis and Arms' biotransfer factor equations for beef and milk are not appropriate for the dioxin-like compounds, and perhaps as a general rule, for other organic compounds with log Kow 6.5 or higher.

Douben, et al. (1997) compares three approaches for air-to-plant-to-milk modeling. One of the approaches is the one of this document. The second employs the "carryover" factor, which is very similar to the biotransfer factor defined above. Whereas the biotransfer factor is defined as the concentration in milk (mg/L, e.g.) divided by the mass of dioxin ingested (mg/day), the carryover factor is defined as the mass of compound excreted in milk (mg/day) divided by the mass of dioxin ingested (mg/day). Douben, et al. (1997) assigns values to the carryover factor based on the data of McLachlan, et al. (1990). The third approach is the "scavenging" approach developed by McLachlan (1995) and described above for the transfer of dioxins from air to grass. McLachlan (1995) developed the concept further to show that the concentration in milk can be estimated as a function of the total mass of dioxins ingested by the dairy cow (equal to the dry weight of vegetation consumed times the scavenging coefficient times the air concentration) times the absorption fraction (the amount absorbed by the dairy cow) divided by the mass of milk excreted each day:

$$C_{milk} = \frac{CA_j \left(SC_g M_g + SC_s M_s \right) ABS_j}{LAC} \qquad (7\text{-}29)$$

where:

C_{milk} = milk concentration, ng/kg (ppt; 1 liter = 1kg)
CA_j = concentration of congener j in air, ng/m^3
SC_g = scavenging coefficient for grass, m^3/g
M_g = mass of grass ingested, g/day
SC_{cs} = scavenging coefficient for corn silage, m^3/g
M_{cs} = mass of corn silage ingested, g/day
ABS_j = absorption fraction for congener j

LAC = lactation rate, kg/day

Assuming 9 kg dry weight of grass and 4 kg dry weight of corn silage ingested per day, and scavenging coefficients for grass and silage to be 9 and 4.5 m^3/g, respectively, Douben, et al (1997) reduced the parenthetical above to a constant of 100,000 m^3/day (actually calculates to 99,000). They were able to test the model assuming a lactation rate of 0.6 kg/day and using absorption efficiencies provided in McLachlan (1995). While differences in specific congener/model predictions were noted, Douben, et al. (1997) generally found comparable predictions for milk TEQ concentrations - all were within a factor of 5 of observed concentrations.

One critical theoretical assumption not explored in these modeling comparison exercises is whether 2,3,7,8-TCDD and other congeners bioaccumulate equally in beef fat and milk fat - are the BCF_{mf} and BCF_{bf} equal? Fries and Paustenbach (1990) emphasize that differences in observed concentrations in beef and milk are critically a function of the differences in the diets of cattle raised for beef versus those raised for milk. They assumed that the beef and milk bioconcentration factor was equal for their example calculations. The key difference Fries and Paustenbach cite is the tendency for beef cattle to graze while lactating cattle are more often barn fed. Grazing cattle intake more contaminated soil than barn fed cattle. Fries and Paustenbach derived F for higher chlorinated dioxin-like compounds from experimental data, noting that the F value is less with higher chlorination. Webster and Connett (1990) made the analogous observation, saying that 2,3,7,8-TCDD equivalents transferred from air to milk less efficiently than 2,3,7,8-TCDD. This is also consistent with the data of McLachlan, et al (1990), which is used in this assessment for assignment of BCFs to dioxin-like compounds.

Besides different diets between beef cattle and lactating cows is that lactation provides a mechanism for dioxin excretion from the body, which theoretically would lead to body fat concentrations in lactating cows being less than body fat concentrations in non-lactating cattle which don't have this excretion mechanism. However, researchers have observed that the dioxin concentrations in the fat of milk and of body fat in non-lactating cattle are similar. McLachlan (1994) attributes this to the fact that cattle are most often slaughtered while they are still growing and increasing their body fat reservoir. Therefore, dioxins appear to reach steady state in the fat of non-lactating cattle at concentrations similar to those found in cow's milk.

Some conclusions from this analysis of these efforts for estimating bioconcentration in beef and milk are:

- Although the biotransfer and carryover frameworks look different than the framework used in this assessment, they are actually the same with a simple mathematical transformation;
- All of these approaches are empirical; that is, values for the critical dioxin-specific parameters (scavenging coefficients, carryover factors, bioconcentration factors, biotransfer factors) are developed from field data. When they are developed by different researchers on different field data, they will (of course) not predict equally. However, and as evidenced by the results of Douben, et al. (1997), they all appear to predict milk TEQ concentrations about equally.
- A caution is noted, nonetheless, with the use of the Travis and Arms (1988) empirical algorithm for the assignment of biotransfer factors for the dioxin compounds: as described above, this empirical relationship does not hold for the dioxin-like compounds, which have higher log Kow than the log Kow of the compounds used by Travis and Arms (1988) to develop their relationship. Provided above are biotransfer factors for dioxins developed from the same data used to develop the bioconcentration factors of this methodology.
- The possible dosage to cattle of 2,3,7,8-TCDD via contaminated air or water was considered in earlier assessments, but was not found to be a significant pathway, and was not considered in this assessment;
- Earlier assessments (before 1990) did not consider vapor phase transfers to vegetation consumed by cattle; key studies in the literature as well as the results of the demonstration scenarios suggest that this transfer is particularly critical;
- Even though the structure of the analysis has been consistent from the earlier to the current approaches, different assumptions on parameter values greatly impacts modeling results. The critical bioconcentration factor, earlier termed BCF_m (for milk) and termed simply BCF in this assessment, has been estimated to be between 5 and 25 for 2,3,7,8-TCDD in different assessments. This assessment uses a BCF value of 5.76 for 2,3,7,8-TCDD. Using Monte Carlo techniques on this model structure for estimating human exposure to milk resulting from air contamination of 2,3,7,8-TCDD, McKone and Ryan (1989) showed a 90% confidence interval spanning 2 to 3 orders of magnitude.

7.2.7. An Alternate Approach to Vapor/Particle Partitioning in the Air

Chapter 3 described the application of the Junge (1977) and Pankow (1987) model for partitioning air-borne dioxin-like compounds into vapor and particle phases. The governing equation for this model is:

$$\phi = \frac{c\,\Theta}{p^{\circ}_{L} + c\,\Theta} \qquad (7\text{-}30)$$

where:

ϕ = fraction of the compound adsorbed to aerosol particles

p°_{L} = saturation liquid phase vapor pressure of the pure compound at ambient temperature, Pa

Θ = the particle surface area per unit volume of air, cm^2 aerosol/cm^3 air

c = a constant which is related to the difference between the heat of desorption from the particle surface, Q_d, and the heat of vaporization of the compound, Q_v. The value of c is often estimated at 17.2 Pa-cm

A disadvantage to using this model is that the parameters Θ and c in this equation must be estimated as they cannot be measured directly. There is also uncertainty is the saturation liquid vapor pressure, p°_{L}, which must be estimated from the solid-phase vapor pressure, p^{o}_{S}. Assignment of these parameters and the development of the vapor/particle partitioning algorithm is provided in Chapter 3.

A second model was developed in the latter part of the 1990s and is now widely used to characterize the partitioning of semivolatile organic compounds to aerosol particles (Finizio et al. 1997, Harner and Bidelman, 1998; Pankow, 1998). The derivation of this model begins with this alternate equation for the particle fraction, ϕ:

$$\phi = \frac{C_p\,(TSP)}{C_g + C_p\,(TSP)} \qquad (7\text{-}31)$$

where:

ϕ = fraction of the compound adsorbed to aerosol particles

C_p = the concentration of semivolatile compounds associated with aerosols, ng/μg particles
C_g = the gas-phase concentration, ng/m^3
TSP = the total suspended particle concentration, μg/m^3

Defining the ratio of the particle phase to the gas phase (C_p/C_g) as K_p, a particle-gas partition coefficient, and dividing all terms on the right side of the equation by C_g, Equation (7-31) can be rewritten as:

$$\phi = \frac{K_p\ (\ TSP\ )}{1\ +\ K_p\ (\ TSP\ )} \qquad (7\text{-}32)$$

Once deriving K_p, ϕ can be solved for in this equation. K_p can be measured in the field, but alternately it has been related to the octanol air partition coefficient, Koa (Finizio et al., 1997):

$$K_p = 10^{-9}\ K_{oa}\ f_{om}\ (\gamma_{oct}/\gamma_{om})(M_{oct}/M_{om})/\rho_{oct} \qquad (7\text{-}33)$$

where:

K_p = particle-gas partition coefficient, m^3/ng
K_{oa} = octanol air partition coefficient, dimensionless
f_{om} = fraction of organic matter in the aerosol involved in partitioning
$\gamma_{oct,\ om}$ = activity coefficients in octanol and aerosol organic matter
$M_{oct,\ om}$ = molecular weights of octanol (130 g/mol) and the organic matter
ρ_{oct} = density of octanol, 820 kg/m^3

Simplifying assumptions that have been made for this formulation include that γ_{oct}/γ_{om} and M_{oct}/M_{om} are equal to 1 (Bidleman and Harner, 2000), leading to:

$$Log\ K_p = Log\ K_{oa} + Log\ f_{om} - 11.91 \qquad (7\text{-}34)$$

Bidleman and Harner (2000) make the further simplification that urban aerosols contain 15% carbon, present as compounds with the average molecular formula of octanol (74% carbon), thus leading to an assignment of 0.20 for f_{om}, and this equation:

$$Log\ K_p = Log\ K_{oa} - 12.61 \quad (7\text{-}35)$$

The octanol air partition coefficient is directly measurable at ambient temperatures and has been reported for several classes of semivolatile organic compounds, including PCBs (Harner and Bidleman, 1996; Komp and McLachlan, 1997), PAHs (Harner and Bidleman, 1998), polychloronaphthalenes (Harner and Bidleman, 1998), and other compounds (Harner and MacKay, 1995). However, measurements of K_{oa} for dioxin-like dioxin, furan, and PCB congeners could not be found in the literature. Alternately, K_{oa} can be estimated from the ratio of the octanol water partition coefficient and the Henry's Constant, as:

$$K_{oa} = \frac{K_{ow}\ R\ T}{H} \quad (7\text{-}36)$$

where:

K_{oa}	=	octanol air partition coefficient, dimensionless
K_{ow}	=	octanol water partition coefficient, dimensionless
R	=	universal gas constant, $8.2*10^{-5}$ atm-m^3/mole-K
T	=	ambient temperature, K
H	=	Henry's Constant, atm-m^3/mole

Lee and Jones (1999) discuss the difference between the K_{oa} calculated in this manner and measured values. For PCBs, they cite literature showing that measurements of K_{oa} were 1.4 to 4.7 times higher than modeled K_{oa}. Using a relationship derived for PCBs, they attempted a correction for the dioxin-like compounds. For this section, Equation (7-36) will be used to model the K_{oa} for dioxin-like compounds.

Another approach taken by some to develop a more site-specific relationship between K_{oa} and K_p is to measure the gas and particle fractions for a given site and compound, and then directly assign values for K_p (as C_p/C_g). Then, these site-specific K_p can be correlated to reported or estimated K_{oa} using the general formula:

$$Log\ K_p = m\ Log\ K_{oa} + b \quad (7\text{-}37)$$

Kaupp and McLachlan (1999) took measurements of polychlorinated dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), napthalenes (PCNs), and polycyclic aromatic hydrocarbons (PAHs) over the course of a year in southern Bavaria. They investigated the relationship between K_p and the saturation liquid vapor pressure, $p°_L$, as well as the relationship between K_p and K_{oa}, using the generalized logarithmic equation shown above. They found a good correlation between K_p and $p°_L$ when they grouped PCDD/Fs and PCBs (r^2 = 0.93) and separately when they grouped PAHs and PCNs (r^2 = 0.98), but not when they grouped all four sets of compounds together. On the other hand, they found a reasonable correlation existed for the whole group of four compound classes when they correlated K_p and K_{oa} (r^2 = 0.76). The linear relationship they found was:

$$Log\ K_p = 0.6368\ Log\ K_{oa} - 8.9111 \quad (7\text{-}38)$$

Given values of K_{oa}, K_p can be solved for using Equations (7-38) or (7-35). In order to compare this approach for assigning vapor/particle partitioning with the one chosen for this document (the Junge-Pankow model based on the saturation liquid vapor pressure), these two versions of the particle-gas partition coefficient, K_p, will be generated from K_{oa}. In both cases, the octanol air partition coefficient, K_{oa}, will be assigned values based on Equation (7-36) since measured values the dioxin-like compounds could not be found in the literature. Then, the two sets of K_ps will be used to predict values of the particle phase fraction, ϕ, as given in Equation (7-32). As described in Chapter 3, four values for the atmospheric particle concentration, the parameter TSP of Equation (7-32), describe four conditions termed, "clean continental", "background", "background plus local sources", and "urban". For this exercise, the value selected for urban conditions, 98 $\mu g/m^3$, will be used. Finally, the two sets of ϕ for the 17 dioxin and furan congeners generated here using K_{oa} will be compared with the ϕ generated in this methodology document using the Junge-Pankow model. This comparison is shown in Table 7-5.

As shown there, while the trend is generally similar between the two models (higher particle fraction as the degree of chlorination increases), there is a large discrepancy between the predictive methods. The calculation of the particulate fraction, ϕ, using the Junge-Pankow model, results in much larger values as compared to the procedure described in this section using

the octanol air partition coefficient. A similar discrepancy is found when calculating ϕ for other atmospheric conditions and lower values of the particle density term, TSP - background plus local conditions, background, and clean continental. There is not much difference in using a theoretical relationship between K_{oa} and K_p given above in Equation (7-35) or the empirical relationship shown as Equation (7-38).

The same discrepancy between the Junge-Pankow model and the K_{oa} model was found in two studies which both measured the concentration and partitioning of dioxin-like compounds in air and then tried to predict the particulate fraction using the same two models described in this section (Lee and Jones, 1999; Oh et al., 2001). Not only did both studies find that the octanol air partition coefficient method predicted a much smaller fraction to occur in the particulate phase for all congeners and homologue groups modeled, but they also both concluded that the octanol air partition coefficient method fit the measured data better. Chapter 3 discussed the general trend that the Junge-Pankow model based on $p°_L$ would lead to greater particulate fractions than measured, but it also discussed issues identified for the measurement of dioxin-like compounds - that "blow-off" and other causes could cause the filter-PUF derived measurements to be overestimates of the vapor phase fraction (equivalently, they would underestimate the particle phase).

In any case, this methodology document recommends use of the Junge-Pankow model for vapor/particle partitioning and, in particular, derives a set of particle-phase fractions for four atmospheric conditions for the dioxin-like compounds. The results of this analysis are shown in Table 3-7 of Chapter 3. Further, these results are used in several model validation exercises in this chapter, including air-to-leaf modeling, air-to-soil modeling, and air-to-leaf-to-beef modeling. Users may, of course, use other modeling approaches for the dioxin-like compounds, including the alternate vapor/particle model based on the octanol air partition coefficient described in this section.

7.3. MODEL VALIDATION EXERCISES

7.3.1. The Impact of Dioxin Soil Contamination to Nearby Soils

Contaminated soils from a bounded area of soil contamination are assumed to migrate via erosion and impact the soils of a nearby exposure site. This section examines the model algorithms for estimating impacts to nearby soils from a contaminated soil source.

Contaminated soils erode onto a nearby site of exposure and mix into a depth of either 2 cm for untilled conditions or 20 cm for tilled conditions. The 2-cm depth was chosen as the mixing depth for both depositing residues in the stack emission source category and for residues

migrating from a contaminated site to a nearby impacted site in the soil contamination source category. This 2-cm depth replaced the 1-cm depth which was the value selected for earlier versions of this dioxin exposure reassessment (EPA, 1992a; EPA, 1994). Principal justification for this assumption came from a report showing soil concentration profiles taken at 2 cm increments to be generally uniform for background undisturbed soils to a depth of 5 cm, with dropoffs in concentrations below this (Brzuzy and Hites, 1995). For two sandy profiles, the peaks were found at greater than 30 cm. The authors speculated that their findings are the result of depositions corresponding to the rise of dioxins in the environment starting 50 or so years ago. A mixing depth of 5 cm may be more appropriate for the algorithms of this assessment if a source being evaluated has been emitting for that length of time. However, exposure durations and source emissions for the categories of this assessment are likely to be emitting for substantially less than the past 50 years, justifying the selection of 2 cm for the untilled mixing depth.

A *contaminant concentration ratio* is defined for purposes of this discussion as the ratio of soil concentration at the site of exposure to the soil concentration at the site of contamination. For example Scenario 3, soil eroded from a 40,000 m^2 (10-acre) contaminated site was assumed to partially deposit onto a 40,000 m^2 exposure site. The contaminant concentration ratio was 0.39 for the 2-cm depth of mixing at the site of exposure and 0.06 for the 20-cm mixing depth**.**

Data to rigorously validate the approach taken in this assessment to model the impacts of soil erosion from a site of contamination to a nearby site is unavailable. However, there have been documented evidence of migration of 2,3,7,8-TCDD away from industrial sites with soil contamination of 2,3,7,8-TCDD, resulting in off-site soil contamination. Off-site soil concentrations of concern were identified in 7 of 100 Tier 1 and Tier 2 sites of the National Dioxin Study (EPA, 1987). The study noted that in most cases, 2,3,7,8-TCDD had not migrated off-site. Most, but not all, Tier 1 and 2 sites did have some off-site soil sampling without detection. It should be noted, however, that soil detection limits for most of these 100 Tier 1 and 2 sites were at 1 ppb; this would have precluded finding concentrations less than 1 ppb in some of the off-site soil sampling, particularly important for many of the sites where on-site detections were in the low ppb range. Summary data from the 7 sites noted above is provided in Table 7-6. Contaminant concentration ratios cannot be evaluated by this summary because of lack of detail provided in the National Dioxin Study.

Further detail on the 1984 sampling at the Dow Chemical site in Midland is provided in Nestrick, et al. (1986). An evaluation of the information in that reference is more informative than the Dow Chemical summary in Table 7-6. The entire site is 607 hectares. On-site sampling

included areas identified as chlorophenolic production areas, a waste incinerator area, and "background" areas. Background areas were within the 607 ha site but away from production areas. Two of the on-site areas were further identified as areas with Localized Elevated Levels (LELs). These two areas comprise less than 0.5% of the total site area, but had the three highest occurrences of 2,3,7,8-TCDD at 25, 34, and 52 ppb. Including these three high occurrences in the total of 33 samples taken on-site at sites of concern (i.e., not including the background sites) leads to an average concentration of 4.3 ppb; excluding them leads to an average of 1.0 ppb. The average of 11 background samples (including two ND assumed to be 0.0) was 0.15 ppb. A contaminant concentration ratio of 0.035 is calculated assuming an average concentration for contaminated soil of 4.3 ppb (0.15/4.3 = 0.035), and a ratio of 0.15 is calculated if the average soil contamination concentration is more like 1.0 ppb rather than 4.3 ppb.

This ratio of 0.035 is about one-tenth as much as the 0.39 ratio estimated assuming the shallow 2-cm depth of contamination, although the ratio of 0.15 is similar to the 0.39 ratio of Scenario 3. The depth of 20 cm led to a modeled ratio of 0.06, which is more in line with the Dow contaminant ratio of 0.035. The 2-cm depth ratios are probably more pertinent for comparison, however, since it is unlikely that there were tillage operations (or other soil practices which would distribute residues) in background areas of the 607 ha Dow site.

It appears reasonable that the no-till contaminant ratio of 0.39 is higher than the Dow ratios for several reasons. First, the contaminated areas sampled were those likely to be of concern and comprising only a small percentage of the total 607 hectare site. That might question the representativeness of 4.3 ppb as average soil contamination in impacted areas; the three highest concentrations came from specifically identified LELs comprising only 0.5% of the 607 ha site area. Second, a map provided in Nestrick, et al. (1986) including a distance scale clearly shows that all of the background samples were much further than 150 meters from the contaminated sample points, with several sample points hundreds to over a thousand meters from the contaminated sample points. The contaminant concentration ratio of example Scenario 3, 0.39, was estimated with a distance of 150 meters. Third, the example scenarios had specific assumptions about erosion which may or may not have been appropriate for application to the Dow site.

Ideally validation of the soil erosion model would involve direct application at the Dow site and comparison of predicted values to measured values. This was not feasible due to lack of information regarding the Dow site. Instead, this analysis has shown that the model predictions of contaminant concentration ratios differ logically from observed ratios at the Dow site.

7.3.2. Soil Concentrations and Concurrent Concentrations in Bottom Sediments and Fish

The Connecticut Department of Environmental Protection (CDEP, 1992; MRI, 1992) established a program in 1986 for monitoring TCDD, TCDF, and other dioxin-like isomers of comparable toxicity in several environmental matrices near resource recovery facilities (RRFs). Matrices monitored include ambient air, residues and leachate from the ash disposal sites, surficial soils, surface water surficial bottom sediments, and whole fish. The purpose of the program is to evaluate the impact of RRFs. Eight locations were evaluated through 1990, with one location serving as a baseline or reference site. Of the seven remaining locations, RRFs began operation in 1983 (1 RRF), 1987 (3), 1988 (1), and 1990 (2). This section will examine the soil, sediment, and fish data from that program.

The soil concentrations throughout all eight sites might be characterized as typical of background concentrations mainly because the concentrations of 2,3,7,8-TCDD measured through 1990 averaged 0.56 ppt (n = 77; assuming non-detects were ½ detection limit), with roughly a 50% non-detect rate (at a detection limit which has varied by data set, but has been around 0.1 ppt). In studies measuring soil concentrations of 2,3,7,8-TCDD in background or rural settings, either none was found, or concentrations were found in the low ppt range - this seems to also characterize the Connecticut data. For example, the soil concentration of 2,3,7,8-TCDD of 0.37 used in the background demonstration scenarios in Chapter 5 was measured at a rural background site located 28 miles from Columbus, Ohio. In a statistical analysis of the Connecticut data collected through 1988, the average soil concentration for 2,3,7,8-TCDD as 0.44 ppt (n = 42; CDEP, 1992; same procedures for estimating average concentrations), which is lower than the 0.56 ppt concentration for all samples through 1990. Concentrations of 2,3,7,8-TCDF taken after 1988, however, are lower than those taken in 1987 and 1988: the average including samples through 1988 was 8.20 ppt (n = 41; CDEP, 1992); while through 1990 was 6.77 (n = 77; CDEP, 1992). (Unlike the concentrations for 2,3,7,8-TCDD, this 2,3,7,8-TCDF concentration in the Connecticut data is higher than the background site near Columbus, Ohio: 0.64 ppt in Columbus versus 6.8-8.2 ppt in Connecticut.) This simple examination of averages over time does not seem to indicate statistically significant change, if any. As well, in a statistical analysis of the data (principal component analysis of the concentration levels of all isomers in soil, fish, and sediment to attempt to identify stratification of the data by year) for four of the RRFs through 1990, MRI (1992) concluded that the RRFs had no apparent effect on the levels of the dioxin-like compounds in the three matrices.

The purpose of developing the argument that levels in soil are low and perhaps typical of background conditions, although that is questionable for 2,3,7,8-TCDF, is to be able to compare

the soil to sediment, and sediment to fish ratios that arise from this data with those that were generated in example Scenarios 1 and 2 in Chapter 5. Those scenarios were crafted to be typical of “background” settings. It is noted that the comparison of soil-to-sediment ratios and the sediment-to-fish ratios in this exercise is not, strictly speaking, a validation exercise since the Connecticut circumstances were not duplicated.

Information and results from the CDEP program for the soil, sediment, and fish matrices are presented in Tables 7-7 through 7-9. The data and supporting documentation was supplied by CDEP (1992). Table 7-7 provides a summary of the eight sites in the CDEP program for which data was available. One "reference" or "control" site includes two areas, which for 1988 was at Union, Connecticut, and for 1990 was at Stafford, Connecticut. No nearby potential sources of dioxin release (industrial, commercial) were identified for these two reference sites. One of the sites, the Hartford site, is near the Connecticut River. All water bodies sampled were coves with direct links to the river. Industrial and commercial enterprises which use the river are speculated to have resulted in the generally higher fish concentrations noted in the Hartford site, as compared to the other sites. Twenty-one water bodies have been sampled, including harbors, channels, impoundments, reservoirs, coves, ponds, rivers, and lakes. Six species of fish have been sampled, including carp, channel and white catfish, white sucker, brown bullhead, and yellow perch. All but the yellow perch are bottom feeders. The yellow perch was sampled mostly when a sufficient sample of bottom feeder could not be obtained. Samples of bottom feeders were sought because it was felt that they would have the highest tissue concentrations due to their association with bottom sediments, and therefore be the best markers for impact and change over time (C. Fredette, CDEP, personal communication). The soil sampling program was not extensive; samples were only taken near ambient air monitoring stations, and only 77 samples were taken through 1990. It certainly cannot be claimed that the samples are statistically representative of soils which drain into the water bodies. However, given the consistency in concentrations noted and their low values, the supposition is made that concentrations are adequately representative of soils which impact the water bodies. Maps of the sites were obtained from CDEP to evaluate the distance from the soil sampling sites to the nearest water bodies. Nearly all soil sampling sites were within 3 miles of the nearest water body, and most were near to and less than one mile away.

Table 7-8 lists the frequency of non-detects for all data through 1990, and incomplete information on detection limits. For determining average concentrations in sampled matrices, non-detects were assumed to equal ½ the detection limit. The detection limits for these matrices varied over time with different data sets. The detection limits noted were those cited for 1987

and 1988 data (from a draft Monitoring Progress Report supplied by CDEP). That report did not list detection limits for three matrices noted. In parenthesis is noted the lowest concentration in the data sets, which would correspond to ½ the detection limit at the time the non-detect was measured. The purpose of presenting this data is simply to argue that assuming ½ the detection limit for computing averages will not greatly impact the averages. This can be demonstrated for the one matrix where this is most likely to be a concern - soil concentrations of 2,3,7,8-TCDD where a 50% non-detect rate was noted. If half the samples were assigned a value of 0.0 instead of perhaps 0.07 ppt (half the noted detection limit of 0.13 ppt), than the overall average would drop from 0.56 ppt to 0.52 ppt.

Table 7-9 summarizes the key results from the CDEP data. The C_{sed}:C_{soil} ratio is the ratio of sediment concentration to soil concentration for the eight sites for 2,3,7,8-TCDD - these are not organic carbon normalized concentration ratios. The second ratio noted is called the BSAF, because it is defined in the same way that the Biota Sediment Accumulation Factor is defined: the ratio of the lipid-normalized whole fish tissue concentration over the organic carbon normalized bottom sediment concentration. The BSAF is used to estimate fish tissue concentrations from bottom sediment concentrations in this assessment. The fish lipid contents and organic carbon contents for each site were supplied by CDEP (1992). The BSAFs for the entire data set and the four concentrations are based on averages of fish lipid and organic carbon contents from the entire data set.

Key observations from the demonstration scenarios and the results of the CDEP program are:

1) Demonstration scenarios 1 and 2 in Chapter 5 estimated the impact from basin-wide soil concentrations of the 17 dioxin congeners that have been found in a typical background setting. The difference in the scenarios was in exposure patterns and exposure site characteristics - the impacts to surface water sediments and fish were the same in both scenarios. The estimated concentrations of 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 2,3,4,7,8-PCDF in bottom sediments were 0.99, 1.22, and 0.51, respectively, and the sediment to soil ratios for these three compounds were 2.55, 1.82, and 2.43. The differences in the sediment:soil ratios of these congeners is due to slightly different organic carbon partition coefficients assumed for the three congeners. These ratios compare to the overall 3.86, 2.59, and 1.58 estimated in the Connecticut data set for 2,3,7,8-TCDD, 2,3,7,8-TCDF, and 2,3,4,7,8-PCDF, respectively. The ratio for total toxic equivalents was 2.69, compared to the modeled 2.64. These ratios tend to support the model's approach.

One of the key model parameters in the soil to sediment algorithm which is uncertain is the soil enrichment ratio. It was assigned a value of 3.0, which means that concentrations in soil eroding from the field are three times higher than concentrations on the field. If the soil enrichment ratio is set to 1.0, it would lead to sediment:soil ratios less than 1.00. The close match of sediment:soil ratios with an enrichment ratio of 3.0 does not necessarily validate the model's approach to evaluating surface water impacts from low basin-wide soil concentrations, however. The model assumes that all surface water impacts are from erosion of basin soils. However, sediment concentrations in water bodies are also a function of direct atmospheric depositions onto water bodies and other direct, industrial related, discharges into water bodies. Such depositions may originate from sources other than soil contamination, such as air emissions from cars or industry. The impact of industrial sources to the sediments in the CDEP data is unclear. As noted, evidence collected so far does not indicate an impact from incinerator emissions. The Hartford site has been cited as being impacted with industrial use of the nearby Connecticut River. However, the sediment concentrations of the water bodies at this site are not higher than other sites - in fact, the sediment concentrations from the Bridgeport, Bristol, Preston, and even the background Union/Stafford sites are comparable or higher. In any case, deposition of air-borne contaminants are likely to impact bottom sediments to some degree, and the soil contamination models of this assessment do not include such an impact (the stack emission source category does include this impact for emissions reaching water bodies).

In summary, the CDEP data appears to indicate that bottom sediment concentrations exceed surface soil concentrations by more than a factor of 2.0 in environmental settings that mostly do not appear to be impacted by industrial activities. The models also predict a similar enrichment of sediment concentrations, mainly due to the use of soil enrichment ratio of 3.0

2) The overall BSAF ratios for the three dioxin compounds and the I-TEQ ratio, ranging from 0.24-0.86, are higher than the BSAF used in the demonstration scenario of 0.09 for 2,3,7,8-TCDD and 0.144 for 2,3,4,7,8-PCDF. Higher BSAF in the CDEP data are expected because the fish species sampled were bottom feeders, except for the yellow perch. The selected BSAF of 0.09 is mainly supported by Lake Ontario data (EPA, 1990a), which was on brown and lake trout, smallmouth bass, and white and yellow perch, all column feeders. Bottom feeders are expected to have more exposure to the contaminants because of their direct contact with sediments. This implies that use of the BSAF for site-specific assessments should consider the dietary pattern of exposed individuals. If a significant portion of local fish consumption includes bottom feeders (such as catfish), then perhaps a BSAF greater the 0.09 used for the demonstration scenarios is warranted.

3) Of the six sites for which BSAFs were individually determined for 2,3,7,8-TCDD, the highest BSAF was from the Hartford site at 0.97. The claim is not made that it is substantially or significantly different from BSAFs at the other sites - it is simply a point of interest for comment. The Hartford site has been previously identified as likely to have been impacted by activity on Connecticut River - all the fish are taken from coves directly connected to the river. Although the bottom sediment concentrations at this site are not different from other sites, one hypothesis is that the water column is more impacted for this site as compared to other sites.

In Chapter 4, Section 4.3.4, a key issue identified for the validity of the BSAF approach is the issue of past versus ongoing contamination. Generally, the hypothesis offered was that fish are likely to be more exposed with ongoing impacts to the water body as compared to a situation where impacts were principally historical. The effluent discharge source category is a case of ongoing impacts. The argument presented in Section 4.6. of Chapter 4 was that the BSSAF (biota suspended sediment accumulation factor) should be greater in numerical value than a BSAF whose value is derived from data on a water body whose impacts have been primarily historical. This was the case for the assignment of a 0.09 for the BSAF, which was based on data on column feeders in Lake Ontario, a lake whose impact has been speculated as primarily historical. Although the numerical difference between the Hartford BSAF, at 0.97, and the next largest BSAF at Bristol, at 0.78, is not that large, perhaps that difference is due to the fact that the fish are more exposed at Hartford due to ongoing impacts from the Connecticut River.

In summary, this section has evaluated data supplied by the Connecticut Department of Environmental Protection on fish, sediment, and soil data. It is the only data set that could be found where soil and sediment data were concurrently taken in areas evaluated as (mostly) not impacted by industrial activity. An examination of the sediment to surface soil concentration ratios, showing them generally to be in the range of 1.6 to 3.9, supports the soil contamination model of this assessment for estimating sediment impacts from uniform basin-wide soil concentrations, which showed sediment to surface soil concentration ratios ranging from 1.8 to 2.6. The BSAFs determined from the CDEP data are higher than the BSAFs used in the demonstration scenarios of this assessment. This was likely due to use of bottom feeders for fish concentration of the CDEP - bottom feeders are likely to have more exposure to dioxin-like compounds in water bodies than column feeders due to their association with contaminated bottom sediments.

7.3.3. Other Bottom Sediment Concentration Data

Assuming elevated sediment concentrations are a function of elevated surface soil concentrations is reasonable when the only source of water body contamination is soil contamination. However, comparing soil and sediment concentrations would not be appropriate if sediments and water were impacted by industrial discharges, which has often been cited as the cause for sediment and water impacts (see Bopp, et al., 1991; Norwood, et al., 1989; e.g.). Sediment concentrations of note have also been found in surface water bodies near urban settings, with car and industrial stack emissions cited as likely causes (Gotz and Schumacher, 1990; Rappe and Kjeller, 1987). Rappe, et al. (1989) collected samples from the Baltic Sea, which were described as background samples. They note that the pattern of tetra-CDF congener concentrations found in the Baltic Sea were typical of what they termed the "incineration patterns" - air and air particulate concentrations that were attributed to sources such as incineration, car exhausts, steel mills, etc. On the other hand, sediment samples collected between 4 and 30 km downstream from a pulp mill revealed a congener pattern typical of bleaching mills. The stack emission and effluent discharge source categories provide separate models for water body impacts. The capability of the effluent discharge model is estimating fish tissue concentrations is examined in Section 7.3.6 below. The remainder of this section examines some of the data available which is not attributed to industrial or urban sources.

Smith, et al. (1995b) evaluated sediment core data from the Hudson River National Estuary Research Reserve system located on the lower (southern) Hudson River. They also took soil cores near the estuaries studied. Using principal component analysis, as well as a mass balance approach, they concluded that the CDD/CDF concentrations in the river sediments were dominated by soil erosion (76% of total influx) and sewage-containing effluents (19%). In doing their mass balance exercise, they used an “organic enrichment factor” of 1.6. Their data was on homologue groups, not on individual congeners, so their data is not directly amenable to comparison to model simulations or other data discussed in this section.

Except for the CDEP data described in Section 7.3.2 above, and possibly this data on Hudson River sediments (Smith, et al., 1995b), data was not found linking sediment concentrations to soil concentrations, in an urban or more pertinent to this assessment, a rural setting. Some sampling has occurred in areas described as rural or background. Sediment sampling in Lake Orono in Central Minnesota in such a setting found no tetra- and penta-CDDs, although occurrences of total hexa-CDDs were found in the low ng/kg (ppt) level, occurrences of hepta-CDDs to a high of 110 ppt, and total OCDD concentrations ranged from 490-600 ppt for three samples (Reed, et al., 1990). A report on sampling of several estuaries in Eastern United States included a "reference" or relatively clean site, central Long Island Sound. There were no

occurrences of 2,3,7,8-TCDD, although 2,3,7,8-TCDF was found at 15 ppt in this clean site. Other sites had identified industrial source inputs and higher noted concentrations (Norwood, et al., 1989). 2,3,7,8-TCDD was extensively found in sediments of Lake Ontario (EPA, 1990a). The average of samples from all depths of sediment collection from 49 stations including 55 samples was 68 ppt. The average of 30 surficial sediment samples was 110 ppt. A modeling exercise implied that an annual load of 2.1 kg/year into Lake Ontario corresponds to a concentration of 110 ppt. One identified source was the Hyde Park Landfill, located about 2000 feet from the Niagara River, which drains into Lake Ontario. Between 1954 and 1975, an estimated 0.7 to 1.6 tons of 2,3,7,8-TCDD were deposited in the landfill. A principal conclusion from the modeling exercise, however, was that a characterization of historical loadings of 2,3,7,8-TCDD into the lake was not available and would be necessary to evaluate the contributions by the Hyde Park Landfill.

7.3.4. Data on Water Concentrations of Dioxin-Like Compounds

Chapter 3 of Volume II summarizes available data on surface water concentrations of the PCDDs and PCDFs. Results summarized there are not directly amenable to comparison because the sources of contamination were unspecified except to note that, in some studies, a portion of the sampling occurred for water bodies known to be impacted by industrial discharges. The 104-mill pulp and paper mill study, which measured discharges of 2,3,7,8-TCDD and 2,3,7,8-TCDF into surface water bodies, was the only such study currently available which measured impacts to surface water bodies. Section 7.3.6 below discusses the use of this data to evaluate the effluent discharge source category. However, this study did not measure water concentrations, and no other studies could be found which measured both source strength and resulting surface water concentrations.

Nonetheless, the data on water concentrations of dioxin-like compounds does indicate that occurrences of PCDDs and PCDFs are generally not-detected or in the low pg/L (ppq) range; detection limits were generally at or near 1 pg/L. The one exception to this is occurrences in tens to hundreds of pg/L range for PCDFs in one of twenty community water systems sampled in New York (Meyer, et al., 1989). Concentrations exceeding 200 pg/L were found in the hepta- and octa-CDFs; concentrations between 2 and 85 pg/L were found in the tetra to hexa-CDFs for this impacted water system.

The highest water concentrations estimated in the demonstration scenarios in this assessment were the concentrations associated with the soil contamination demonstration. There, soil concentrations in a bounded area of soil contamination were 1 ppb for the three example

compounds. Also, watershed soils were assumed to be at 0.00 in order to demonstrate the incremental impact from the bounded area only. Water concentrations for 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, and 2,3,3',4,4',5,5'-HPCB were 0.012, 0.091 and 0.0016 pg/L, respectively. Water concentrations for the effluent discharge scenario, #6, were comparable to these at 0.018, 0.029, and 0.0029 pg/L for the three example compounds, respectively. For Scenarios 1 and 2, where watershed soil concentrations of 2,3,7,8-TCDD and 2,3,4,7,8-PCDF were set at 0.39 and 0.67 ng/kg (ppt), respectively, surface water concentrations were lower $8*10^{-3}$ pg/L (ppq) for 2,3,7,8-TCDD and $9*10^{-3}$ pg/L for 2,3,4,7,8-PCDF. For Scenarios 4 and 5 demonstrating stack emission depositions and where watershed soil concentrations of toxic equivalents, WHO_{98}-TEQ_{DF}, were estimated to be in the10^{-3} ppt range, surface water concentrations were in the 10^{-5} ppq range.

7.3.5. Data on Fish Concentrations in the Literature

This assessment estimated fish lipid concentrations of 2,3,7,8-TCDD for the various source categories to be: 1) background conditions - 3.0 ppt, 2) soil contamination - 4.3 ppt, 3) stack emission source category - 0.0003 ppt, and 4) effluent discharge source category - 6.4 ppt. The fish lipid content assumed was 0.07. Therefore, whole fish tissue concentrations are estimated at about one order of magnitude lower than these lipid concentrations. Data was not found to appropriately compare the stack emission source category results, and data on the effluent discharge source category is examined in the next section below. This section will examine some available data on fish concentrations in order to compare results from the first two categories with measured results.

The most appropriate study with which to make comparisons is the National Study of Chemical Residues in Fish (EPA, 1992b; hereafter abbreviated NSCRF). Fish tissue data on a variety of species and contaminants of concern in aquatic environments and fish from around the country were developed. Most important for current purposes, the sites were carefully characterized in terms of potential sources of fish contamination. There were 353 sites from which fish tissue data were available, of which 347 had data on 2,3,7,8-TCDD. Results from four site categories might be appropriate for comparison with concentrations estimated to occur from low, possibly background, soil concentrations of 2,3,7,8-TCDD. The four categories and number of sites per category were: the USGS water quality network NASQAN - 40 sites; Background (B) - 34 sites, Agricultural (A) - 17 sites, and Publicly Owned Treatment Works (POTW) - 8 sites. The average 2,3,7,8-TCDD whole fish tissue concentrations (lipid contents not provided) measured for these four categories were: NASQAN - 1.02 ppt; B - 0.56 ppt; A -

0.75 ppt, and POTW - 0.90 ppt. Background conditions were demonstrated in Chapter 5 using a soil concentration of 2,3,7,8-TCDD that was found in an actual background conditions - 0.37 ng/kg (ppt). The resulting fish tissue concentrations estimated for this soil concentration was 0.2 ppt (on a whole tissue basis assuming a fish lipid fraction of 0.07). Four of the site categories of the NSCRF might be considered representative of sources characterized as land areas of high soil concentrations of 2,3,7,8-TCDD. These were: Industrial/Urban site (IND/URB) - 105 sites, Refinery/Other Industry (R/I) - 20 sites, Wood Preservers (WP) - 11 sites, and Superfund Sites (NPL) - 7 sites. Average fish tissue concentrations measured for these site categories were: IND/URB - 4.04 ppt, R/I - 4.38 ppt, WP - 1.40 ppt, and NPL - 30.02 ppt. The source category of this assessment most similarly characterized to these would the category of soil contamination, where a bounded area of contaminated soil had 2,3,7,8-TCDD concentrations at 1.00 ppb. The resulting fish tissue concentration predicted was 0.3 ppt (assuming a fish lipid fraction of 0.07). The two remaining site categories of the NSCRF were Paper Mills Using Chlorine (PPC), and Other Paper Mills (PPNC). These data served as the basis for the comparison discussed below in the effluent discharge source category.

In general, the range of fish tissue concentrations measured for (perhaps) background conditions, 0.56 - 1.02 ppt, were comparable to the 0.21 ppt fish tissue concentration estimated assuming the background soil concentration of 0.37 ppt. The same may not be true, however, in the comparison of fish tissue concentrations ranging from 1 to 30 ppt associated with urban/industrial contamination. The fish tissue concentration modeled in the demonstration of the soil contamination source category was much lower at 0.3 ppt. However, it may not be entirely appropriate to compare the demonstration of the soil contamination source category with the urban/industrial sites of the NSCRF. For the demonstration scenario, the contaminated site was 4 ha within a 100,000 ha watershed which had concentrations of 2,3,7,8-TCDD set to 0.0. The fact that the background demonstration predicted a fish concentration 0.2 ppt, which was within a factor of 3 to 5 of observations from the NSCRF (or closer to values in the NSCRF if the fish lipid content was higher than 0.07), might be considered a limited validation of the models. This is not a validation exercise, strictly speaking, since specific field data were not input and compared.

One data point from that study of interest is the 30.02 ppt concentration found for the NPL site. This is two orders of magnitude higher than the 0.3 ppt estimated for the soil contamination source category. No insights can be gained from this difference because information was unavailable on the seven sites which were characterized as Superfund sites and which were expected to have been the cause of the 30.02 ppt fish concentration. It would be

interesting to know the surface soil concentrations of the 7 NPL sites, the size of these sites including the receiving water body, and their proximity to the receiving water body - that information may be sufficient to conduct a partial model validation exercise.

Another comprehensive data base of fish concentrations of 2,3,7,8-TCDD is from EPA's National Dioxin Study (EPA, 1987; abbreviated NDS), which actually provided the motivation for the NSCRF when significant residues of 2,3,7,8-TCDD were found in fish in the NDS. Fish concentrations from the NDS are also listed and discussed in Kuehl, et al. (1989). Travis and Hattemer-Frey (1991) summarized the fish data from the NDS. Their summary is as follows. Data collected from 304 urban sites in the vicinity of population centers or areas with known commercial fishing activity, including the Great Lakes Region, showed concentrations to range from non-detected to 85 ng/kg (ppt). The geometric mean concentration was 0.3 ppt, and only 29% had detectable levels of 2,3,7,8-TCDD. The Great Lakes data had more contamination, with 80% detection rate and a geometric mean concentration of 3.8 ppt.

The NSCRF also collected data on 2,3,4,7,8-PCDF, the second example compound demonstrated. Briefly, the range of average fish tissue concentrations noted for the site categories evaluated as background above is 0.42-0.78 ppt, very similar to the 2,3,7,8-TCDD range of 0.56-1.02 ppt. The modeled fish tissue concentration of 2,3,4,7,8-PCDF for background conditions was about the same as that for 2,3,7,8-TCDD at 0.17 ppt. The range of 2,3,4,7,8-PCDF average fish concentrations for the sites of elevated soil concentration was 1.86-5.44 ppt, which, like the comparison above for 2,3,7,8-TCDD, is higher than the modeled 2,3,4,7,8-PCDF concentrations of 0.18 for the soil contamination source category with initial soil concentrations of 1.0 ppb.

The NSCRF also collected data on PCB concentrations in fish, although the results were expressed in terms of total tetra-, hepta-, and so on. The data indicates concentrations well into the part per billion range for this breakout, and even higher considering total PCBs. The average concentration of total heptachlorobiphenyls over all study sites was 96.7 µg/kg (ppb). The average concentration of total PCBs over all sites was estimated as 1897.88 ppb, and the average concentration of total PCBs for background sites was 46.9 ppb. The modeled concentration of the example heptachlorobiphenyl, 2,3,3',4,4',5,5'-HPCB, for the soil contamination source scenario, where the soil concentration was 1 ppb, was 7.6 ppt.

Data from the Great Lakes region indicate that PCB concentrations are significantly higher than CDD/F concentrations in this area. PCB concentrations from fish in Lake Ontario are in the tens to hundreds of ppb level (Niimi and Oliver, 1989), while 2,3,7,8-TCDD contamination in Lake Ontario was in the tens of ppt level (EPA, 1990a) - a three order of

magnitude difference. Other data in Table B.10, Appendix B, Volume II, where concentrations were similarly in the tens to hundreds of ppb level were from Lake Michigan (Smith, et al. 1990) and Waukegan Harbor in Illinois (Huckins, et al., 1988). The single data point from that table for 2,3,3',4,4',5,5'-HPCB, the example PCB congener in Chapter 5, was for carp in Lake Michigan, and was 29 ppb (29,000 ppt).

While the modeled CDD/F fish concentrations for background settings seem reasonably in line with measured concentrations from similar settings, this assessment may have underestimated concentrations of 2,3,3',4,4',5,5'-HPCB. As noted, concentrations for fish in the Great Lakes Region were in the tens to hundreds of ppb range, while this assessment derived estimates in the low ppt range. It is inappropriate to make direct comparisons without also comparing source strengths. Concentrations of PCBs in bottom sediments ranged from the low ppb for the tri-PCBs, to the tens of ppb for the tetra through hexa-PCBs, back to the low ppb for the hepta and octa-PCBs, in Lake Ontario (Oliver and Niimi, 1988). Another literature source showing fish concentrations in Waukegan Harbor, IL, in the hundreds of ppb range, had sediment concentrations of specific congeners as low as 5 ppb to as high as 131 ppm. The concentration of 2,3,3',4,4',5,5'-HPCB in bottom sediments was estimated to be 1.6 ppt in the soil contamination scenario. Therefore, one reason PCB concentrations in fish estimated in this assessment are as much as four orders of magnitude lower than noted in the literature is because sediment concentrations estimated for the source categories in this assessment are also about four orders of magnitude lower. The BSAF for PCBs also was noted to be variable, with values below 1.0 to values over 20.0 (see Chapter 4, Section 4.3.4). The BSAF for the example PCB congener in this assessment was 2.0. Higher BSAFs would also increase PCB concentrations estimated for fish.

The fish concentration of 2,3,7,8-TCDD estimated for the stack emission source category was lowest at 0.00002 ppt. Data was unavailable to place this in any comparative framework. This is because the incinerator modeled was a well-controlled incinerator and the impacts modeled were incremental - they did not include a background load into the water body which would undoubtably drive fish concentrations in an area where there is a well-controlled incinerator.

7.3.6. Impact of Pulp and Paper Mill Effluent Discharges on Fish Tissue Concentrations

a. Description of Exercise and Model Parameters

This section describes a validation exercise of the effluent discharge algorithm. The description of this exercise as a "validation" exercise tentative, since much of the data used is of uncertain quality. Discharge rates of 2,3,7,8-TCDD (mass/time units) into surface water bodies

from a subset of 104 pulp and paper mills, which were sampled on a one-time basis in 1988 for such discharges and other parameters (EPA, 1990b; hereafter referred to as the 104-mill study), represent the key observed source term for this exercise. Fish concentrations of 2,3,7,8-TCDD for fish sampled downstream of these sources as part of the National Study of Chemical Residues in Fish (EPA, 1992b; abbreviated NSCRF hereafter) represent the key predicted model result for this exercise.

The National Council of the Paper Industry for Air and Stream Improvement (abbreviated NCASI hereafter) has already performed this exercise, and a brief description of their efforts and results can be found in Sherman, et al. (1992). NCASI carefully matched NSCRF data to appropriate mills of the 104-mill study. In many cases, they found more than one fish sample to correspond to a given discharge. Also, they considered circumstances where more than one mill effluent discharge can be considered to have impacted the environment where fish were sampled. In these cases, discharge rates from the contributing mills were fed into the model as source terms.

In NCASI's careful examination of the available data, they only considered 47 of the 104 mills as appropriate for this type of model testing. From these 47 mills, 95 fish samples with detectable residues of 2,3,7,8-TCDD were identified. Some mills had only one fish sample corresponding to it while others had up to four fish samples. The following explains why 57 of the remaining mills were not considered for this exercise:

1. Downstream of 10 pulp and paper mills was an estuary. NCASI considered the model appropriate for riverine situations only and did not calculate fish concentrations for estuarine settings.

2. The measurement for 2,3,7,8-TCDD in the effluent was listed as non-detect, and no further data examination and modeling occurred. There were 13 mills in this category.

3. NCASI could not identify appropriate fish measurements in the NCSRF downstream of the mill, and did not model further. Seven mills were in this category.

4. Some of the mills in NCASI's exercise were only considered "proximate" mills adding to the source term associated with another mill and one or more fish concentrations. Five mills were described in this manner.

5. For the remaining 22 mills, no explanation was provided for their lack of inclusion in the validation exercise.

Details of the NCASI modeling assumptions were supplied to EPA by NCASI (personal communication, Steven Hinton, PhD., P.E., NCASI, Inc.; Department of Civil Engineering, Tufts University, Medford, MA, 02155) and adopted for this exercise. Several other source materials

were used to develop the parameters for this exercise. First, Figure 7-5 shows the effluent discharge model and all the numerical quantities required, including the source term and the observed fish concentration, and model parameters associated with the mill discharge and the aquatic environment. Further description of the effluent discharge model can be found in Chapter 4. The model parameters and their source materials are now listed.

1) **Mill parameters including the 2,3,7,8-TCDD discharge rate, the effluent flow rate, the suspended solids content of the effluent flow, and the organic carbon content of the suspended solids in the effluent flow:** The 104-mill pulp and paper mill study (EPA, 1990b), a cooperative study between EPA and the paper industry, measured mass releases of 2,3,7,8-TCDD (actually effluent flow and concentrations, from which mass releases can be estimated), effluent flow, and total suspended solids content of the effluent flow (and other information such as releases of 2,3,7,8-TCDF, which were not needed for this exercise). For purposes of this validation exercise, actually only the total suspended solids content of effluent discharges was used from the primary reference of this study (EPA, 1990b). Data from the 104-mill study was also used in a modeling study, described more fully below, and in that reference, it was more conveniently organized and compiled. As such, effluent flow and 2,3,7,8-TCDD discharge rates came from a secondary reference. The organic carbon content of the solids in the effluent was assumed to be 0.36. This was the value used in the example scenario of Chapter 5, and was based on the fact that effluent solids are principally biosolids).

2) Receiving water body parameters including flow rate, suspended solids content, and organic carbon content of suspended solids. A modeling study conducted by EPA (EPA, 1990c) used a simple dilution and the EXAMS model to evaluate the impact from discharges of 2,3,7,8-TCDD and 2,3,7,8-TCDF from chlorine bleaching mills. Mills from the 104-mill study were the ones evaluated in this report. This study developed key receiving water parameters for these mills which are pertinent to the dilution model of this assessment, including harmonic mean flows at the point of effluent discharges, which were based on the nearest STORET sampling point, and suspended solids concentration of the receiving water body at this point. Details on how these key quantities were developed are included in that report and will not be discussed here. The organic carbon content of the suspended solids was assumed to be 0.05, which was also the content assumed for the example scenarios in Chapter 5.

3) Parameters associated with 2,3,7,8-TCDD, including the organic carbon partition coefficient, Koc, and the biota suspended sediment accumulation factor (abbreviated BSSAF). The Koc for 2,3,7,8-TCDD was the same 3.98×10^6 otherwise assumed in this

assessment, and the BSSAF value was assumed to be 0.09, which is the same value as the BSAF, Biota (bottom) Sediment Accumulation Factor. Sections in Chapter 4 further discuss the Koc, BSAF, and BSSAF.

4) Fish data including the fraction lipid and the observed fish concentrations: The core reference for this information is the National Study of Chemical Residues in Fish (EPA, 1992b), as noted above. NCASI compiled the fish concentrations and associated lipid content of the samples as part of their modeling exercise, and these were used here as well.

Table 7-10 lists the parameters used for each identified mill and receiving water body, as well as the modeled and observed fish concentrations. Not included in this table are the parameters assumed for all model runs, including the organic carbon contents of the suspended solids terms, and the 2,3,7,-TCDD Koc and BSSAF.

b. Results and Discussion

One important point to discuss up front is that 38 of the 47 eligible mills discharged into surface water bodies that were characterized as "low", while the remaining 9 mills discharged into "high" receiving water bodies. This characterization refers to the flow rates of the receiving water bodies. The average harmonic mean flow rate of the 38 low water bodies was $5.3 * 10^8$ L/hr, with a range of 10^7 to 10^9 L/hr, while for the other nine, the average flow was $2.6 * 10^{10}$ L/hr, with a narrow range of 1 to $4 * 10^{10}$ L/hr.

This distinction appears to be non-trivial for a few reasons. One, model predictions appear to more closely match observations for the smaller water bodies. The average of 38 mills and 74 fish for modeled and observed fish concentrations is 7 ppt and 15 ppt, respectively. The average of 9 mills and 21 fish associated with large receiving water bodies for modeled and observed fish concentrations is 0.1 and 5.3 ppt, respectively. However, some paired data (predicted versus observed fish concentration) showed over 3 orders of magnitude difference - 0.001 pg/g TCDD predicted versus 1.4 pg/g TCDD observed, for example. As evaluated by NCASI, another important feature of the larger receiving water bodies that they were the ones principally considered to have multiple discharges.

A final observation concerning the large receiving water bodies is that the suspended solids data is also significantly different than the low receiving water bodies. For the 38 water bodies associated with the small water bodies, the receiving water body solids content averaged 9 mg/L, while for the nine high receiving water bodies, the suspended solids content averaged 73 mg/L. This importance of the suspended solids content is principally seen for mills 39-42. The solids content of these water bodies ranged from 107 to 221 mg/L. The average modeled fish

concentration for these mills was 0.005 ppt, while the average observed fish concentrations was 3.0 ppt. The impact is one of "dilution": discharged 2,3,7,8-TCDD mixes into a larger reservoir of suspended particles, leading to a low 2,3,7,8-TCDD concentration on suspended solids concentration and lower predicted fish tissue concentrations. This dilution effect may also be real, as the average observed fish concentrations for these circumstances of 3.0 ppt may indicate a significant difference with the average 15.0 ppt observed for the smaller receiving water bodies. Nonetheless, these high suspended solids data must be considered suspect; if the suspended solids concentration were, in fact, lower on average, than model predictions would have closer than 3 orders of magnitude away from measurements.

Considering all 47 mills and 95 fish observations, it was found that 73 and 87% of predictions within a factor of 10 and 20 of observed concentrations, respectively. The predicted and observed results of this exercise for these 47 mills is shown graphically in Figure 7-6, which also shows the bounds of + or - a factor of 10 difference in predictions and observations Of note and perhaps not ironically, the highest observed fish concentration of 143.3 ppt is matched by the highest predicted fish concentration of 89.2 ppt. .

While Figure 7-6 appears to show a poor match in predictions and observations, the data available must be carefully considered. Only one discharge measurement is made, and a limited number of fish at various points downstream were available for this exercise. It would certainly be more meaningful if several discharge measurements per mill were made and several fish measurements were made downstream of the discharge. To be more rigorous, several measurements of discharge would have to be made over time to best reflect an average discharge. Likewise, other mill-specific parameters are uncertain, such as receiving water body flow, suspended solids in the water body, and so on. Finally, and perhaps most importantly, the assumption of this exercise is that the mill discharges of 2,3,7,8-TCDD represent the only sources impacting the fish. This is most unlikely to be the case for the large receiving water bodies, which may be receiving other industrial point discharges or non-point sources (runoff, atmospheric deposition). Given the factor of 2 difference in average predicted and observed fish concentrations for the low receiving water bodies, one might cautiously conclude that the effluent discharge model of this assessment is generally valid for, at least, receiving rivers with flows in the range of 10^8 L/hr.

Given this last cautious statement, one can continue this exercise by attempting a calibration on an appropriate parameter(s) so that predictions better match observations. The appropriate parameter for calibration is the BSSAF. The choice of 0.09 for the 2,3,7,8-TCDD BSSAF was based on data from Lake Ontario (EPA, 1990a). Specifically, 0.09 was the BSAF -

lake bottom sediment to fish lipid accumulation factor - for measured fish and bottom sediments of Lake Ontario. As this is a lake and not a riverine situation, and inasmuch as 2,3,7,8-TCDD contamination of Lake Ontario sediments have been attributed to historical impacts and not ongoing causes, the 0.09 may be inappropriate. As well, a range of BSAFs for 2,3,7,8-TCDD were noted in the literature in Chapter 4 of this assessment, ranging from less than 0.05 to greater than 1.00. EPA (1993) suggests that data collection methods limit the usefulness of some of the available literature, particularly those showing very high BSAF, and in a similar examination of BSAF data, suggests a range of 2,3,7,8-TCDD BSAF from 0.03 to 0.3. In any case, this suggests that the BSSAF is a reasonable candidate for calibration in this exercise.

A different selection for BSSAF significantly improves model performance. If the BSSAF is increased to 0.20 (up from 0.09), the average predicted fish tissue concentration for the 38 mills discharging into the smaller water bodies increases as expected from 7.0 to 15.6 ppt, comparing better now to the average observed concentration of 15.0 ppt.

Conclusions from this exercise include:

1. For at least smaller receiving water bodies, those with harmonic mean flows on the order of 10^7 to 10^9 L/hr, the effluent discharge model is appropriate for assessing effluent discharge impacts to fish for 2,3,7,8-TCDD and perhaps other dioxin-like compounds.

2. There appears to be a distinction in model performance for the large and small receiving water bodies. The high suspended solids concentrations generated in an earlier modeling exercise for the larger water bodies is one cause for model underprediction; these solids concentrations should be further reviewed. Also, these water bodies were evaluated by NCASI as ones with multiple sources. Other sources not identified by NCASI could also have been the cause for higher measured fish concentrations as compared to model predictions. The NSCRF report (EPA, 1992b) contains an appendix giving a matrix indicating point source categories of discharges which may have affected fish concentration results. Pulp and paper mills with and without chlorine were listed as point sources for 125 episodes (an episode is a fish sampling site). In 37 of these episodes, other point sources were identified, including one or more of the following: refinery (refinery using the catalytic reforming process), NPL site (a Superfund site), or other industry (an industrial discharge other than a paper mill or refinery). Given other sources, it is in fact a benefit to the exercise that predictions were lower than observations.

3. The model more closely predicts fish concentrations for the smaller receiving water bodies when the BSSAF is calibrated from 0.09 to 0.20. Considering that 0.09 was a value for 2,3,7,8-TCDD developed with data from Lake Ontario, a standing water body with principally

historic and not ongoing 2,3,7,8-TCDD impacts, this setting is probably an inappropriate surrogate for ongoing discharges to a riverine situation. This would argue that a calibration is warranted.

7.3.7. Air Dispersion and Soil Concentration Modeling Around an Incinerator Known to be Emitting Large Amounts of Dioxins

The Columbus Municipal Solid Waste-to-Energy (CMSWTE) Incinerator in Columbus, OH, operated between June 1983 and December 1994, and processed an average of 1600 metric tons of solid waste per day during its operation. A stack test taken in 1992 (EERC, 1992) indicated that the annual emission rate of dioxin I-TEQs was 984 g. Measures were taken to reduce dioxin emissions by the operators of CMSWTE. A second stack test was taken in 1994 (EMC, 1994) to evaluate the effectiveness of these dioxin reduction measures. The rate of emission from this test was calculated at 267 g TEQ/yr, indicating about a 75% reduction in dioxin emissions. These rates of emission can be compared against United States estimates of total annual emissions from all known sources of dioxin release of 12 kg TEQ in 1987 and 3 kg in 1995; see Volume I of these Dioxin Exposure Reassessment documents.

An ambient air monitoring study undertaken by the Ohio Environmental Protection Agency (OEPA) included two rounds of sampling in 1994, one during a concurrent stack test, and one round in 1995 after the incinerator had shut down (OEPA, 1994; 1995). For both sampling events in 1994, the concentration was highest in the air monitor (1 of 6 total monitors; 5 operational for each sampling event) located in the downwind direction (southeast) from the CMSWTE. Also, the profile of dioxins in the air matched the stack emission profile much more closely than the other air samples, which had lower and more typical urban air concentrations. A soil monitoring study conducted during 1995 and 1996 included 34 soil samples taken on-site and up to 8 km in all directions from the plant (Lorber, et al., 1998). An evaluation of these soil data clearly showed an imprint from the CMSWTE, with concentrations decreasing as a function of distance from the stack, approaching a local background after about 3 km.

Complete descriptions of the stack, air, and soil measurements conducted around the CMSWTE are available in previous papers (EERC, 1992; EMC, 1994; Ohio EPA, 1994, 1995; Lorber, et al., 1998) and only summarized here.

The ISCST3 was run twice, once to obtain predicted concentrations over the 48-hour period corresponding to the two ambient air monitoring events in 1994, and once to obtain annual average wet and dry deposition of sorbed dioxins to input into a simple soil reservoir mixing model to predict dioxin concentrations. The objective of this exercise was to use current

EPA guidance on the use of ISCST3 for air dispersion/deposition modeling of dioxins (EPA, 1994;1995b), coupled with a soil concentration model, and after doing so, determine how well the model was able to reproduce observed air and soil concentrations. This might be described as a "model validation" exercise because it has these characteristics: 1) all available site-specific information - stack emission rates, meteorological data, stack parameters, and others - are input into the model, 2) all other parameters for which no site-specific data is available - soil half-lives, atmospheric particle densities and mass fractions, and others - are input into the model using best available information with no attempts at "calibration" in order to make the model results best match observations, and 3) model results including predicted air and soil concentrations are compared against corresponding monitored concentrations.

On the other hand, it is recognized that this exercise falls short of a rigorous model validation exercise for ISCST3. The observed ambient air data set includes only two monitoring dates, with five ambient measurements for one date and four for the other date. Actual stack measurements of emissions are available for one of those dates, so a comparison of measured and predicted air concentrations for the second date does not qualify as a "validation" exercise. It must be assumed that emissions were the same for this second air sampling date. This is admittedly a small data set and a resulting rigorous test for ISCST3 dispersion model testing. Also, ISCST3 (and similar gaussian dispersion models) is expected to perform better for longer averaging periods (e.g., annual) than for short term events. Expectations for the "success" or characterization of the "failure" of the ISCST3 dispersion algorithms have to be tempered by these considerations.

The input of the average predicted depositions of dioxins into a simple soil mixing model to predict soil concentrations, and then comparing those to observed soil concentrations, is an exercise that may come closer to being a "model validation" exercise. In that case, the ISCST3 is applied in an hourly short-term mode over one year's worth of meteorological data to predict average long-term depositions to soil. These depositions are input into a soil mixing model to predict soil concentrations, and then the model results are compared with observations of soil concentrations. Unlike 48-hour air measurements, soil impacts are "long-term", particularly since dioxins are known to accumulate in soils over time and not undergo very meaningful dissipation. Also, there are 34 soil measurements around the CMSWTE available, and this number allowed for a reasonable characterization of the elevation of dioxin concentrations near the facility and the decline of concentration with distance.

In any case, discrepancies between predictions and observations in both the air and soil model comparison exercises were examined in order to gain insight on the capability of the

ISCST3 model to predict ambient air and soil impacts of emitted dioxins, and to gain insight on potential issues for further study of atmospheric and soil fate for dioxins.

7.3.7.1. *Modeling Procedures*

ISCST3 Modeling: ISCST3 is a Gaussian plume model, which accepts a variety of source geometries and emissions schedules in order to compute ambient air concentrations and surface deposition fluxes at specified receptor points. Two applications of ISCST3 were conducted for this effort. In one, the air dispersion algorithms alone were run, and meteorological data requirements included hourly wind speed, wind direction and stability for describing dispersion. These runs were conducted for the purpose of predicting 48-hr air concentrations, to compare with the 48-hr ambient air measurements. For the other, the particle-phase deposition algorithms were employed and dioxins were depleted from the plume by an amount equal to that depositing as the plume moved outward from the CMSWTE. The key output from these runs were long-term average dry and wet deposition of particle-bound dioxins, which were used for predicting soil concentrations of dioxins, to compare with the soil measurements.

For the dispersion model test, there were, in fact, two separate tests of the air dispersion algorithm - each test had a different meteorological data set: an “airport” set and an “on-site” meteorological data set. The airport set includes surface data (wind speed, wind direction and atmospheric stability) from the Columbus, OH, airport and upper air data for the mixing height from Dayton, OH. airport (BEEline Software, Inc. ISCST3 driver diskette 1998). The airport data was applied only for the first of two air monitoring events. On-site data for both of the 1994 measurement periods include wind speed and wind direction (Ohio Environmental Protection Agency. private communication 1998). The Columbus stability and Dayton mixing height were used in the on-site set. The purpose of obtaining and testing two meteorological data sets was to be able to evaluate the importance and uncertainty associated with key input stream. Besides meteorological data, other required inputs for modeling dispersion alone included: (1) building configuration data, (2) emissions data, and (3) receptor data. These dispersion model runs omitted particle-phase deposition, plume depletion, and chemical decay in the air. The dioxins were modeled as if the entire emission were in the form of a conservative pollutant, with no differentiation in fate of the individual compounds as a function of vapor/particle partitioning behavior, or atmospheric degradation or transformations.

For the deposition application of ISCST3, wet and dry deposition of particle-bound dioxins were modeled and then input to a separate soil mixing model to predict soil

concentrations. Therefore, additional meteorological data required were precipitation data. The prediction of depositions of particle-bound CDD/Fs with ISCST3 relies on particle-specific (particle diameter, e.g.) and dioxin-specific (vapor/particle partitioning, e.g.) parameters which are not required for dispersion modeling. The ISCST3 model estimates deposition flux values by multiplying the pollutant concentration in airborne particles by a deposition velocity. The deposition velocity is calculated considering gravitational settling velocities and atmospheric resistance. Annual average depositions were predicted using a single year of meteorological data from 1989; modeling from 1983 to 1994 would obviously have been preferable, but only one year of data was available. Meteorological data was provided by the National Climatic Data Center and from EPA's Support Center for Regulatory Air Modeling internet page (www.epa.gov/ttn/scram). The surface and precipitation data was collected at the Columbus, Ohio Weather Service Office. Atmospheric mixing heights were determined using upper air data collected at the Dayton, Ohio Weather Service Station. An examination of the meteorological data from 1989 compared with historical averages showed that the wind speed and direction were very similar to historical means, and the precipitation was slightly above normal for 1989 (111 cm for 1989 compared to an historical average for Columbus, OH, of 96 cm/yr). The ISCST3 was run in plume depletion mode, meaning that dioxins were depleted from the plume moving away from the incinerator by an amount equal to the dioxins depositing by dry and wet particle-phase deposition.

Like the air dispersion tests of ISCST3, two sets of outputs were generated for soil concentration modeling. There were two stack tests available, and it was unclear as to which would better characterize long term emissions of dioxins from CMSWTE. Both were used to predict soil concentrations. This is described in more detail in the next section below on Source Characterization.

The ISCST3 model was run on a "unitized" basis for both dispersion and deposition simulations, meaning that ambient air concentrations and deposition results were generated for an emission rate of 1 g/sec. For the dispersion-only runs, the individual total emission rates of all 25 CDD/Fs (17 congeners on non-zero toxicity and 8 homologue groups) were multiplied by the predicted unit concentration to give the predicted ambient concentrations at the receptor points. Deposition predictions for the CDD/Fs were generated using this two-step procedure: 1) the total amount of the CDD/F emitted was assumed to partition into vapor and particle fractions according to ambient conditions at 20 °C (in contrast to partitioning assuming conditions at the stack exit); this step allowed for an estimation of dioxin-specific particle-bound emission rates in g/sec, 2) then, these particle-bound mass emission rates were multiplied by the unitized dry and

wet deposition rates predicted to occur at the receptor point to provide the compound-specific deposition rates.

All model parameters for both runs, with the exception of the details on receptor locations (air and soil monitoring locations around the CMSWTE) are provided in Table 7-11. Further detail on modeling algorithms for the ISCST3 can be found in EPA (1995b).

Source Term Characterization: Two stack tests were available to supply the critical source term for this exercise (EERC, 1992; EMC, 1994). The first was conducted in 1992 by the Ohio Environmental Protection Agency (OEPA) for purposes of permit renewal. High dioxin emissions at 6799 ng total/dscm concentration (total = sum of the homologue group concentrations; dscm = dry standard cubic meter) and 976 g TEQ/yr (when extrapolating the results from 1 stack to the 3 stacks at CMSWTE and assuming historical average operation times for the CMSWTE) mass emissions were found, leading to regulatory actions by the state and federal environmental agencies. Process modifications were undertaken for purposes of reducing dioxin emissions, and the CMSWTE was retested in March of 1994. Total concentrations were reduced to 3685 ng/dscm and the mass TEQ emissions were reduced by about 75% to 267 g TEQ/yr (estimated using the same historical CMSWTE operation practices).

This second stack test occurred during March 16-18 of 1994. This corresponds closely to the time that the OEPA was sampling the air for dioxins - on the 15-17th of March. Therefore, the air dispersion model tests for March used the March stack test results. Unfortunately, the CMSWTE was not stack-tested during the April air sampling events. It was necessary to use the March stack test results for the April dispersion model tests, and then, of course, to assume that the April emissions were similar to the March stack test emissions.

For deposition modeling, a decision also needed to be made regarding characterization of long-term emission rates. Rather than select either the 1992 or the 1994 stack emission test for this evaluation, or an average of the two, to represent long-term dioxin emission rates, results were generated for both emission tests to demonstrate the importance of this critical and uncertain term in the modeling procedure.

Soil Concentration Modeling: Wet and dry depositions are summed and become the source term for a simple reservoir mixing model for predicting soil concentration C_s, as:

$$C_s = \frac{F\,(1 - e^{-kt})}{k\,M} \qquad (7\text{-}39)$$

where:

Cs	=	the soil concentration, pg/g
F	=	the annual total (wet + dry) deposition of dioxins as predicted by ISCST3, pg/m^2-yr
k	=	the first order annual soil dissipation rate, yr^{-1}
t	=	the time during which deposition occurs, yr
M	=	the soil mixing mass, g/m^2

The dissipation rate assumed here for all dioxin compounds was 0.02772 yr^{-1} (half-life of 25 years), a mid-range value selected to be between a value of 0.0693 (half-life of 10 years) often assumed for surficial dioxin residues (EPA, 1994) and 0.00693 (half-life of 100 years) speculated to be an upper range for subsurface dioxin residues (Paustenbach, et al., 1992). The best validation of this choice of half-lives for all dioxin congeners comes from McLachlan, et al. (1996), who reported on an analysis of soil taken from experimental plots which had been amended with sewage sludge in 1968 and sampled in 1972, 76, 81, 85, and 90. These archived samples were analyzed for all 17 dioxin-like CDD/Fs, and based on an analysis of results, McLachlan and coworkers concluded that half-lives were on the order of 20 years, with dioxin removal from the plots being mainly physical removal processes (overland runoff, wind erosion). Furthermore, their results suggested that all congeners had been removed at roughly the same rate, which is why they concluded that removal processes were mainly physical and very little in-situ degradation appeared to be occurring. A time of operation, t, of 11.5 years was used, corresponding to the time of operation of the CMSWTE. The soil mixing mass, M, equaled 112,500 g/m^2, which assumes a mid-range soil bulk density of 1.5 g/cm^3 and the soil sampling depth of 7.5 cm.

Description of the Measured Air and Soil Concentrations: Ambient air monitoring was conducted by the Ohio Environmental Protection Agency (OEPA) in 1994 to evaluate ambient air concentrations after process modifications reduced dioxin emissions from the CMSWTE. General Metal Works model PS-1 high volume samplers were used to collect 48-hr samples. Concentrations were, therefore, the sum of vapor + particle phase concentrations. Six monitors

were in the city of Columbus between 1.8 and 3.0 km from the site, mostly in the historical downwind direction, northeast, but one in the upwind southwest direction. Two of the samplers were co-located (for purposes of quality control), so results from these two samplers were averaged to represent one sampling point A seventh sampler was located 45 km southwest of the facility in a rural "background" setting; results from this sampler were not used in this modeling study. Five samples (4 sampling locations; the co-located samples were averaged) were taken in March and 6 samples (5 locations) were taken in April, 1994. The March set, taken on the 15-17th of the month, occurred at nearly the precise time that the March 1994 stack testing occurred, on the 16-18th. The April sampling event occurred during April 19-21. Exact starting and stopping times of the air monitors were not available for this test. For purposes of air dispersion modeling, the starting and stopping times were assumed to be the mid-day of the beginning and ending days of each sampling periods. In all, there were 9 urban air sampling events taken during 1994 that comprise the "observed" air concentration data set used in this modeling study. Wind rose data for the March and April sampling periods were also available, and the provided insights into the expected impact patterns. A final round of air samples from the seven air monitors was taken in 1995 after the CMSWTE had shut down. The purpose of this data set was to evaluate the air quality now that the CMSWTE was no longer operating. Full details on the air monitoring studies, including analytical methodologies, quality control, and final results, are described in OEPA (1994, 1995).

A first phase of soil sampling was conducted by the United States Environmental Protection Agency (EPA) in December of 1995. Sampling in this round included 4 samples on the site of the incinerator, 18 samples within about 3 km of the incinerator in the city of Columbus, and 3 samples at a background site 45 km from the CMSWTE. This background site was the same as the air monitoring background site. The study design for this phase employed a stratified random selection process, involving sites in the four major quadrants around the incinerator (northeast, southwest, etc.) with an emphasis of sampling in the quadrant which was historically downwind from the incinerator, the northeast quadrant. The following conditions were sought during site selection: 1) level, undisturbed soils, 2) away from trees, 3) not adjacent to roads, 4) not near pressure treated wood, and 5) not known or suspected to have high dioxin concentrations for any other reason. All samples were collected using pre-cleaned equipment dedicated to each sampling location. Each sample site consisted of an area of 1.5 m x 1.5 m. A grid of 25 sections was established at each site and used for random selection of aliquot sample sites. Four random aliquots were collected for each sample. A "sample" for this study was, therefore, a composite of four aliquots. Aliquots were collected using a stainless steel tulip bulb

planting device. This device removed a plug approximately 7.5 cm in diameter to a depth of about 7.5 cm.

A second phase of soil sampling was undertaken in August of 1996. Thirteen samples were taken from about 2 km away from the incinerator to about 8 km distant. The purpose of this second phase was to ascertain whether a background concentration for the city of Columbus could be determined. A similar selection criteria for sample sites was employed in this second phase.

Altogether, there were 4 soil samples on the incinerator property, 31 samples in the city of Columbus taken from right outside the incinerator to upwards of 8 km away, and 3 background samples taken 45 km away, for a total of 38 soil samples. This modeling used 34 of the samples - it did not have use for the 3 background samples, and 1 of the remaining samples was found to be contaminated by a local source not associated with the CMSWTE. Full details of the soil monitoring study can be found in Lorber, et al. (1998).

Figure 7-7 shows the location of the CMSWTE in relation to the 32 soil samples in Columbus and the 5 urban air sampling locations. Not shown in this figure are 3 of the 4 soil samples taken on the site of the incinerator, and the background site in which 3 soil samples were taken and the 1 background air sampler was located. This figure identifies the groupings of the soil samples, as described in the results section below.

Subtracting Local Background Concentrations From Measured Concentrations:

The ISCST3 will predict only the increments of dioxin concentration in the air and soil that are due to emissions from the CMSWTE. Therefore, a procedure had to be developed to subtract a local "background" of dioxins from both the air and soil observed data.

The average of 6 air measurements taken in 1995 after the CMSWTE shut down was assumed to represent the background dioxin air concentrations for this site. The average total concentration from 1995 was 2870 fg/m^3, with a range of 2030 to 4760 fg/m^3. The 1995 average concentrations of each dioxin-like congener as well as those of the homologue groups were subtracted from each of the March and April 1994 corresponding measurements. When such a subtraction resulted in a concentration less than 0, the concentration was assumed to be 0 for purposes of this exercise.

An analysis of the observed soil data in Lorber, et al. (1998) showed that concentrations decrease to the local soil background at about 3 km from the CMSWTE, at a TEQ soil concentrations of 4.0 pg/g (ppt). The soil profile of CDD/Fs for this background provided in

Lorber, et al. (1998) was subtracted from each of the 34 observed soil measurements; when this subtraction resulted in a concentration less than 0, the concentration was set to 0.

Procedures for Evaluating the Performance of the Models: The paucity of the observed data, particularly the air measurements, makes a rigorous "goodness-of-fit" statistical comparison of predicted versus observed inappropriate. Rather, tabular summaries of predicted and observed concentrations are utilized, and simple qualitative discussions address the goodness-of-fit. For the air dispersion comparisons, predicted air concentration quantities associated with a 48-hour air monitoring event are compared with the appropriate observed quantities. For the deposition comparisons, soil samples are "clustered" and simple mean concentrations are generated for both modeled and observed concentrations. Four clusters which are displayed include: 1) "on-site" - 3 soil samples taken on the site on the CMSWTE, 2) "off-site" - 5 samples just off-site and in the historical downwind direction, northeast, within 500 meters of the incinerator, 3) "urban" - 14 samples taken from about 500 meters to about 3 kilometers, and 4) "urban background" - 12 samples taken from about 3 to about 8 kilometers. As discussed in Lorber, et al (1998), the high soil concentrations found in the on-site cluster were speculated to have resulted in ash drift from piles or trucks transporting the ash to nearby landfills rather than deposition. Therefore, a comparison of predicted and observed concentrations for this on-site cluster are displayed for information purposes only, not to be considered in the context of model testing. Otherwise, all observed soil samples, and clusters, can be considered to represent long-term deposition trends as the monitoring study protocols insured that they were in relatively flat, undisturbed locations away from any nearby potential dioxin sources (roadways, PCP treated wood, etc.). The predicted and observed concentration quantities which are displayed include: 1) homologue group concentrations, 2) total concentrations, which are sum of the 10 homologue group concentrations, and 3) TEQ concentrations. These terms were defined above.

In addition to tabular summaries, isoline figures were generated. These are lines of equal concentration around the CMSWTE, either air or soil concentrations, that were generated using ArcView® - a desktop GIS package. First the point data, measured or modeled concentrations, are brought into ArcView® as point coverages. Then, using the ArcView® kriging routing, surfaces of the concentrations are generated using the exponential function to estimate the semivariogram. For the air and soil concentration isoline generation, modeled concentrations were generated for 250 meter intervals to about 3 km in all directions, and these were input as point coverages into ArcView®. There were too few observed air concentration measurements,

so isolines could not be generated for these. Instead, measured air concentrations were overlain on the predicted isolines. For soil concentration, there was judged to be sufficient coverage with 34 soil samples to generate "observed" isolines to compare with predicted isolines.

Finally, it is reiterated that all "observed" concentrations, both soil and air, were generated by subtracting out background concentrations in the procedure described above. Therefore, all tabular or figure notations of a "0" observed concentration means that, if subtracting out the background concentrations from the measured concentrations resulted in a negative concentration, the measured concentration was set to zero for purposes here.

7.3.7.2. *Results and Discussions*

Air Dispersion Modeling: Even before air dispersion modeling was undertaken, examination of the data revealed clear trends. Analyses of on-site wind roses for the March and April 1994 sampling dates reveal that there is one dioxin monitoring station likely to have been influenced by the CMSWTE. This station, termed SE-3 by the Ohio Environmental Protection Agency (OEPA) was about 2 km east of the source and was downwind from the source approximately 53% of the time during the sampling period in March 1994 and 78% of the time in April 1994 (OEPA, 1994). In contrast, none of the other 5 stations was downwind for time fractions approaching those of SE-3. The measurements confirmed that SE-3 was the most impacted of the samplers, with TEQ measurements of 168 fg TEQ/m^3 in March and 353 fg TEQ/m^3 in April. The average of the measurements from the other 5 samplers over the two dates (a total of 8 samples; one sampler was not operational for both events) was 52 fg TEQ/m^3, with a range of 10 to 98 fg TEQ/m^3 (note: background not subtracted out for these observations). Lorber, et al (1998) examined this trend further, showing also that the profile of CDD/Fs found in March and April in SE-3 matched the stack emission profile of CDD/Fs more closely than the other ambient air samples, which displayed profiles more typical of background air.

Table 7-12 compares the observed total concentrations at each reporting monitoring station with the model predictions for both meteorological data sets, the "on-site" and "airport" sets. As noted earlier, two important considerations for evaluating the comparison of predicted and measured air concentrations are: 1) having 4 and 5 air measurements for sample dates in March and April, respectively, is a small sample size, and 2) one can expect the ISCST3 to perform better for longer averaging times as compared to shorter averaging times. It would be fair to conclude that the paired comparisons of predicted and observed 48-hr air concentrations are severe tests of model performance, and Table 7-12 shows the large scatter expected from this test.

Still, some meaningful observations might be possible from Table 7-12. First, it does not appear that either of the meteorological data sets provides a superior fit to the data for the March sampling event. The on-site runs appeared to better identify SE-3 as the monitor of most impact, and also to identify the sampler SN-2 as having some impact, but not as much impact as SE-3. The airport meteorological set appeared to show a significant impact to SN-2, but not as much of an impact for SE-3. On the other hand, the simulations using on-site meteorological data identified SNW-1 as having the highest concentrations, while the simulations using the airport data correctly modeled this site perhaps more correctly as having little impact. Both meteorological data sets correctly identified SSW-4 as the monitor which showed no impact.

For the April sampling date, the on-site meteorological data correctly identified SE-3 and SSW-4 as monitors having some impact, with little or no impact for the other three monitors. However, SE-3 was not simulated to have the most impact, as was found.

The difference between using the on-site and air meteorological data was further examined using isoline figures. Six such isoline drawings, with observed concentrations overlain, are shown in Figure 7-8. These include TCDD, OCDD, and TEQ predicted/observed results from March for the on-site data and the airport data set. Observations from this figure include:

1) ISCST3 modeling runs using both meteorological data sets appear to have correctly identified the western quadrants (northwest and southwest) as being areas of little impact. The observed “0" concentration in the southwest quadrant (sampler SSW-4) is consistent with this trend, as are wind rose that are displayed and discussed in OEPA (1994). Both figures appear to have identified the northeast and southeast as areas of principal impact, with little impact due east. The two observed air measurements in the northeast quadrant (samplers SN-2 and SNW-1) do, in fact, suggest low impact due north with increasing impact as one moves in the northeast direction. The observed air measurement in the southeast quadrant (sampler SE-3) may, in fact, have missed areas of higher impact during the two days, which the model runs suggest are either further north or further south.

2) The discussion above comparing the measured point estimates with the modeled point estimates suggests that there may be significant differences in the way the two meteorological data sets simulated impacts. More specifically, the “airport” data simulation showed three times as much impact for sampler SN-2 compared to the “on-site” simulation: 20,833 fg/m ^{3} total (airport) vs. 6,606 fg/m^3 (on-site). On the other hand, the “on-site” simulation showed 7 times more impact for sampler SNW-1: 8943 fg/m ^{3} (on-site) vs. 1270 fg/m ^{3} (airport). Looking at Figure 7-8, however, the differences do not appear that meaningful. The on-site simulations

seemed to push the plume a little more northeast and southeast compared to the airport runs, which showed more impact due north and south. Sampler SN-2 was simulated to be in a zone of important impact according to the airport meteorological data set, while sampler SNW-1 was simulated to approach this zone more so with the on-site meteorological data set. These types of trends emphasize the potential problems and misinterpretations that can occur when one attempts a validation exercise with ISCST3 with short-term data and a limited number of air measurements.

3) The biggest discrepancy for the three dioxin quantities compared in Figure 2 is for OCDD. It appears as though much higher concentrations, ranging from 1 to almost 5 pg/m^3 in the northeast and southeast were modeled, while measurements of 0.5 pg/m^3 and less were observed. These high modeled OCDD concentrations were the main reason that the ISCST3 modeled much higher observed total concentrations than were measured (see Table 7-12). For the other quantities, TCDD and TEQ, while the location of high impacts may not have been perfectly identified, at least the magnitude of the high measurements were in the range of the high modeled concentrations. This important trend is discussed in more detail below.

As mentioned above, station SE-3 stands out in both the March and April sampling as having the highest impact of all stations. Thus, the data from this station have the best chance of avoiding the uncertainties introduced by background fluctuations. Predicted and observed homologue group concentrations for SE-3 for the both sampling dates are compared in Table 7-13. These results were generated using on-site meteorological data. Table 7-13 also shows the CMSWTE stack emission rate of these homologue groups.

Being only an exercise in air dispersion modeling (no wet/dry deposition; no stack speciation; no atmospheric chemical reactions), there is a perfect correlation between the homologue profile of the emissions and air concentration predictions for both March and April. The observed air concentrations clearly do not have this stack emission profile, however. Specifically, the speciation pattern from source to receptor has shifted in these ways: 1) the lower chlorinated tetra and penta CDD/Fs have greatly magnified in importance in the ambient air profile as compared to the stack profile, and 2) conversely, the hexa through octa homologues, with the exception of OCDF, have been reduced in importance in the ambient air profile as compared to the stack profile. Said another way, the model predicted lower concentrations for the lower chlorinated CDD/Fs than were measured, and higher concentrations for the higher chlorinated CDD/Fs. The total concentration predictions were, however, within about a factor of two of observations. Not that it has meaning with regard to fate and transport considerations, but

the TEQ concentrations were comparable: 125 and 309 fg TEQ/m^3 measured during March and April compared with 142 and 156 fg TEQ/m^3 modeled for SE-3.

Three possible explanations are offered to explain why the model did not predict the measured shift in homologue profile between the stack and field:

1) It is known that CDD/Fs with fewer chlorines have higher vapor to particle (V/P) ratios; indeed, high temperatures in the stack could generate even higher V/P ratios (Eschenroeder, 1994). If stack sampling methods underestimate the amount of vapor pollutant being emitted, than the lower chlorinated dioxin emission rates are being underestimated - an error that would be exacerbated by the even higher V/P ratios in the high temperature stack gas. The PS-1 samplers capturing both vapor and particle-phase CDD/Fs in ambient air are well tested and not expected to have caused error in the characterization of total ambient air concentrations of dioxins. There has been some speculation that PS-1 samplers may overestimate the vapor fraction of dioxins, but this would not affect their characterization total concentrations (sum of vapor and particle phase concentrations; see Chapter 3 for a complete discussion of vapor/particle partitioning).

2) Running the air dispersion algorithms of ISCST3 alone did not account for particle deposition, yet some of the higher chlorinated CDD/Fs, expected to be sorbed to ambient air particles or fly ash, may have deposited by dry deposition prior to the air sampling locations. The results for the deposition modeling described below support this hypothesis, at least for the dioxins. It compares model predictions of soil concentration with measured soil concentrations. One clear trend was that the model consistently underpredicted the soil concentration of the hepta and octa dioxin homologue groups. This result, combined with the observation that the higher chlorinated dioxins were the most overpredicted in air concentrations in this paper, suggests that the plume is being depleted of higher chlorinated dioxins by deposition. However, this trend was not duplicated by the higher chlorinated furans. There, modeled soil concentrations were more nearly consistent with measured soil concentrations, with a small degree of overprediction.

3) Another possible physical explanation is that dechlorination may occur between the emission point and the ambient measuring station a kilometer or two downwind. Workers at Monsanto Laboratories (Orth, et. al., 1987) and at the Agro-Environmental Science Institute in Japan (Koshioka, et al., 1989) have observed photolysis of TCDD. Generally, polychlorinated organic compounds easily experience photochemical loss of chlorine atoms. If the higher chlorinated CDD/Fs dechlorinated to form lower chlorinated CDD/Fs in the atmosphere, than more lower chlorinated CDD/Fs would have arrived at the ambient air monitoring stations to cause the distinct ambient air profile.

Deposition and Soil Concentration Modeling: Table 7-14 provides results from this exercise, which are observed and predicted homologue and TEQ concentrations for 4 clusters of soil samples. These clusters were developed for purposes of displaying results from the soil monitoring study conducted around the CMSWTE (Lorber, et al., 1998), and generally correspond to increasing distance in all directions from the incinerator. As discussed above, the observed and predicted soil concentrations for soil samples taken on-site, the first cluster of Table 7-14, are shown for informational purposes only; it is not expected that the on-site soil samples represented long-term deposition trends. Some trends that may be observed from the results in Table 7-14 include:

1) Since emission rates between the 1994 and 1992 stack tests differed by about a factor of 4, subsequent predictions of soil concentration made with each stack emission rate also differed by this factor of 4. Generally, the 1994 stack test predictions appear to better match the observed soil concentrations compared to the 1992 stack test with all homologue groups except TCDD; the TCDD predictions using the 1992 stack test are a better match. Most of the time, however, both sets of predicted homologue group soil concentrations were higher than observed soil concentrations, sometimes by more than a factor of 10 when using the 1992 stack test.

The question that this study is unable to answer is which stack test is more likely to have been representative of long term emission trends from the CMSWTE. The 1994 test occurred specifically after measures had been taken to reduce dioxin emissions. Because of process changes made to the CMSWTE, it would be reasonable to assume that the 1994 test is not representative of long term emissions. On the other hand, the 1992 test was occurring during heavy rainfall, which soaked the refuse to be burned. Data on the refuse moisture content showed that the average moisture content of the refuse burned in 1992 was about 10% higher than in 1994 - it was about 38% during the 1992 test compared to 28% in 1994. Some have suggested that wetter refuse may result in higher dioxin emissions (personal Communication, K. Jones, Zephyr Consulting, Seattle, WA.), although this hypothesis is unproven and the moisture content of feed materials is not considered to be a principal factor in predicting dioxin emissions - factors such as feedstock content, combustion efficiency, pollution control device, and pollution control inlet gas temperature are more often cited as the critical factors.

2) Noteworthy for results with both stack tests is that much more OCDD is found in the soil than predicted, and the same is true but to a lesser, although still noticeable, extent with HpCDD; in other words, the model under-predicted the soil concentrations of these homologue groups. As noted above in the description of air dispersion results, the ISCST3 was found to greatly over-predicted OCDD and HpCDD ambient air concentrations. Taken together, these

trends suggest that OCDD and HpCDD deposited near the incinerator to a much greater extent than was modeled. Since both dioxin homologue groups exist in the atmosphere principally sorbed to particles, this may reflect inappropriate parameter assignments relating to particle phase deposition algorithms, or possibly inappropriate deposition algorithms in general. However, the model appears to *overpredict* OCDF and HpCDF, and like OCDD/HpCDD, OCDF and HpCDF are also tightly sorbed to airborne particles, so perhaps the model's treatment of particle fate may not be the cause of significant underprediction of OCDD.

3) With both stack test results, the model would appear to proportionally overpredict most congeners (not OCDD/HpCDD) to a greater degree the further downwind one gets. This suggests that more dioxin mass is being removed from the plume as it disperses downwind than ISCST3 is able to simulate. Removal mechanisms include particle and vapor phase deposition, plant capture, and atmospheric degradation (photolysis and photooxidation).

Figure 7-9 shows a series of 9 isoline maps crafted to additionally display the trends of the measured versus the modeled soil concentration. Each group of three isoline maps pertains to one CDD/F compound; there are three isoline figures each for TCDD, OCDD, and TEQ concentrations. The first in the sequence of three are isoline maps drawn from the measured data, and the next two are maps drawn from using the 1992 and then the 1994 stack test. Observations from Figure 7-9 include:

1) The shape of the isoline figures developed using the 1992 stack emission test will be the same as those developed using the 1994 stack emission test, because they were all developed from the same unitized simulation - the only difference will be the mass of particle-bound emissions as a function of the compound and stack test.

2) The observed maximum soil concentration appears to occur in the northeast quadrant about a kilometer away. The predicted maximum soil concentrations are also found in the northeast quadrant, but they are a bit closer, at about ½ kilometer away. Also, the isolines drawn from model simulations seem to suggest that the maximum will occur more due north of the CMSWTE as compared to isolines drawn from measured data.

3) As was noted above, these isolines suggest much higher OCDD concentrations, in the thousands of parts per trillion (or equivalently, parts per billion), are found near the CMSWTE, as compared to modeled OCDD concentrations, which are in the hundreds of parts per trillion. It is noted that smooth isolines could not be drawn from the observed OCDD data because of the inhomogeniety of the results. Specifically, of the 8 highest soil samples nearest the CMSWTE, 5 had observed concentrations of OCDD above 1900 pg/g, ranging from 1930 to 6651 pg/g, but the

other 3 measurements were less than 1000 pg/g, ranging from 309 to 731 pg/g. The observation that OCDD was elevated in soils well above 1000 pg/g is supported by the data, despite oddly shaped isolines. The observed TCDD concentrations in the vicinity of the CMSWTE appear in range from 40 to a peak of 160 ppt, which is close to the range of 50 - 200 ppt modeled when using the 1992 stack emission test. However, when using the 1994 stack emission, the elevation in TCDD is only suggested to be in the 5 - 20 ppt range. Although not meaningful with regard to fate and transport, per se, the 1994 stack test appears to better duplicate the observed range of elevated TEQ concentrations - between 20 and 50 ppt, while the 1992 stack test simulations suggest elevations as high as 200 ppt TEQ.

7.3.7.3. *Discussion and Concluding Remarks*

Caution was expressed in the opening paragraphs that this exercise should not be characterized as a "model validation" exercise, mainly because of the weaknesses and uncertainties in the data and model parameters. To reiterate, some of those weaknesses/uncertainties include: a) a very small number of observed air monitoring data points (and the lack of precise information on when the air monitors were turned on and off, which can be important for short term air dispersion testing), and a relatively small number of soil measurements, b) the lack of consideration of all possible plume depletion mechanisms in the dispersion and deposition modeling. For the deposition modeling, the plume depletion by particle-phase deposition was considered, but other plume depletion mechanisms include atmospheric degradation of either vapor or particle phase dioxins, vapor phase deposition, and vapor- and particle-phase vegetative capture, c) a reasonable but still possibly flawed means to subtract "background" from measured air and soil concentrations. It is possible, for example, that air monitoring locations have their own, very localized, "background". Therefore, averaging all 5 air concentration measurements from 1995 to represent "background" to subtract equally from all measurements in 1994 may not be appropriate, d) uncertainties in dioxin-specific fate parameters including vapor/particle partitioning of the CDD/Fs and soil half-lives, and e) uncertainties and/or lack of representativeness in the important source term, the rate of dioxin emissions from the stack, and the equally important meteorological data used to drive the model simulations.

These latter uncertainties in source term and meteorological data were evaluated by using different data sets. Specifically, two meteorological data sets were used in the dispersion modeling exercise - an "on-site" meteorological data set supplied by Ohio EPA (who took the air samples), and a publicly available data set from a nearby airport. Two possible stack tests were

used to characterize long term emission rates for deposition and soil concentration modeling. As discussed above, there were no clear "superior" choices in either meterological data set or stack emission test. While it was clear that air concentration and soil concentration results differed when by using both data sets, in fact it was also clear that both data sets seemed to predict some quantities better than the counterpart data set.

With these cautions, it may be fair nonetheless, to make these statements regarding the ability of the ISCST3 to model the impact of dioxin emissions from the CMWSTE:

1) Elevations of dioxins in air and soil were clearly identified in the sampling programs, and they were also clearly modeled by ISCST3. Predicted and measured dioxin elevations in air and soil appear to generally be within a factor of 10 of each other, with both under and over predictions identified above. These elevations appear to be restricted to only within a few kilometers, 2-3 kilometers, and this was also found in the dispersion and deposition modeling. From the soil modeling exercise, it appears as though the model overpredicted soil concentrations to a greater degree the further downwind one went. This suggests that the plume was being depleted by dioxins in a manner that was not duplicated by the ISCST3 modeling.

2) It is clear from the analysis in this paper that the stack emission profile of CDD/Fs is very different from the profiles measured in the soil and in the air. This could be explained by "changes" in the profile at some point between the stack and both air and soil measurement sites, or it could be that there were problems in the measurement of CDD/Fs in either the stack or the environmental media. Assuming no major problems with measurement, it can be said that these trends cannot be duplicated in ISCST3 without the input of congener-specific atmospheric degradation rates, and/or congener-specific soil dissipation rates. Also, one hypothesis offered to explain the change in the dioxin profile from stack emission to air measurement was that some dechlorination might be occurring - the higher chlorinated CDD/Fs may be dechlorinating to form lower chlorinated CDD/Fs. If so, and if attempting to duplicate this trend, the ISCST3 model would need additional algorithms to model these transformations.

While admittedly a limited field test of deposition and soil concentration models, the data used here had these important features, which are not readily (if at all) available for similar model testing of ISCST3 with CDD/Fs: multiple stack tests offering a full suite of dioxin homologue and congener data; a historically high emission rate and over 11 years of emissions such that a signal is left behind in the soil and an imprint in the ambient air while monitoring was occurring, and a reasonable approach to determining the local background of dioxin soil and air

concentrations that could be subtracted from the total measured soil and air concentrations to characterize a "signal" of higher dioxin concentrations found near the incinerator.

7.3.8. Air-to-Soil and Soil-to-Air Modeling

The observed air and soil data used in the background demonstration scenarios in Chapter 5 were from the rural background site of the Columbus site described above. These rural data also allow for an opportunity to test the air-to-soil modeling and the soil-to-air modeling algorithms. To summarize those scenarios, actual air concentrations and soil concentrations of the 17 dioxin-like congeners from the rural background site in Ohio were used as source terms. The I-TEQ air and soil concentrations from this site were 0.019 pg/m^3 and 1.37 pg/g, respectively. The individual congener concentrations in air and soil were used to predict concentrations in terrestrial foods (vegetables/fruits, animal food products) and the aquatic environment (water, fish, and sediments). Soil concentrations were not predicted from air concentrations and likewise, air concentrations were not modeled from soil emissions. For this model validation exercise, however, the opportunity presents itself to model air-to-soil impacts and soil-to-air impacts, and then to compare model predictions with observations.

Chapter 4 describes the models for estimating soil concentrations based on dry and wet deposition of particle-bound dioxins. The models were used in the stack emission source category, and in that context, dry and wet deposition amounts are modeled using the ISC3 air dispersion and deposition model. The full amounts of dry and wet deposition (i.e., no subtraction for plant interception) are mixed into a reservoir of soil and dissipated according to a defined dissipation rate. The reservoir of soil for this exercise will be that defined by a 7.5-cm depth, which was the depth of the soil sampling at the rural site in Ohio, and the assumed soil bulk density will be 1.50 g/cm^3. The dissipation rate is 0.0277 yr^{-1}, which corresponds to a half-life of 25 years. Since deposition was not monitored at the rural site, it will be estimated as the particle bound air-borne reservoir times a velocity of deposition. Koester and Hites (1992) measured a dry deposition rate of 0.002 m/sec for dioxins in Indiana. They also measured wet deposition and found it be roughly comparable for two sites. On this basis, dry deposition in this exercise will be modeled using the 0.002 m/sec velocity of deposition and wet deposition will be assumed to be equal to dry deposition.

Chapter 4 also described models for estimating air concentrations given soil concentrations. These algorithms were for the soil source category. The algorithms for volatilization were developed for PCBs and made simplifying assumptions such as no degradation, an infinite source of contaminant, and so on. An "unlimited reservoir" approach

was used to estimate the flux of particle bound dioxins from soils due to wind erosion. A near-field dispersion algorithm estimated air borne concentrations given flux estimates of vapor and particle-bound dioxins. Despite using an "unlimited reservoir" approach, it was observed in Chapter 5 that the particle-bound air-borne concentrations were about an order of magnitude less than the vapor-phase concentrations for the demonstration of the soil contamination source category.

The results of this validation exercise are shown in Table 7-1. There is a clear dichotomy in the results. The air-to-soil model appears to model soil impacts reasonably well, with modeled soil concentrations somewhat lower but within the realm of field observations. On the other hand, the soil-to-air modeling did not show a good match. All predicted congener concentrations were 2-3 orders of magnitude lower than observed congener concentrations, and there was a 500-fold difference in observed and predicted TEQ air concentrations.

Regarding the air-to-soil modeling, 11 of the 17 observed soil concentrations were higher than model predictions. All but three congeners were modeled to within a factor of five of observations, and the three other congeners were about a factor of 10 from observations (i.e., either observations were 5 to 10 times higher than predictions, or predictions were 5 to 10 times higher than observations) . The four highest observations are matched with the four highest predictions as follows: 17.7 ppt observed 1,2,3,4,6,7,8-HpCDD versus 9.1 ppt modeled, 161.0 versus 36.2 ppt for OCDD, 4.06 versus 2.74 ppt 1,2,3,4,6,7,8-HpCDF, and 10.7 versus 2.70 ppt OCDF. The observed I-TEQ soil concentration of 1.37 ppt matches well with the predicted TEQ concentration of 0.70 ppt.

While the soil model appears to work reasonably well based only on impact of particle depositions, vapor impacts are not considered, and consideration of such would increase predictions of soil concentrations. As noted above, it does appear that soil concentrations may generally be underpredicted, although for six congeners, the model predictions were higher than observations. Direct vapor deposition could impact soils, but for the soil observations in the rural site in Ohio, all samples were taken in grassy areas, and with a vegetative cover, it is speculated that there would little direct vapor deposition. Therefore, detritus production would be a mechanism for vapor impacts to soils. Barbour, et al. (1980) list a detritus production rate for a setting described as "tallgrass prairie" as 520 g/m^2-yr. Given the concentrations predicted to occur in grass due to vapor transfers, one can estimate the loadings of dioxin corresponding to a detritus production of this magnitude. The predicted TEQ concentration in leafy vegetation due to vapor transfers was 0.27 pg/g dry weight given the rural air concentrations at this site in Ohio. This concentration times the detritus rate leads to a loading of 112 pg TEQ/yr. In contrast, the

dry and wet deposition loading estimated by dry and wet deposition of particle-bound dioxins (as described above) is 2130 pg TEQ/yr. Therefore, on a TEQ basis, vapor impacts via detritus production would only be about 5% of loadings by dry and wet deposition of particle bound dioxins. There was also a reasonably narrow range for individual congeners, where detritus loadings were about 5-15% of atmospheric deposition of particle-bound dioxins. Particle-bound dioxins also impact vegetation, and detritus production might be considered as an additional loading due to particle bound dioxins. However, since 100% of atmospheric depositions are loaded into the soil model, detritus production is inherently handled, and considering detritus production would double-count the impact of particle-bound dioxins.

Another factor to consider is the representativeness of the air concentrations. The air concentration profile was generated as the average of 3 samples, one taken in March, 1994, one in April, 1994, and one in June, 1995. It has been observed that air concentrations are higher during winter months (Reed, et al., 1990), and perhaps the inclusion of additional winter samples from the site in Ohio would lead to a higher air concentration profile and higher predicted soil impacts.

Regarding soil-to-air modeling, it is not that clear that emissions and resulting air concentrations above soils at background levels should be lower by up to 2 orders of magnitude than what would occur in background setting. The argument has been made in Volume II, Chapter 2 of this assessment that emissions from tall industrial stacks, followed by long range transport, are principal sources of these compounds in rural environments where the food supply is produced. The question remains as to how much of the contaminant in rural air is due to urban emissions followed by long range transport versus emissions from the soil reservoir source. If the modeling of this assessment is correct, than soils contribute very little to rural air concentrations. However, other evidence developed in this assessment suggests that the soil release and dispersion algorithms of this assessment may be underestimating air concentrations. One piece of that evidence is discussed in the next section below. Plant:soil ratios, defined as the ratio of 2,3,7,8-TCDD concentration in plants divided by that in the soil, were found to be lower in model predictions as compared to literature values. Two possible hypotheses were offered below: 1) the model is underpredicting air concentrations resulting from soil releases, and/or 2) plant:soil ratios derived in experiments are not only the result of soil related impacts, but also from distant sources of air-borne release and long range transport - i.e., the air reservoir is not solely explained by soil releases. This is the same issue that is discussed for the soil-to-air model exercise here. One other possibility for the difference in the inability of the model to duplicate plant:soil ratios would be that the algorithms estimating air to plant transfers are modeling too

low a transfer rate. However, the air to plant transfer algorithms were examined in Section 7.2.1 above and in Section 7.3.12 below, which describes a broader air-to-beef food chain validation exercise. In both sections, concentrations of the dioxin congeners in leafy vegetation were compared with model predictions for leafy vegetation, and predicted concentrations were found to be in line with observations. Also, the vapor-phase air-to-leaf transfer coefficient was calibrated with field data, and since it is shown that vapor phase transfers tend to dominate plant concentrations, air-to-plant transfers should, by definition, be modeled adequately.

In summary, this section has shown that the air-to-soil model based on deposition of particle-bound dioxins appears to work well. Vapor impacts would occur primarily by die-back of vegetative materials, but the additional increment to soil concentrations are estimated to be less than 10% by this route. Inclusion of winter-time air concentrations in the average air profile used to predict soil concentrations could lead to higher predictions of soil concentrations and a superior match of predicted and observed soil concentrations in this exercise. The soil-to-air models may be underpredicting air concentrations. The observed air concentrations are 2-3 orders of magnitude higher than predicted to occur by soil emissions alone. This is due, in part, by the fact that some fraction of the observed air concentration is due to long range transport from distant sources. It is not known what fraction this is, but other evidence has suggested that dioxins in rural settings distant from known sources of dioxin release originate, in fact, from those distant sources. Other evidence suggests that the soil-to-air models may still be underestimating the impacts to air from contaminated soils. The only way to truly test the soil-to-air models would be to have air concentrations measured above soils, where it is known that there are no other sources to measured air concentrations. Unfortunately, this data would be hard to develop for the ubiquitous dioxins and none was available for testing.

7.3.9. Transfer of Dioxins From Soils to Below Ground Vegetables

This section describes a validation of the transfer algorithm from soils to below ground vegetables. The equation for calculating the concentration of dioxins in below ground vegetables is:

$$C_{bgv} = \frac{C_s \; RCF \; VG_{bg}}{Kd_s} \qquad (7\text{-}40)$$

where:

C_{bgv} = fresh weight concentration of below ground vegetables, pg/g

C_s	=	contaminant concentration in soil, ppt or pg/g
Kd_s	=	soil-water partition coefficient, L/kg
	=	$Koc*OC_{sl}$
Koc	=	contaminant organic partition coefficient, L/kg
OC_{sl}	=	fraction organic carbon in soil, unitless.
RCF	=	root concentration factor equaling the ratio of the contaminant concentration in roots (fresh weight basis) and the concentration in soil water, unitless
VG_{bg}	=	empirical correction factor for below ground vegetation which accounts for the differences in the barley roots for which the RCF was derived and bulky below ground vegetables, unitless

The key contaminant-specific parameter, RCF, was developed from data developed by Briggs, et al. (1982) on the transfer of organic contaminants from solution into barley roots. The soil concentration, C_s, is divided by the soil partition coefficient, Kd_s, so as to convert it to a soil water concentration. The VG_{bg} is an empirical factor introduced to describe the difference between the thin barley roots of the Briggs experiments and the bulky below ground vegetation to which it is applied for the dioxin documents. Evidence shows that dioxins translocate only to a small degree into bulky below ground vegetables (see next section). The assignment of values to VG_{bg} in this assessment also considers other factors pertinent for estimating concentrations for human exposures, including factors which would further reduce whole vegetable concentrations including washing or peeling. Further detail on the algorithm can be found in Chapter 4.

Data from Muller, et al. (1994) was used to validate this model. Specifically, carrots were grown in pots with soil of two concentrations, a control soil and a contaminated soil. Muller, et al. (1994) provided graphs showing the congener group concentrations for soil, and for three parts of the carrot: peel, cortex, and stele. The precise concentrations from these graphs was unavailable. However, the graphs were digitized by Cambridge, Environmental (58 Charles Street, Cambridge, MA; concentration values contained in discussions in a public comment provided to EPA), and their concentrations were used in this exercise. Data in this article also included the soil organic carbon content, 8.1% (OC_{sl} = 0.081).

Part of this data set was used in conjunction with the model displayed above. The VG_{bg} was taken out of the equation and the soil concentration data was input into the model to predict the peel concentrations. The cortex and stele concentrations were not used in the validation exercise. These predicted peel concentrations were compared with the observed peel

concentrations. Since the data was available in congener groups and not individual congeners, the values for the parameters RCF and Koc were estimated as the congener-specific value if only one dioxin-like congener was in the congener group (2,3,7,8-TCDD, e.g.), or as the average of the congener-specific values of the multiple dioxin-like congeners in the congener group (the three HxCDDs, e.g.). Finally, the data in Muller, et al (1994) was only given in dry weight terms without discussion of the dry weight fraction, and the model predicts a fresh weight. For this exercise, it was assumed that carrots are 15% dry weight; the fresh weight was divided by 0.15 to estimate the dry weight concentration.

Table 7-16 shows the data that went into this validation exercise and the results. It would appear that the model works reasonably well. The difference in peel concentrations due to soil concentrations is apparent in both the data and the model predictions, and the magnitude of the difference appears to be captured. With one exception, the predictions and observations are within a factor of 4 of each other, with the exception being a factor of 5. Thirteen of 20 predictions/observations are within a factor of 2 of each other. The biggest discrepancies are the HpCDF and OCDF congener groups, with predictions exceeding observations by a factor of about 4 for both the control and contaminated soils. This data is further examined in Chapter 4 to determine the VG_{bg} parameter. Generally, it is concluded from this validation exercise that this data supports the use of the Briggs, et al. (1982) RCF empirical formulation to predict the peel concentration in underground bulky vegetation.

7.3.10. Impacts of Contaminated Soils to Vegetation

There have been several studies in addition to the carrot study described above which have measured plant concentrations of 2,3,7,8-TCDD for plants grown in soils with known concentrations of 2,3,7,8-TCDD or dioxin Toxic Equivalents (TEQs) or dioxin congener groups. One quantity that can be estimated from these studies is a *plant:soil contaminant concentration ratio*. The plant:soil ratio equals the concentration in the plant divided by the concentration in soil in which the plant is growing. Concentration ratios predicted to have occurred in the demonstration scenarios can be compared against those that have been measured in the various studies.

These ratio comparisons cannot strictly be considered model validations. Only the exercise described in the previous section, where experimental data were duplicated with modeling, can be considered a model validation. Still, trends ascertained from the literature will be compared with concentration ratios from the demonstration scenarios. The literature articles measuring soil and resulting plant concentrations of dioxin-like compounds are summarized in

Table 7-17. This table also includes concentration ratios, and separates sections for above and below ground vegetation.

In measuring both the soil and the plant concentration, several of the early literature articles, particularly those from Seveso (Wipf, et al., 1982; and Coccusi, et al., 1979) presumed that the soil in which the plant was growing was the ultimate source for the 2,3,7,8-TCDD contamination of above ground plant parts, if not from direct uptake than from deposition of suspended particles. However, recent research has concluded that the contamination of above ground plant parts is due principally to air-to-plant transfers (Hulster and Marschner, 1993; Muller, et al, 1993; Muller, et al., 1994; Welsch-Pausch, et al, 1995; and others). These cited research efforts have concluded that there is no consistent relationship between soil concentrations of dioxin-like compounds and above ground vegetative concentrations of these compounds, which has led the researchers to conclude that air-to-plant transfers explain plant concentrations (one study did strongly imply a direct soil/plant for dioxin-like compounds for at least one family of above ground vegetables, the cucumber family (Hulster, et al., 1994); this will be discussed below). This fact, coupled with the fact that sources of airborne contamination by dioxins include both distant sources and soil releases, make it difficult to compare literature reports of plant:soil contamination concentrations with those predicted by the soil contamination modeling of this assessment.

Recall that for the soil contamination source category, the presumption is that air concentrations and depositions to which the plant are exposed originate only from the contaminated soil. One would expect that the modeled plant:soil ratio for above ground plant parts would be lower than plant:soil ratios measured in actual field settings, since the field measured ratios are influenced by more than just the soil releases into the air.

What is more pertinent in the demonstration scenarios for comparing plant:soil ratios for above ground vegetation are the results for the “background” scenarios. Here, air concentrations from an actual setting provide the source of dioxins for above ground plants. Simultaneously, soil concentrations which correspond to the actual setting where air concentrations were measured are input into the scenario. Therefore, plant:soil ratios from this demonstration should be analogous, at least, to plant:soil ratios derived from other actual field settings.

Unlike above ground vegetation, the literature is consistent in concluding that soil provides the source for underground soil to root transfers. For this reason, Table 7-17 and the following discussions distinguish between above and below-ground vegetation.

The following plant:soil contaminant concentration ratios for TEQs were estimated for the two scenarios demonstrating background conditions in Chapter 5, Scenarios 1 and 2: below

ground vegetables - 0.19 (dry weight basis, assuming vegetables are 15% dry matter, and using tilled soil concentrations which are 50% of untilled soil concentrations), above ground vegetables/fruit - 0.10 (dry weight basis, 15% dry matter, tilled soil concentrations), grass - 0.33 (dry weight, untilled soil concentrations), and feed 0.16 (dry weight, untilled soil concentrations). Some observations from experimental results found in the literature, and comparison with the results of the model, are:

1) The largest body of consistently developed experimental data on soil-plant relationships of dioxin-like compounds comes from a research group in Germany who have published numerous articles for different vegetation and experimental conditions in the 1990s (Hulster and Marschner, 1991; Hulster and Marschner, 1993; Hulster, et al., 1994; Muller, et al., 1993; Muller, et al, 1994). Some of the earlier literature showed much higher impacts to vegetation than measured by these German researchers (Coccusi, et al., 1979; Facchetti, et al., 1986; Young, 1983), which, in the judgement of the authors of this assessment, renders them suspect. One early report, that of Wipf, et al. (1982), does show results consistent with the German research. The observations following will focus mainly on this research from Germany.

2) Experimental results for both above and below ground vegetation suggest that plant:soil ratios decrease as soil concentration increases. For below ground vegetation, this suggests that the movement into plants is not a passive and unimpeded process occurring with transpiration water, for if it were, plant:soil ratios would be constant as concentration increases. For above ground vegetation, the observations given above that air-to-plant transfers and not soil-to-plant transfers better explain plant concentrations, and that air concentrations include soil releases as well as long term transport, leads one to conclude that a consistent relationship between soil concentrations and plant concentrations is not to be expected. An explanation for this trend for below ground vegetative trends could not be found.

The models of this assessment - soil to below ground vegetation, soil to air to above ground vegetation, and air to above ground vegetation - cannot duplicate these observed trends, that is, the models will not show a decrease in plant:soil ratios as soil concentration increases. When soil is the only source of contamination, as in the soil contamination source category, above and below ground vegetation concentrations are a linear function of a biotransfer factor and an appropriate media concentration - air, soil, water. For particle depositions, no transfer parameters are used, but plant concentrations are a linear function of model inputs, including deposition rates, plant interceptions and yield, and a plant washoff factor. Therefore, plant concentrations will be a linear function of soil concentrations for the soil contamination source category.

3) Plant:soil ratios for below ground vegetables for soil concentrations in the low ppt range would appear to be in the 10^{-1} to 10^{-2} range (Muller, et al, 1993; Hulster and Marschner, 1991), which may be a little lower than the 0.19 predicted by the model. Much higher ratios were found in the earlier studies (Coccusi, et al., 1979; Facchetti, et al., 1986; Young, 1983), which earlier had been speculated as being questionable. One earlier study, that of Wipf, et al. (1982), does report ratios similar to these later studies, as noted above. At higher soil concentrations in the sub to low ppb range, plant soil ratios are more in the 10^{-4} to 10^{-3} range (Hulster and Marschner, 1993; Hulster and Marschner, 1991).

4) The results for above ground bulky vegetation, fruits and vegetables, indicate plant:soil ratios that are lower than plant:soil ratios for bulky below ground vegetation, for comparable soil concentrations. The data of Muller, et al. (1994) can be used to demonstrate this point. This data was used over others because the soil concentrations, at 5 and 56 ppt TEQ, are nearer to the background soil concentration of 1.37 ppt TEQ used in the background demonstration scenarios than any of the other studies found. First, their results include total crop dry weight concentrations of TEQs for carrots, lettuce, and peas (including pods) in soils with TEQ concentrations of 5 and 56 ppt. At these two soil concentrations, the carrot:soil ratios were 0.07 (at 5 ppt TEQ soil concentration, dry weight of the carrot) and 0.017 (at 56 ppt). Their lettuce and pea pod:soil ratios for the control and contaminated plots ranged from 0.0016 to 0.016 (total crop, dry weight basis). The modeled plant:soil ratio of 0.10 for vegetables/fruits in the background scenarios is higher than the 0.0016 to 0.016 for lettuce and peas in the Muller, et al. (1994) experiments. This could suggest an overestimation of the modeling of air-to-plant impacts.

5) Several of the articles, both from the German work and the earlier work, noted that most of the concentration was in the outer portions of the below and above-ground vegetation, and not the inner portions. Despite significant increases in soil concentration from the ppt to the ppb range, inner potato tuber concentrations remained constant (Hulster and Marschner, 1991, 1993). This evidence was the principal justification for the use of the empirical adjustment factors termed VG for soil to below ground transfers, VG_{bg}, and vapor-phase air transfers to bulky above ground vegetation, VG_{ag}. The chemical-specific empirical transfers factors for both of these transfers were developed in laboratory experiments with several chemicals using thin vegetation - solution phase transfers to barley roots for below ground vegetation concentrations, and vapor phase transfers to azalea leaves and grass leaves for vapor phase transfers. For the dioxin-like compounds, direct use of these transfer factors would be most appropriate for the outer few millimeters, perhaps, of below and above ground bulky vegetation. The assignment of

a VG of 0.01 for bulky above and below ground vegetation was based on an outer surface volume to whole plant volume ratio for a common vegetation such as a carrot or an apple. A VG of 1.00 was used for grass, since that is a thin vegetation.

Further evidence for the above ground VG came from a study by McCrady (1994), who measured the uptake rate constants of vapor-phase 2,3,7,8-TCDD to several vegetation including grass and azalea leaves, kale, pepper, spruce needles, apple, and tomato. The uptake rate for the apple divided by the uptake rate for the grass leaf was 0.02 (where uptake rates were from air to whole vegetation on a dry weight basis). For the tomato and pepper, the same ratios were 0.03 and 0.08. The VG_{ag} was 0.01 for fruits and vegetables in this assessment. McCrady (1994) then went on to normalize his uptake rates on a surface area basis instead of a mass basis; i.e., air to vegetative surface area uptake rate instead of an air to vegetative mass uptake rate. Then, the uptake rates were substantially more similar, with the ratio of the apple uptake rate to the grass being 1.6 instead of 0.02; i.e., the apple uptake rate was 1.6 times higher than that of grass, instead of 1/50 as much when estimated on an air to dry weight mass basis. The ratios for tomato and pepper were 1.2 and 2.2, respectively. Therefore, since the B_{vpa} in this assessment is an air to plant mass transfer, the McCrady experiments would appear to justify the use of an above-ground VG of a magnitude less than 0.10.

6) An experiment by the Hulster, et al. (1994) on vegetation of the cucumber family contradicted the conventional wisdom that direct soil to root to above ground plant impact would not occur for the dioxin-like compounds. Their results were most striking for zucchini, which showed uniform plant concentrations from inner to outer portions of the zucchini fruit, and the highest whole fruit concentrations and plant:soil ratios they had ever measured, despite careful experimental conditions which physically isolated the fruit from the soil. Pumpkins also showed high plant contamination and plant:soil ratios, with more expected plant concentrations measured for the cucumber. No explanation was offered for these results. It was assumed for this exposure assessment that the fruits and vegetables for human consumption, and the grasses, hay, and other vegetation animals consume, would not follow this pattern.

A principal observation that can be drawn from this examination is that the plant:soil contaminant concentration ratios from the background scenario may be higher than observed in experiments, although this conclusion must be tempered by the fact that the soil concentrations in the experiments were always higher than the 1.29 ppt WHO_{98}-TEQ_{DF} soil concentrations used in the background scenario. One other important observation made above was that, as the soil concentration increased, the plant:soil concentrations decreased. For the experiment where soil

concentrations were closest to background, the 5 and 56 ppt TEQ concentrations in the experiments of Muller, et al. (1994), the overprediction by the model was on the order of 10.

The same story is not necessarily told, however, when comparing results from the demonstration of the soil contamination demonstration with these literature ratios. The plant:soil ratios for the background scenarios ranged from 0.10 to 0.33. The following plant:soil contaminant concentration ratios were estimated for the soil contamination scenario. Again, tilled soil concentrations and dry weight vegetative concentrations were used: below ground vegetables - 0.22, above ground vegetables/fruit - 0.00005, grass - 0.003, and feed 0.002. These ratios were calculated using the soil concentrations predicted to occur at the site of exposure, which is valid for the below ground vegetables, but not quite for the above ground vegetation. Ratios calculated by using the near field dispersion models and assuming plants are grown on the impacted soils would result in slightly higher ratios, by about a factor of three. Below ground vegetables still show a clear relationship with soil concentrations, as in the background scenarios. However, now it appears that plant:soil ratios for above ground vegetation are much lower for this demonstration scenario as compared to the background scenarios.

In fact, in a slight variation to this exercise, one could use near background soil concentrations for the soil contamination algorithms and show similarly low plant:soil ratios. In this instance, one can observe that at low background soil concentrations, the soil-to-plant algorithms of the soil contamination source category underestimate above ground plant concentrations.

This observation that plant:soil ratios for above ground vegetation are higher in the literature as compared to modeled ratios for the soil contamination algorithm has to be carefully considered. Two explanations are offered. For experiments conducted outdoors, the source of air reservoirs of dioxin-like compounds are the soil in which the plant is growing as well as from distant sources and long-term transport. Also, it is possible that the model is underpredicting air concentrations and hence underpredicting soil-to-air-to-plant transfers. The same issue arose in Section 7.3.8 earlier, where it was noted that the soil contamination model predicted very low air concentrations given background soil concentrations, much lower than observed background air concentrations. In that section, like in this section, it was unclear whether long range transport explained most of background air concentrations and/or the model was underpredicting air concentrations.

7.3.11. Comparison of Measured and Modeled Vapor/Particle Distributions for Semivolatile Compounds Other Than Dioxin

In Chapter 3, the Junge-Pankow model was described and applied to the dioxin-like compounds in order to partition air-borne dioxins into a vapor and a particle phase. These modelled particle percentages were then compared to measured particle percentages, and a consistent pattern among several field measurements versus model predictions emerged: the model tended to predict that more of the dioxin would be in the particle phase compared to what was measured. Whether the model is "correct" or the measurements are "correct" is a matter of ongoing debate, as described in Chapter 3. This section will compare measured and modelled particle percentages for semivolatile organic compounds (SOCs) other than the dioxins. These include PAHs, PCBs, and organochlorine pesticides.

Table 7-18 presents a summary of the analysis of monitoring data on SOCs from several cities and rural locations. The parameters in this table come from the following empirical correlation, which is described in more detail in Chapter 3:

$$Log\ K_p = m\ Log\ p^\circ_L + b \qquad (7\text{-}41)$$

where:

K_p = particle/gas partition coefficient, $m^3/\mu g$, defined as: Cp (ng/μg)/C_g (ng/m^3), where C_p is the concentration associated with aerosols, and C_g is the gas-phase concentration

p°_L = liquid sub-cooled vapor pressure, Pa

m, b = empirically derived slope and intercept from the data sets

The sub-cooled liquid vapor pressures for the SOCs were taken from reports in the literature including values for PAHs (Yamasaki et al., 1984), PCBs (Falconer and Bidleman, 1994), and OC pesticides (Hinckley et al., 1990). The particle-bound fraction, ϕ, is related to K_p, as follows:

$$\phi = \frac{K_p\ [\ TSP\ ]}{1 + K_p\ [\ TSP\ ]} \qquad (7\text{-}42)$$

where:

ϕ = particle bound fraction, unitless (not the same as the particle bound concentration, C_p)

K_p = particle/gas partition coefficient, $m^3/\mu g$

TSP = total suspended particulates, $\mu g/m^3$

If TSP was not reported in the original paper (in most cases), it was assumed that TSP = 98 $\mu g/m^3$ for urban air and 10-42 $\mu g/m^3$ for non-urban air of varying cleanliness.

The two equations above, in combination with the data reported in the literature article, were used to develop the dotted line "observed" particle percentages shown in Figures 7-10 and 7-11. The modeled particle fractions were determined for these sites using the Junge-Pankow model detailed in Chapter 3. According to that model, the particulate fraction is estimated as:

$$\phi = \frac{c\,\Theta}{p^{\circ}_{L} + c\,\Theta} \qquad (7\text{-}43)$$

where:

ϕ = fraction of the compound adsorbed to aerosol particles

p°_{L} = saturation liquid phase vapor pressure of the pure compound at ambient temperature, Pa

Θ = the particle surface area per unit volume of air, cm^2 aerosol/cm^3 air

c = a constant which is related to the difference between the heat of desorption from the particle surface, Q_d, and the heat of vaporization of the compound, Q_v, estimated at 17.2 Pa-cm

In applying this model, values of Θ assumed include $4.2*10^{-7}$ for "clean continental", $3.5*10^{-6}$ for "background plus local sources" and $1.1*10^{-5}$ for "urban" conditions. Further detail on this model can be found in Chapter 3.

The agreement between the measured and predicted aerosol-bound fractions of PAHs is remarkably good, as seen in Figure 7-10. Two model curves are shown for rural air in Figure 7-10b, representing "clean continental background" and "background plus local sources" regimes. Experimental PAH distributions fall reasonably close to the range of particulate values predicted by the model, although the fraction of aerosol-bound PAHs at rural sites (e.g., Lake Superior) is greater than expected for the more volatile compounds. This may be due to a portion of these PAHs being "non-exchangeable" (Pankow, 1988).

Fewer data are available for non-dioxin organochlorine compounds. Figure 7-11 shows the measured particulate percentages of PCB congeners and chlorinated pesticides in comparison to predictions. Again, the two depictions of model predictions for rural conditions, Figure 7-11b,

show a range from clean continental to background plus local sources. The monitored data fall below the model values, but the discrepancy is generally not as great as for the PCDD/Fs.

Overall, it can be concluded the Junge-Pankow model appears to predict vapor/particle partitioning very similar to measurements for PAHs, but not as similar for PCBs and chlorinated pesticides, although the match there is still superior to that of PCDD/Fs. This exercise does lend additional credibility, in general, to the Junge-Pankow Model. However, the model and the measurements for PCDD/Fs do diverge, as described at length in Chapter 3, and the debate remains as to which is "correct" for the PCDD/Fs - the model or the measurements.

7.3.12. An Update of the Air-to-Beef Model Validation Exercise

In the previous version of this dioxin exposure document (EPA, 1994) as well as in a journal article (Lorber, et al., 1994), a validation of the air-to-beef food chain model used in this assessment was presented. As a result of public comments received on the review of the dioxin exposure document, that exercise has been refined and updated. This section will review the principal comments made and these updates. Except for a brief overview, this section will not describe the previous air-to-beef model validation exercise.

Figure 7-12 presents an overview of the air-to-beef food chain model. The premise of this modeling exercise to test the beef food chain model for dioxin-like compounds is that air-borne reservoirs of these compounds in rural environments are the "source term" explaining concentrations found in beef. The principal assumption in the validation exercise is that one can define an "average" rural air profile of dioxins, route this profile through the food chain model, and predict an "average" beef concentration. This exercise probably would not qualify as a validation exercise in the traditional sense. Most environmental model validation exercises rely on data obtained from a single site. For a traditional model validation of the air-to-beef model, one would need the following: a representative air concentration profile, including all the dioxin-like congeners, during the lifetime of the cattle, information on the cattle diet during his lifetime, a set of vegetation congener-specific concentrations typical of the cattle diet (and the cattle should be fed from vegetation grown in the area corresponding to the air concentration), and a set of congener-specific concentrations from beef from the slaughtered cattle. As this information was unavailable, the model validation exercise proceeded by attempting to define these "average" air profiles, vegetative profiles, and beef concentration profiles.

The key components of the previous model validation exercise were:

1. The representative air profile was crafted based on a representative profile of urban air concentrations generated as the average of 85 data points of air concentrations from urban settings, coupled with information suggesting that rural air profiles were lower than urban air profiles, by about a factor of 5. The rural air profile was crafted, therefore, by dividing each congener concentration in the urban air profile by 5.
2. Each congener was separated into a vapor fraction and a particle fraction. The vapor/particle partitioning model is described in Chapter 3.
3. The vapor fraction "transfers" into cattle vegetation, including categories described in Chapter 4 as "grass" and "hay/silage". The particle bound fraction is assumed to deposit onto these vegetation. Dry deposition was modeled as a product of the concentration times a deposition velocity of 0.002 m/sec, based on the findings of Koester and Hites (1992). Also, wet deposition was assumed to equal dry deposition, based on measurements of Koester and Hites (1992) showing these two components to be roughly comparable for settings in Illinois and Indiana.
4. Forty-eight percent of the cattle diet was assumed to be in grass, 48% was assumed to be in hay/silage, and 4% was assumed to be in soil. The concentration in the fat of beef was modeled as a function of the concentrations in these media times a bioconcentration factor.
5. The cattle were assumed to undergo a period of feedlot fattening prior to slaughter. This is a predominant practice in the United States, and it was felt that the observed beef concentrations were from cattle which went through feedlot fattening. Based on previous modeling efforts, the impact of this fattening regime was to reduce concentrations in the body fat by about a factor of 2 compared to body fat concentrations prior to entry into the feedlot. Therefore, concentrations predicted to occur without this feedlot consideration were reduced by 50% to model the impact of feedlot fattening.
6. The "observed" beef concentration profile was crafted as the average of 14 samples from 3 "grab bag" studies measuring the concentration in beef and veal from grocery stores.

Four principal comments received on the air-to-beef model validation exercise following the release of the 1994 dioxin exposure document were:
1. Although the final predicted TEQ beef concentration was reasonably close to the observed beef TEQ concentration, there was not a good match in the concentrations of the individual congeners not a good match of total concentrations (i.e., the sum of the concentrations of all congeners).
2. The air-to-leaf transfer factor was overestimating the impact of vapor-phase dioxins to vegetation.

3. A simple division of the crafted urban profile by 5 to arrive a crafted rural profile would not appropriately consider changes in the profile from urban to rural centers that have been studied and are believed to occur.
4. The results of the USDA/EPA beef study that is described in Volume I of this Exposure Reassessment and in Winters, et al. (1996) is preferable as an observed data set to the grab sample of 14 data points.

The first comment was addressed by revising the air-to-beef model validation exercise based on the next three comments. The discussion of the revised model exercise will now proceed by first reviewing the model changes made, then reviewing the revised air and the new beef concentration profiles used, and how the revised model validation exercise compares with the original validation exercise.

a. Revisions to the air-to-beef model parameters: Table 7-19 compares the four key changes made to the model validation exercise. Following are brief notes on each:
1. B_{vpa}: Chapter 4 describes how this version of the air-to-leaf transfer factor was derived from experiments conducted by Welsch-Pausch, et al. (1995). As seen in Table 7-19, this procedure resulted in a lowering of the transfer factor for all congeners by an order of magnitude and less, except the octa congeners which were lowered by 2-3 orders of magnitude and the hepta furan congeners, which were slightly higher in their current form. It is noted that these B_{vpa} are slightly different than a set of B_{vpa} published as proceedings of the 15th International Symposium on Chlorinated Dioxins and Related Compounds (Lorber, 1995). The procedure to derive the B_{vpa} in this assessment is the same as in that publication. However, this assessment uses a different set of vapor/particle fractions based on a reassignment of dioxin fate parameters. With different v/p fractions, the calibrated B_{vpa} was slightly different.
2. As just noted, the vapor/particle partitioning changed slightly in the current version, due to the reassignment of critical parameters required for the calculation of the vapor/particle percentages. These parameters include the Henry's Constants and the liquid sub-cooled vapor pressures. In their current form, there is generally less concentration predicted to occur in the vapor form, particularly for the penta dioxin, the tetra furan, and the two penta furans. It is noted that the 1994 vapor percentages for the octa congeners were assigned a value of 0.00. In fact, if the percentages were calculated to two decimal places with the 1994 parameters, they would equal 0.02% (or, on a fraction basis, 0.0002) instead of 0.00 as noted. Although a small percentage, it is seen that the air-to-leaf transfer factors for the octa congeners were on the order 10^8 to 10^9. As

discussed in the prior air-to-beef model validation (EPA, 1994; Lorber, et al., 1994), this became critical as assignment of the very small vapor fraction did make a significant difference to octa vegetation predictions, and hence octa beef concentration predictions. For the current exercise, there was no rounding to 0.00; the values calculated and used are 0.2% for both octa congeners with the revised fate parameters.

3. The bioconcentration factors for each congener were uniformly increased by about 30% as compared to the 1994 version. This was due to a recalculation using the same data as was used for the 1994 version. Based on a personal communication with the study author, it was determined that the total dry matter intake by the lactating cow was miscalculated for the 1994 version. Instead of 15 kg/day, the correct total dry matter intake was 21 kg/day. Therefore, intake concentrations decreased by about one-third, and so calculated bioconcentration factors increased by about one-third.

4. The soil concentrations used in the current version were the actual measured soil concentrations corresponding to the site where the air concentrations were taken. As will be described below, the air concentration profile was taken from an actual rural site near Columbus, Ohio. These were the same air profile and soil profile used in the demonstration background scenario in Chapter 5. The soil concentrations used in the 1994 model validation exercise were not model inputs, but were rather predicted by the deposition of particle-bound dioxins. There does not appear to be substantial differences in the two profiles, and as soil is a small part of the cattle diet, these changes were not meaningful to final predictions of beef concentrations.

b. New air profile: While a straight division of an urban profile by a factor of 5 may recognize overall reductions in air concentrations when going from an urban to a rural location, and concurrent reductions in TEQ air concentrations, they may not recognize a key trend observed by researchers concurrently studying urban and rural air profiles. The trend was best stated by Eitzer and Hites (1989), who studied such profiles including a statistical analysis of profiles. As they stated, "The geographic variability suggests the following atmospheric transport scenario. Urban air is contaminated with PCDD/F by proximity to the combustion sources of these compounds. As the air mass moves away from the urban area, it is diluted with cleaner air, lowering the PCDD/F concentrations. As the air is transported, transformations occur changing the profile. One transformation is photodegradation of vapor-phase PCDD/F. The less chlorinated PCDD/F have greater proportions of their total concentration in the vapor phase. Thus, vapor-phase photodegradation during the transport process would have a greater effect on the less chlorinated PCDD/F. Like the washout process, these degradation processes

would favor an ultimate PCDD/F profile with enhanced concentrations of the more chlorinated compounds." Simply dividing an urban profile by a factor of 5 did not account for these changes. It should be noted that photodegradation has not been definitely proven to occur and explain the trends noted by Eitzer and Hites (1989). Most importantly, they identified a trend that appears to be true, not only for their profiles, but for air concentration profiles from the Columbus area, as will be described shortly.

Ideally, one would want several rural profiles representing beef production areas in the United States. Lacking that information, what was available was a profile derived from a study of ambient air in the city of Columbus undertaken by the Ohio EPA (OEPA, 1994;1995), and described above in Section 7.3.7 on a model validation exercise of the ISCST3 model. That study included two sampling events of urban air in 1994 and one sampling in 1995. Concurrent with the urban samples were two background rural samples in 1994 and a third in 1995. The rural sampling site was located 28 miles in the upwind direction from Columbus (i.e., it was least likely to be impacted by urban sources in the nearest largest city, Columbus). The sampling program was undertaken to evaluate air quality in the vicinity of a municipal solid waste incinerator. There were six samplers in the city of Columbus, 5 operating for each of the 1994 sampling events (not the same 5), and 6 operating in 1995. Therefore, there were a total of 16 urban air samples. This incinerator was operating in 1994, but was shut down in 1995. Therefore, the 1995 sampling was undertaken to evaluate the air quality in the absence of the incinerator. During the sampling in 1994, OEPA (1994) identified a clear trend in the data: that the measurements were highest in the air samplers which were located in the predominant wind direction, from the incinerator to the air sampler, during the sampling. The 1995 did show a reduction in the measured air concentrations (OEPA, 1995). There was one rural air sampler, so the sampling program included three rural air samples. The three rural air samples did not show any trend related to the incinerator, and as will be seen, were lower in magnitude than the urban samples. Chapter 5 describes how the rural air profile for the background scenario was crafted from these three rural samples.

This revised air-to-beef model validation exercise will use the rural air profile that was crafted for the background scenario. Table 7-20 compares the air concentration profiles discussed above, including the crafted 1994 urban and rural air profiles compared against the Columbus urban air profile and the Columbus rural air profile. The Columbus urban air profile was developed as the average of the 16 data points from the three air sampling, including the assumption that the air concentration was ½ detection limit for all non-detects. The final

column shows the ratio of the Columbus urban air concentration with the Columbus rural air concentration.

The Columbus urban air concentration looks substantially like the crafted urban air profile with notable differences only for 1234678-HpCDD, OCDD, and 2378-TCDF. In each of these cases, the Columbus air profile is smaller than the crafted urban profile. The Columbus 2378-TCDF concentration is more than a factor of 5 lower than the crafted urban concentration of 2378-TCDF. OCDD in Columbus is almost a factor of 3 lower than the crafted urban profile, and the absolute difference in the OCDD concentrations of nearly 2.0 pg/m^3 explains most of the difference of about 2.2 pg/m^3 of total dioxin in the profiles (with "total" being defined as the sum of the 17 dioxin-like congeners). The I-TEQ concentrations in the urban profiles are similar - the Columbus urban air I-TEQ concentration of 0.070 pg/m^3 is about 75% of the crafted urban profiles of 0.095 pg/m^3.

The two rural air profiles have the same I-TEQ concentration of 0.019 pg/m^3, but the Columbus rural total concentration is about 50% higher than the crafted rural profile. This is due principally to the higher OCDD and 1234678-HpCDD concentrations in the Columbus profile. Most importantly, it would appear that the Columbus urban and rural profiles conform to the expectations as laid out earlier in the quote from Eitzer and Hites (1989). Specifically, it does appear that the lower chlorinated congeners undergo more of a loss, proportionally speaking, as compared to the higher chlorinated congeners. The ratio of the urban hepta and octa dioxin and furan congeners to their rural counterparts ranges from 1.2 to 3.8; while the range for the tetra through hexa dioxin and furan congeners is 1.0-6.3. The 1.0 ratio is for a congener which has a very low concentration to start with, 0.003 pg/m^3, and whose rural concentration is driven by detection limits. Without this congener, the second lowest ratio is 2.4. In other words, it would appear that a more appropriate range for the tetra through hexa congeners is 2.4-6.3. Of note are the very low changes in the hepta dioxin congener and octa dioxin congener, whose ratios are 1.2. Also of note is the very lower tetra furan congener, which dropped by a factor of 6.3 and is also 6 times lower than the concentration for this congener in the crafted rural profile of the 1994 exercise. These trends for the OCDD and tetra furan congener will later be important in explaining improvements in beef concentration predictions for the current model validation exercise.

c. New beef profile:

The EPA/USDA study on dioxins in beef is described in Chapter 3, Volume II of this assessment and also in Winters, et al. (1996). The congener profile for this study is compared

with the congener profile for the 14 grab samples from three studies in the next section on results. It is noted that the EPA/USDA study shows lower congener concentrations for all but one congener, and total and TEQ concentrations that are 2-3 times lower that the 14 grab samples. The precise reason for this difference in profiles is not known, but some possible reasons could be:

1) The three studies from which the 14 samples originated were not statistically designed studies, and may have simply taken samples with higher concentrations.

2) There may, in fact, be a trend of reduced concentrations in the beef because of the time periods in which the data was obtained. Two of the three studies took samples prior to 1990, the other one taking samples in 1992. The EPA/USDA study took samples in 1994. Furst and Wilmers (1995) did note nearly a 25% reduction in cow milk concentrations of I-TEQs taken in 1994 as compared to 1990. This is a much smaller reduction than the 60-70% reduction noted in the two groups of beef samples.

3) There was no detailed examination of the quality assurance programs for the three studies taking grab samples from the grocery stores. There may have been laboratory problems.

4) There has been some data suggesting the leaching of dioxins into milk from milk cartons. The packaging and handling of beef may also introduce dioxins into beef. Since the EPA/USDA beef study obtained samples directly from the slaughterhouse, such introductions by packaging and handling would not occur. However, this explanation was contradicted by three additional grocery store grab samples of ground beef taken in Mississippi in 1995 (Cooper, et al., 1995), which showed concentrations quite comparable to the EPA/USDA beef sampling program. If packaging and handling did effect the 14 grab bag samples, they did not affect the Mississippi sampling.

5) The EPA/USDA samples were from back fat. The back fat samples were from a reservoir in the cow, which at a point nearby, is the fat which is the outer part of meat cuts from the cattle rib area. Back fat itself is not used or consumed. There is very little data on the differences in concentrations of dioxin-like compounds in the different edible and non-edible fat reservoirs of cattle. A recent study showed that there are not significant differences in dioxin and dioxin-like coplanar PCBs among fat reservoirs except a much higher concentration in the lipid of liver (Lorber, et al., 1997). Nonetheless, the grocery store samples were from different reservoirs of fat than the back fat of the EPA/USDA study.

If it is true that the fat concentrations of dioxins are similar across different body reservoirs of fat (with the exception of the lipid in liver), than it is certainly appropriate to conclude that the results of the EPA/USDA statistical monitoring study are a more appropriate

representation of edible fat in beef as compared to the compilation of 14 grab samples used in the prior air-to-beef model validation exercise.

d. Results of the revised validation exercise: Table 7-21 shows the 1994 and 1996 model predictions for leafy vegetation, and compares then against five available data sets for leafy vegetation. The data on hay in the US (Reed, et al., 1990) seems to conflict the other available data on the table - it has significantly higher concentrations of the congeners it does have available, particularly the value for 285 ppt concentration of OCDD. This data could have been influenced by a local source, or because of the particular type of hay it was, it may have had much higher particulate dioxin contributions as compared to other grass data sets. One set from a rural setting in the UK (Jones and Duarte-Davidson, 1997), however, also has somewhat high OCDD concentrations at 94 ppt. All other sets had OCDD concentrations less than 25 ppt OCDD. This site in the UK also had relatively high air concentrations at 0.21 pg I-TEQ/m^3 compared to the rural air profile of 0.019 pg I-TEQ/m^3 from the Columbus site used in the exercise here. As described in Section 7.2.1. above, the modeling framework of this assessment used this data set to model a grass concentration of 3.7 pg I-TEQ/g, which is reasonably close to the measured 6.0 pg I-TEQ/g. The other two data sets from the UK are reasonably similar, with the more recent data set (Kjeller, et al., 1996) showing lower concentrations, and in fact, this data was used by the authors (among other data) to suggest that emissions of dioxins are being reduced in the UK. The data set on alfalfa is consistent with this data on grass in the UK.

It is easily seen that the current set of model predictions of dioxins in grass is much more in line with these two UK observations and the US alfalfa observation as compared to the predictions in the 1994 data set. There was a general reduction in the concentrations predicted between 1994 and the current predictions, due primarily to the reductions in the air-to-leaf vapor transfer factor, B_{vpa}. There were noticeable improvements in some of the congeners, particularly the predictions for 2378-TCDF and 12378-PCDF, and to a lesser extent but still noticeable, improvements in 12378-PCDD, 123478-HxCDD, 23478-PCDF, 123478-HxCDF, 123678-HxCDF, 234678-HxCDF, and OCDF. There was also an improvement to OCDD. It was noted above that the vapor fraction assumed for OCDD was 0.00 in the 1994 exercise, but in a detailed examination in Lorber, et al. (1994) and EPA (1994), use of a vapor fraction of 0.0002 for OCDD, which is what the V/P model calculated for the vapor fraction for OCDD, actually resulted in grass concentration approaching the hay concentration found in Reed, et al. (1990). Given the other leafy concentrations, it would appear that an OCDD grass concentration in the 10-30 ppt range is more appropriate than one greater than 100 ppt.

As a final and simple test of the current model predictions for leafy vegetation, the two data sets from the UK were averaged with the one set from alfalfa in the United States and correlated against the two sets of model predictions. The best fit regression line for the 1994 model predictions and this average of three observations had a slope of 0.26, an intercept of 0.84, and importantly a rather poor r^2 of 0.14. In contrast, the best fit regression line for the 1996 model predictions had a slope of 1.13, an intercept of 0.007, and a much improved r^2 of 0.98.

Table 7-22 compares the final predicted and observed beef data sets from the 1994 and the current validation exercise. There are reductions in both the observed and predicted beef concentrations from the 1994 results to the current results. However, given the conclusion stated above regarding the superiority of the EPA/USDA beef data set for this validation exercise, it is most appropriate to compare the predictions made in 1994 and those made in the current exercise with this observed data set. Just by visual inspection, it is seen that notable improvements in model predictions are noted for the following congeners: 12378-PCDD, OCDD, and 2378-TCDF. There are some congener predictions for which the 1994 validation exercise appears to result in a superior match, including 123478-HxCDD, 12378-PCDF, 123789-HxCDF, and 234678-HxCDF. Overall, the TEQ concentration in the current validation is closer to the observed TEQ concentration, although the total concentration appears more favorable for the 1994 validation exercise.

A simple correlation test suggests that the current model validation is superior to the 1994 model predictions. The following shows the results of linear regressions of the 1994 and 1996 model predictions with the EPA/USDA monitoring results assuming ND = ½ detection limit and ND = 0.0:

	Slope	Intercept	r^2
1994 model/ND = ½ detection	0.70	0.58	0.11
1994 model/ND = 0	0.74	0.13	0.16
1996 model/ND = ½ detection	1.02	0.55	0.57
1996 model/ND = 0	0.76	0.25	0.41

As seen, there is a better regression with the current modeling exercise as compared to the 1994 model exercise, with current r^2 of 0.57 and 0.41 compared against r^2 of 0.11 and 0.16.

It is also easy to see why individuals commenting on the air-to-beef model validation exercise of 1994 would note a poor correlation between observed and predicted concentrations. Very poor matches between predicted and observed are seen for 123678-HxCDD, 1234678-

HpCDD, OCDD, 2378-TCDF, 123478-HxCDF, 1234678-HpCDF, 1234789-HpCDF, and OCDF. Overall, the r^2 for the 1994 predictions against the observations from the 14 grocery store samples was 0.16. Also, the slope for this test was the highest of all the tests so far at 2.4, indicating that, for the best fit regression line, observations were higher than predictions by a greater margin than when testing against the EPA/USDA data set. For these tests, the slopes ranged from 0.74 to 1.02.

e. Remaining uncertainties in the validation exercise and in air-to-beef modeling in general: Following is a summary of the key uncertainties of this exercise and of food chain modeling in general:

1. A characteristic rural air environment: A profile of air concentrations of dioxin-like congeners in a rural environment would be better achieved as the average of several profiles in appropriate environments instead of just one.

2. A better understanding of the differences in the EPA/USDA sampling program and the grocery store samples taken earlier: There were 5 possible explanations listed as to why the earlier beef samplings appeared to have uniformly higher concentration profile as compared to the USDA/EPA beef profile. Before fully relying on the EPA/USDA sampling of cattle back fat, it would be appropriate to understand how the concentrations may differ, if any, with fat in beef purchased at grocery stores.

3. Vapor/particle partitioning: A theoretical modeling approach was used to partition the total reservoir of congeners into particle and vapor phases. Monitoring data suggests a different partitioning regime. This dichotomy was discussed in Chapter 3 and further in this Chapter in Section 7.3.11. A carefully designed monitoring experiment could shed some light on vapor/particle partitioning for dioxin-like compounds. This is obviously critical given the major conclusion of the dominance of vapor phase concentrations in explaining beef concentrations.

4. Vapor transfers to vegetation: Like the partitioning issue, the quantification of transfers onto vegetation is critical. There is some suggestion that the Welsch-Pausch experiments for which the air-to-leaf vapor transfer factor was developed may be unrealistic for field situations. Factors which make it unrealistic includes pots raised off the ground, and the grass being a dense monoculture. More typical field situations - at ground level with varied vegetation of lesser density may lead to lower transfers of vapors from the atmosphere to the canopy (M. McLachlan, Bayreuth University, FRG, personal communication). A data set including both field level pasture measurements coupled with a corresponding air profile would

be preferable to the data set of Welsch-Pausch for calibrating a vapor transfer factor, but none could be found for this assessment.

5. Particle depositions onto vegetation: The impact of wet deposition needs to be further investigated. A literature article suggesting that about 30% of particles depositing in rain are retained on the canopy after the rainfall justified the assignment of 0.30 to the parameter, R_w (fraction retained on vegetation from wet deposition). The weathering half-life of 14 days, while often used for dioxins, is also identified as uncertain. This half-life was based on studies on particle depositions on plants. It is possible that the dioxins would preferentially sorb onto the plants. Therefore, while particles themselves may have a 14-day half-life on the plants, the dioxins on the particles may remain behind on the plants and have a much longer half-life. Umlauf and McLachlan (1994) modeled the deposition of particle bound semi-volatile organic compounds (SOCs) to spruce leaves and assumed that the SOCs were fully retained on the leaves. In their publication, they did discuss the transfer of the SOCs from the particles to the leaves. Finally, the deposition velocity of 0.2 cm/sec should be considered further.

6. The bioconcentration factor: Only one study was found from which congener-specific bioconcentration factors for the suite of congeners could be developed, and this was for one cow, for one lactating period, and was for milk and not beef. The differences in bioconcentration between beef and milk need to be further investigated and quantified.

7. Cattle diet and the impact of feedlot fattening: A cattle diet was simplistically assumed to consist of 4% soil and equal parts of grass and non-grass feeds. Perhaps a more representative diet could be crafted, which would lead to a different exposure pattern by the beef cow prior to feedlot fattening. Equally if not more important is the impact of this feedlot fattening. It is clear that commercial beef cattle in the United States undergo a period of feedlot fattening. However, before and after monitoring quantifying the impact of this practice could not be found. Two modeling studies, which assumed that dilution and depuration were occurring during feedlot fattening, estimated that concentrations were halved due to this process. This was the assumption also made in this paper, and it needs to be further evaluated.

7.3.13. *Expansion of the Terrestrial Food Chain Model for Dioxins and Applications to other Foodstuffs in the United Kingdom*

Harrad and Smith (1997) adopted the food chain model developed initially in the first draft of the Dioxin Reassessment (EPA, 1994), expanded it to include soil-to-above ground plant transfers, and applied it to UK data in very much the same manner as in the air-to-plant-to-beef exercise described just above in Section 7.3.12. Soil-to-above ground impacts are assumed not

to occur in this assessment, and in Harrad and Smith (1997), they found that soil-to-above ground translocations explained very little of the predicted grass concentrations. They also expanded the initial development of this approach in EPA (1994) to include poultry and eggs, both of which are now modeled in this current assessment.

Although they didn't exactly state where the air data come from in their exercise, it is surmised that they selected a rural air concentration profile of the 17 dioxin-like CDD/Fs they deemed to be typical of UK conditions. Then they routed this concentration through the food chain models to predict the dioxin concentrations in various kinds of animal feeds, and then the concentration in animal meats. They compared predictions of dioxins in grass (one of the animal feeds) to those reported for a bulk herbage representing the years 1979-1988 reported in Kjeller, et al. (1991). They found the ability of the air-to-grass model to predict grass concentration to be "reasonably satisfactory" with predictions falling within an order of magnitude of observations, and I-TEQ predicted and observed concentrations to be close at 1.3 pg/g (predicted) and 0.86 pg/g (observed). They did note more variability in congener-by-congener predictions for the other food products but found that I-TEQ concentrations were reasonably well predicted, including: 1) retail meat products (assumed to be beef, but not identified as such), pg/g fresh weight: predicted - 0.252, observed - 0.254; 2) milk, pg/g fresh weight: predicted - 0.090, observed - 0.057; 3) poultry, pg/g fresh weight: predicted - 0.630, observed - 0.399; 4) eggs, pg/g fresh: predicted - 0.262, observed - 0.194; and 5) potatoes, pg/g fresh: predicted - 0.0072, observed - 0.037.

7.3.14. *Beef and Milk Fat Concentrations when Soil is the Source of Contamination*

Sampling of beef and milk near areas of elevated soil concentrations, or where cattle were raised on soils with known high concentrations of 2,3,7,8-TCDD, were not found in the literature. Therefore, the beef fat concentration of 60 ppt estimated to occur near an area where the soil concentrations of 2,3,7,8-TCDD was 1 ppb cannot easily be evaluated. There are some studies on other animals indicating high tissue concentrations in areas of high soil contamination of 2,3,7,8-TCDD. Lower, et al. (1989) studied animal tissues for wild animals in the abandoned town of Times Beach, Missouri, and compared their results for similar wild animals tissue concentrations found in Eglin Air Force Base in Florida; Seveso, Italy; and Volgermeerpolder, Holland. With 2,3,7,8-TCDD soil levels in these areas in the hundreds to thousands of ppt, tissue levels for earthworm, mouse, prairie vole, rabbit, snake, and liver samples from some of these animals, were in the tens to thousands of ppt.

There is an episode of beef and dairy cows being raised on lots where the soil was heavily contaminated with polybrominated biphenyls (PBB; details can be found in Fries and Jacobs, 1986; and Fries, 1985). Soil concentrations to which dairy and beef cows were exposed were 830 and 350 μg/kg (ppb), respectively. Body fat of the dairy cows had PBB concentrations of 305, 222, and 79 ppt (dairy heifers, primiparous dairy, and multiparous dairy, respectively). Body fat for the beef cows exposed to 350 ppb soil levels were 95 (cows) and 137 ppt (calves). Milk fat concentrations from the primiparous dairy and multiparous dairy cows exposed to 830 ppb soil levels were 48 and 18 ppt.

Fries (1985) estimated a quantity which is useful for purposes of comparison - this quantity is the ratio of concentration in animal fat to concentration in soil to which the animal is exposed. His justification for deriving this ratio is that soil was speculated as the principal source of body burdens of PBB in the data listed above. This is also the case for the soil contamination source category of this assessment. Ratios he derived for body fat of dairy heifers ranged from 0.10 to 0.37, while it was 0.02 and 0.06 for milk fat. For body fat of beef cows, these ratios were 0.27 and 0.39. Fries also measured a ratio of 1.86 for sows and gilts. He attributes much higher sow ratios to their tendencies to ingest more soil.

Analogous ratios can be derived for the demonstration of the soil contamination source category for beef and milk fat. For the demonstration in Chapter 5, the soil concentration predicted to occur at the farm was 0.36 ppb, and the beef fat and milk fat concentrations were predicted to be 0.06 and 0.03 ppb, respectively. These correspond to ratios of 0.17 for beef fat and 0.08 for milk fat. The milk fat ratio compares favorably with PBB ratios derived by Fries (1985), but the beef fat ratio appears generally lower. The beef fat concentrations in the demonstration scenarios were driven by the fraction of soil in the diet of the beef cattle, as were the concentrations in the milk fat. It may be possible that the cattle slaughtered for beef raised in the lots with high PBB concentrations were exposed to more soil than was assumed in the demonstration scenarios. There, soil was 4% of the diet. If this value were increased to 8%, than predicted beef fat concentrations would also double, and the beef fat:soil ratio would be 0.34 instead of 0.17.

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Table 7-1. Observed data for the air-to-plant model comparison exercise.*

Compounds	Rural Background Site			Industrial Site		
	Air	Deposition	Grass	Air	Deposition	Grass
2378-TCDD	0.01	<0.46	0.72	0.017	1.6	2.8
12378-PCDD	0.03	2.3	1.3	0.04	3.8	<0.08
123478-HxCDD	0.04	2.3	0.93	0.04	3.2	0.73
123678-HxCDD	0.08	4.8	2.3	0.09	10.8	6
123789-HxCDD	0.1	3.8	1.8	0.13	8.9	4.2
1234678-HpCDD	0.82	41	22	0.84	51	13
OCDD	2.5	166	94	2.5	153	43
2378-TCDF	0.33	12	14	0.57	18	16
12378-PCDF	0.06	2.5	1.8	0.1	2.2	<0.09
23478-PCDF	0.1	4.1	2.2	0.19	6	1.2
123478-HxCDF	0.3	11	5.6	0.45	12	4.6
123678-HxCDF	0.1	4.5	2.2	0.16	5.7	1.8
123789-HxCDF	0.02	1.8	0.61	0.07	1.9	0.54
234678-HxCDF	0.14	4.8	2.6	0.19	6	2.4
1234678-HpCDF	0.53	19	12	0.71	25	11
1234789-HpCDF	0.11	2.9	1.1	0.14	3.2	0.89
OCDF	0.42	28	13	0.48	35	8
TCDD	0.72	73	66	3.1	509	750
PCDD	0.56	54	33	1.2	477	410
HxCDD	0.65	38	26	0.78	73	38
HpCDD	0.71	41	22	0.73	48	11
TCDF	1.6	24	93	3.3	131	290
PCDF	0.84	27	31	2.3	64	21
HxCDF	0.45	18	13	1.4	26	19
HpCDF	0.22	<1.8	<0.22	0.43	<1.6	<0.31

* Units: air - pg/m^3; deposition - pg/m^2-day; grass - pg/g dry weight of dioxin in the grass. Grass yield for rural = 89 g/m^2 dry weight, for industrial = 42 g/m^2 dry weight.

Table 7-2. Model results comparing the EPA vapor transfer model and the Vapor Deposition Model with the field data for 2,3,7,8-TCDD (concentrations in pg/g dry weight).

Description	2,3,7,8-TCDD grass concentrations, pg/g dry	
	Rural	Industrial
Observed data	0.72	2.8
EPA vapor transfer model	0.25	0.21
Smith et al. (1995) model	0.06	0.05
Trapp & Mattheis (1995) model	0.13	0.1

Table 7-3. Model parameters used in the Hwang and the alternate volatilization models tested in this comparison exercise.

Description	Jury model	Simplified Jury model	Hwang model	Vapor diffusion
I. Soil Parameters				
C_0, initial soil concentration, mg/kg	0.001	0.001	0.001	0.001
θ, volumetric water content, cm^3/cm^3, or unitless	0.23	0.23	NR	NR
a, soil air content, cm^3/cm^3, or unitless	NR	0.2	NR	0.2
ϕ, soil porosity, cm^3/cm^3, or unitless	0.43	0.43	0.43	0.43
BD, soil bulk density, g/cm^3	1.5	1.5	NR	NR
Psoil, soil particle bulk density, g/cm^3	NR	NR	2.65	NR
J_w, water flux, cm/sec	0	NR	NR	NR
foc, fraction organic carbon	0.01	0.01	0.01	0.01
d_z, soil depth of constant concentration, cm	10	NR	NR	10
II. Chemical Properties				
D_g^{air}, chemical gaseous diffusion coefficient in air, cm^2/sec	$4.7*10^{-2}$	$4.7*10^{-2}$	$4.7*10^{-2}$	$4.7*10^{-2}$
D_l^{water}, chemical liquid diffusion coefficient in water, cm^2/sec	$5.6*10^{-6}$	$5.6*10^{-6}$	NR	NR
Koc, organic carbon partition coefficient, cm^3/g	$3.98*10^{6}$	$3.98*10^{6}$	$3.98*10^{6}$	$3.98*10^{6}$
H, Henry's Constant, atm-m^3/mole	$3.2*10^{-5}$	$3.2*10^{-5}$	$3.2*10^{-5}$	$3.2*10^{-5}$
μ, soil degradation rate, 1/sec	0	NR	NR	NR
III. Model Solution Parameters				
BL, boundary layer thickness, cm	0.5	NR	NR	NR
Time of Volatilization, days	10950	10950	10950	NR

NR = Not required for solution

Table 7-4. Results of model volatilization comparison exercise.

Description	Volatilization, g/cm^2-sec
Hwang model	$1.03 * 10^{-18}$
Full Jury model as coded in EMSOFT	$2.81 * 10^{-19}$
Simplified Jury Model as used in Superfund Soil Screening	$3.89 * 10^{-19}$
Vapor diffusion solution only	$4.03 * 10^{-21}$
Full Jury model, boundary layer = 0.01 cm	$3.02 * 10^{-19}$
Full Jury model, half-life = 25 years	$2.16 * 10^{-19}$

Table 7-5. Comparison of the derivation of the fraction of sorbed dioxin congener based on the octanol air partition coefficient, K_{oa}, or based on the sub-cooled liquid vapor pressure, as done for this document as described in Chapter 3.

Congener	Solving for K_{oa} [1]			ϕ for urban conditions[2]		ϕ for urban conditions as in Chapter 3
	log K_{ow}	H	log K_{oa}	theoretical	empirical	
2378-TCDD	6.81	$3.95*10^{-5}$	9.63	0.09	0.14	0.75
12378-PCDD	6.64	$2.60*10^{-6}$	10.58	0.48	0.40	0.95
123478-HxCDD	7.80	$1.05*10^{-5}$	11.13	0.76	0.60	0.99
123678-HxCDD	7.30	$1.10*10^{-5}$	10.61	0.49	0.41	0.99
123789-HxCDD	7.30	$1.10*10^{-5}$	10.61	0.49	0.41	0.99
1234678-HpCDD	8.00	$1.26*10^{-5}$	11.25	0.81	0.64	0.997
OCDD	8.20	$6.75*10^{-6}$	11.72	0.92	0.78	0.999
2378-TCDF	6.10	$1.44*10^{-5}$	9.29	0.05	0.09	0.73
12378-PCDF	6.79	$5.00*10^{-6}$	10.44	0.40	0.35	0.91
23478-PCDF	6.50	$4.98*10^{-6}$	10.15	0.26	0.26	0.94
123478-HxCDF	7.00	$1.43*10^{-5}$	10.19	0.27	0.27	0.98
123678-HxCDF	7.00	$7.31*10^{-6}$	10.49	0.42	0.36	0.98
123789-HxCDF	7.00	$1.10*10^{-5}$	10.31	0.33	0.31	0.99
234678-HxCDF	7.00	$1.10*10^{-5}$	10.31	0.33	0.31	0.99
1234678-HpCDF	7.40	$1.41*10^{-5}$	10.60	0.49	0.40	0.99
1234789-HpCDF	8.00	$1.40*10^{-5}$	11.20	0.79	0.62	0.997
OCDF	8.80	$1.88*10^{-5}$	11.88	0.95	0.82	0.999

[1] K_{oa}, the octanol air partition coefficient, is solved as, [Kow*R*T]/[H], where K_{ow} is the octanol water partition coefficient, dimensionless; R is the universal gas constant, $8.2*10^{-5}$ atm-m^3/mole-K;T is ambient temperature, 273 °K, H is the Henry's Constant, atm-m^3/mole.

[2] ϕ, the fraction of sorbed particle, is solved as $[K_p (TSP)]/[1 + K_p (TSP)]$. K_p is solved for either "theoretically", where log K_p = log K_{oa} -12.61, or "empirically" based on field data, as done by Kaupp and McLachlan (1999) as, log K_p = 0.6368 log K_{oa} -8.9111. See Section 7.2.7 for more detail on these algorithms.

Table 7-6. Summary of off-site soil contamination from Tier 1 and 2 sites of the National Dioxin Study.

Site name	On-site # samples/range (ppb)	Off-site # samples/range (ppb)	Comments
Diamond Alkali Newark, NJ	9/60-51,000	537/ND-725	Facility involved in the manufacture of 2,4,5-T; off-site sampling covered a 4000-ft radius including public areas such as a public housing unit, park, streets, and river. Two of 11 samples from a park were positive at 1-3.1 ppb; detection limit was 1 ppb. Other off-site positives were from streets and river sediments.
Brady Metals Newark, NJ	10/1.9-3500	30/1.7-1156	Site directly associated with the Diamond Alkali site summarized above; text did not provide any further detail on off-site soil sampling.
Love Canal Niagara, NY	NA/NA-6.7	20/3-263	Love Canal contamination well documented elsewhere; few details provided in reference for soil sampling programs; it was noted that 3,000 cubic yards of fly ash and BHC cake were taken from Love Canal in 1954 and used as fill at the nearby 93rd Street School, a subsurface sample 3+ ft deep showed a concentration of 6.7 ppb. The off-site summary provided here was from an area identified as Hyde Park.
Vertac Jacksonville, AR	45/<1-1,200	320/<1-33.4	A site manufacturing 2,4,5-T; it is not clear than any of the off-site sampling was for surface soil - summary tables identified it as "various"; text description did not mention off-site soil contamination and indicated that solid and liquid waste were buried on-site in a series of landfills. 2,3,7,8-TCDD was found in fish as far away as 100 miles.
Hooker Chemical Niagara, NY	17/ND-18,600	4/ND-430	A site manufacturing 2,4,5-TCP; subsurface soil sampling ranged from ND to 18.6 parts per million; one off-site surface soil detection noted at 1.1 ppb.
Bliss Tank Property Rosat, MO	NA/ND-430	NA-ND-430	No summary text provided in primary reference; tabular summary identified soil sampling as on/off-site soil; non-detects were noted in 13 off-site dust sampling.
Dow Chemical Midland, MI	#1: 43/0.041-52 #2: 106/ND-1500	11/0.0006-0.45 42/0.003-2.03	Site most extensively studied of those in National Dioxin Study; data identified as #1 was a summary of 1984 data supplied in NDS; #2 was a summary of 1985 data; the 1984 data was further detailed in Nestrick, et al. 1986; see text for further discussions on this site.

Source: EPA (1987)

Table 7-7. Description of soil, sediment, and fish sampling program of dioxin-like compounds undertaken by the Connecticut Department of Environmental Protection.

Site/Sampling Media	Description	Data Available
1. Bridgeport	Year RRF began operation	1987
Soil	Years of collection Number of sampling sites Total number of samples	1987, 1988, 1990 7 21
Sediment	Years of collection Number of sampling sites Water body descriptions Total number of sediment samples Range, samples per water body	1987, 1988, 1990 6 harbor (2), channel (1; off harbor), river, pond (2) 66 4 - 22
Fish	No fish sampling at this site	
2. Bristol	Year RRF began operation	1987
Soil	Years of collection Number of sampling sites Total number of samples	1987, 1988, 1990 4 12
Sediment	Years of collection Number of water bodies sampled Water body descriptions Total number of sediment samples Range, samples per water body	1987, 1988, 1990 2 pond (2) 60 29 and 30
Fish	Years of collection Number of water bodies sampled Water body descriptions Total number of fish samples Range, samples per water body Fish species	1987, 1988, 1989, 1990 2 pond (2) 140 68 and 72 brown bullhead, white sucker, yellow perch

(continued on following page)

Table 7-7. (cont'd).

Site/Sampling Media	Description	Data Available
3. Hartford	Year RRF began operation	1987
Soil	Years of collection Number of sampling sites Total number of samples	1987, 1988, 1990 4 12
Sediment	Years of collection Number of sampling sites Water body descriptions Total number of sediment samples Range, samples per water body	1987, 1988, 1990 3 impoundment (1), cove (2) 90 30 from each water body
Fish	Years of collection Number of water bodies sampled Water body descriptions Total number of fish samples Range, samples per water body Fish species	1987, 1988, 1989, 1990 2 cove (2) 159 81 and 78 carp, channel catfish, white catfish, white sucker
4. Preston	Year RRF began operation	1990
Soil	Years of collection Number of sampling sites Total number of samples	1990 4 4
Sediment	Years of collection Number of water bodies sampled Water body descriptions Total number of sediment samples Range, samples per water body	1990 3 2 ponds, 1 reservoir 30 10 from each water body
Fish	no fish sampling at this site	perch

(continued on following page)

Table 7-7. (cont'd).

Site/Sampling Media	Description	Data Available
5. Sterling	Year RRF began operation	1990
Soil	Years of collection Number of sampling sites Total number of samples	1990 4 4
Sediment	Years of collection Number of sampling sites Water body descriptions Total number of sediment samples Range, samples per water body	1990 2 pond (2) 20 10 from each pond
Fish	Years of collection Number of water bodies sampled Water body descriptions Total number of fish samples Range, samples per water body Fish species	1990 2 pond (2) 40 20 from each pond white sucker, yellow perch
6. Union/Stafford	No associate RRF, used as "control" or "reference" site	
Soil	Years of collection Number of sampling sites Total number of samples	1988 (Union), 1990 (Stafford) 4 (Un), 4 (St) 4 (Un), 4 (St)
Sediment	Years of collection Number of water bodies sampled Water body descriptions Total number of sediment samples Range, samples per water body	1988, 1990 2 pond (Un), reservoir (St) 20 10 from each water body
Fish	Years of collection Number of water bodies sampled Water body descriptions Total number of fish samples Range, samples per water body Fish species	1988, 1990 2 pond and reservoir 47 27 (reservoir), 20 (pond) brown bullhead, white sucker, yellow perch

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Table 7-7. (cont'd).

Site/Sampling Media	Description	Data Available
7. Windham	Year RRF began operation	1983
Soil	Years of collection Number of sampling sites Total number of samples	1988, 1990 4 8
Sediment	Years of collection Number of sampling sites Water body descriptions Total number of sediment samples Range, samples per water body	1988, 1990 1 reservoir 20 20 from each water body
Fish	Years of collection Number of water bodies sampled Water body descriptions Total number of fish samples Range, samples per water body Fish species	1988, 1989, 1990 1 reservoir 59 59 white sucker, brown bullhead, yellow perch
8. Preston	Year RRF began operation	1988
Soil	Years of collection Number of sampling sites Total number of samples	1988, 1990 4 8
Sediment	Years of collection Number of water bodies sampled Water body descriptions Total number of sediment samples Range, samples per water body	1988, 1990 2 impoundments 40 20 from each water body
Fish	Years of collection Number of water bodies sampled Water body descriptions Total number of fish samples Range, samples per water body Fish species	1988, 1989, 1990 2 impoundments 75 59 brown bullhead, carp, white sucker

Source: CDEP, 1992

Table 7-8. Frequency of non-detects and detection limits for soil, sediment, and fish, for three congeners in the Connecticut Department of Environmental Protection data set.

Congener/Description	Soil	Sediment	Fish
2,3,7,8-TCDD			
Percent of non-detects	50	27	3
Detection limit, ppt	0.13	0.25	0.05
2,3,7,8-TCDF			
Percent of non-detects	3	2	0.2
Detection limit, ppt	NDA (0.09)	0.17	NDA (0.09)
2,3,4,7,8-PCDF			
Percent of non-detects	1	5	7
Detection limit, ppt	NDA (0.09)	0.26	0.04

Source: for percent non-detects: MRI, 1992; for detection limits, draft Monitoring Progress Report for 1988, supplied by CDEP (1992) specific to MRI laboratories; NDA = no data available; number of parenthesis is ½ detection limit for time when non-detect was noted, see text for further information and interpretation

Table 7-9. Results for Connecticut Department of Environmental Protection sampling, including soil, sediment and fish concentrations, and the key concentration ratios of sediment to soil and the Biota Sediment Accumulation Factor (BSAF) ratio.

Site/Description	Soil	Sediment	Fish
A. 2,3,7,8-TCDD RESULTS			
1. Bridgeport			
Number of samples	21	66	no data
Range of concentration, ppt	0.07-4.62	0.20-51.50	
Mean concentration, ppt	0.59	4.53	
C_{sed}:C_{soil} Ratio: 7.7			
2. Bristol			
Number of samples	12	59	140
Range of concentration, ppt	0.01-0.61	0.16-6.50	0.03-0.83
Mean concentration, ppt	0.17	1.67	0.26
fish lipid: 0.038			
sediment organic carbon: 0.190			
C_{sed}:C_{soil} Ratio: 9.8			
BSAF: 0.78			
3. Hartford			
Number of samples	12	90	159
Range of concentration, ppt	0.07-0.32	0.04-23.10	0.03-10.90
Mean concentration, ppt	0.16	1.96	2.41
fish lipid: 0.072			
sediment organic carbon: 0.056			
C_{sed}:C_{soil} Ratio: 12.3			
BSAF: 0.97			
4. Bridgeport			
Number of samples	4	30	no data
Range of concentration, ppt	0.14-0.80	0.08-17.9	
Mean concentration, ppt	0.39	2.75	
C_{sed}:C_{soil} Ratio: 7.1			

Table 7-9. (Cont'd)

Site/Description	Soil	Sediment	Fish
5. Sterling			
Number of samples	4	20	40
Range of concentration, ppt	0.01-7.96	0.07-3.08	0.03-0.37
Mean concentration, ppt	2.12	0.90	0.11
fish lipid: 0.053			
sediment organic carbon: 0.067			
C_{sed}:C_{soil} Ratio: 0.4			
BSAF: 0.15			
6. Union/Stafford			
Number of samples	8	20	48
Range of concentration, ppt	0.02-1.56	0.23-3.69	0.07-0.85
Mean concentration, ppt	0.28	1.58	0.26
fish lipid: 0.041			
sediment organic carbon: 0.178			
C_{sed}:C_{soil} Ratio: 5.6			
BSAF: 0.71			
7. Windham			
Number of samples	8	20	59
Range of concentration, ppt	0.15-0.54	0.18-1.97	0.07-0.60
Mean concentration, ppt	0.25	0.97	0.25
fish lipid: 0.044			
sediment organic carbon: 0.129			
C_{sed}:C_{soil} Ratio: 3.9			
BSAF: 0.76			
8. Wallingford			
Number of samples	8	40	75
Range of concentration, ppt	0.07-6.00	0.03-3.10	0.03-8.92
Mean concentration, ppt	1.61	0.54	1.37
fish lipid: 0.071			
sediment organic carbon: 0.019			
C_{sed}:C_{soil} Ratio: 0.3			
BSAF: 0.68			

Table 7-9. (Cont'd)

Site/Description	Soil	Sediment	Fish
B. TOTALS BY CONGENER (fish lipid = 0.0557, organic carbon fraction = 0.0982 for results below; these are means for the full data set)			
1. 2,3,7,8-TCDD Number of samples Mean concentration, ppt **C_{sed}:C_{soil} Ratio: 3.86** **BSAF: 0.86**	770.56	3462.16	5211.06
2. 2,3,7,8-TCDF Number of samples Mean concentration, ppt **C_{sed}:C_{soil} Ratio: 2.59** **BSAF: 0.25**	776.77	34617.52	5212.53
3. 2,3,4,7,8-PCDF Number of samples Mean concentration, ppt **C_{sed}:C_{soil} Ratio: 1.58** **BSAF: 0.47**	773.56	3465.62	5211.49
4. I-TEQ Number of samples Mean concentration, ppt **C_{sed}:C_{soil} Ratio: 2.69** **BSAF: 0.24**	778.42	34622.69	5213.1

Source: CDEP, 1992

Table 7-10. Model parameters and results for effluent discharge model validation testing.

Number	Company/City	Plant flow L/hr*10^6	TCDD mg/hr	TSSe mg/L	River flow L/hr*10^8	TSSu mg/L	Lipid %	Fish concentrations pg/g (ppt) whole wt		Multiple Discharges Mill Numbers
								Predicted	Observed	
I. Mills with receiving water bodies of lower magnitude; suitable for model testing according to NCASI (see text for more explanation)										
1	James R. Corp, Old Town	2.52	0.098	127	8.57	2	10.9	1.9	8	49
2	International Paper Co, Jay Second fish listing Third fish listing Fourth fish listing Fifth fish listing	6.31	0.56	89	3.21	2	6.2 0.6 0.9 6.3 2.1	8.8 0.9 1.3 8.9 3.0	41.0 3.6 2.9 16.1 23.1	
3	James R. Corp, Berlin	2.74	0.104	47	5.13	4	3.7	2	7.8	
4	Westvaco Corp, Luke Second fish listing	3.12	0.05	57	0.3	13	4.9 4.7	2.8 2.7	58.2 35.5	
5	Penntech Pap, Johnsonburg Second fish listing	0.87	0.01	44	0.39	17	1.6 2.5	0.2 0.3	3.6 5.8	
6	Chesap. Corp, West Point Second fish listing Third fish listing Fourth fish listing	2.35	0.038	94	0.41	13	2.1 2.1 6.2 4.1	0.6 0.6 1.7 1.1	0.8 1.1 2.5 1.9	
7	Westvaco Corp, Covington Second fish listing	4.18	0.227	46	0.31	13	1.2 9.7	2.4 19.2	5.9 54.1	
8	Union Camp Corp, Franklin	19.7	1.343	60	0.35	0.3	1.9	5.1	1.8	
9	Champion Int, Courtland	9.3	0.716	23	43.3	10	11.1	1.9	3.4	26

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Table 7-10. (cont'd)

Number	Company/City	Plant flow L/hr*10^6	TCDD mg/hr	TSSe mg/L	River flow L/hr*10^8	TSSu mg/L	Lipid %	Fish concentrations pg/g (ppt) whole wt		Multiple Discharges Mill Numbers
								Predicted	Observed	
10	Cont Corp Amer, Brewton	5.63	0.037	13	1.01	6	2.2	0.8	0.6	
11	Boise Casc Corp, Jackson	3.08	0.332	19	8.25	10	5.3	2.1	8.8	5657581213
12	Kimb-Clark Corp, C. Pines Second fish listing	6.91	0.242	19	6.41	18	1.4 5.8	0.4 1.4	8.8 30.0	1357
13	Alab River Pulp, Claiborne Second fish listing	3.53	0.148	87	15.2	12	3.8 15.5	0.3 1.3	16.8 28.7	1257
14	Buckeye Cellulose, Perry	8.71	0.235	39	0.003	2	8.4	14.1	13.2	
15	Geo-Pac Corp, Palatka	5.84	0.093	8	0.04	2	20.3	81.8	1.4	
16	Fed Pap Bd Co, Augusta	4.73	0.076	101	6.56	8	4.1	0.4	4.5	
17	ITT-Rayonier, Inc, Jesup Second fish listing	9.42	0.226	26	7.12	8	2.0 5.9	0.6 1.8	0.9 4.6	
18	Int. Paper Co, Moss Point Second fish listing	2.71	0.434	57	0.25	12	0.7 7.7	3.4 37.6	7.8 34.4	
19	L.R. For Prod, New Aug Second fish listing	2.76	0.552	46	1.62	12	0.9 8.8	1.6 15.2	3.8 98.9	
20	Champion Int, Canton Second fish listing	6.94	0.104	22	0.3	3	3.4 6.9	4.3 8.8	12.0 75.7	
21	Wayerhauser Co, Plymouth Second fish listing	6.15	1.968	15	0.56	8	0.9 3.9	20.6 89.6	18.2 143.3	

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Table 7-10. (cont'd)

Number	Company/City	Plant flow L/hr*10^6	TCDD mg/hr	TSSe mg/L	River flow L/hr*10^8	TSSu mg/L	Lipid %	Fish concentrations pg/g (ppt) whole wt		Multiple Discharges Mill Numbers
								Predicted	Observed	
22	Wayerhauser, New Bern Second fish listing	3.77	0.166	14	1.22	4	0.8 8.2	1.3 13.2	5.5 49.2	
23	Fed Pap Bd, Riegelwood Second fish listing	4.42	0.124	241	2.32	7	0.9 8.2	0.2 1.7	0.9 22.3	
24	Bowater Corp, Catawba Second fish listing	5.3	0.127	13	2.89	5	1.4 6.1	0.8 3.4	3.2 15.3	
25	Union Camp Corp, Eastover Second fish listing	1.4	0.028	2	3.95	15	1.5 8.5	0.1 0.5	1.2 9.1	
26	Mead Corp, Kingsport Second fish listing	1.53	0.01	88	1.53	6	6.4 10.7	0.4 0.6	1.0 6.6	
27	Champion Int, Quinnesec Second fish listing Third fish listing	2.02	0.018	32	1.92	3	1.4 1.6 16.8	0.2 0.2 2.2	1.4 1.4 21.0	
28	Badger P M, Inc, Pestigo Second fish listing	0.24	0	124	0.64	4	24.4 1.9	0.5 0.04	8.5 0.3	
29	James R. Corp, Green Bay	1.57	0.017	177	3.02	14	8	0.3	5.6	
30	Nekoosa Papers, Inc., Nek Second fish listing	4.78	0.191	36	3.18	6	1.7 21.5	1.0 13.1	7.1 67.2	
31	Wayerhauser Co, Rothchild Second fish listing	0.99	0.012	27	2.54	5	1.3 16.3	0.1 1.0	0.2 4.6	

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Table 7-10. (cont'd)

Number	Company/City	Plant flow L/hr*10^6	TCDD mg/hr	TSSe mg/L	River flow L/hr*10^8	TSSu mg/L	Lipid %	Fish concentrations pg/g (ppt) whole wt		Multiple Discharges Mill Numbers
								Predicted	Observed	
32	Int. Paper - Bastrop Second fish listing Third fish listing Fourth fish listing	4.44	1.47	82	10.7	13	1.0 12.3 3.0 6.2	1.1 13.3 16.4 33.9	1.0 3.6 5.5 5.2	
33	Int Paper Co, Pine Bluff Second fish listing	4.34	0.478	71	9.97	7	5.2 10.4	2.8 5.5	8.9 33.9	
34	Nek Pap, Inc, Ashdown Second fish listing	6.07	0.249	21	4.02	42	3.5 1.8	0.8 0.4	4.2 1.7	
35	Boise Casc Corp, Derrider Second fish listing	3.66	0.034	59	0.12	10	8.2 1.4	2.8 0.5	13.7 1.4	
36	Temple-East Inc., Evadale Second fish listing	8.67	0.763	26	1.5	7	1.0 8.0	3.5 28.0	0.7 0.4	
37	Potlatch Corp, Lewiston Second fish listing	5.43	0.407	126	36.4	19	4.4 6.4	0.3 0.5	0.7 0.5	
38	Pope and Talbot, Inc, Halsey Second fish listing	1.83	0.055	14	7.75	7	8.8 9.6	0.8 0.8	4.6 0.8	
SIMPLE MEANS		4.7	0.31	58	5.3	9	5.8	7	15	38 mills / 74 fish
I. Mills with receiving water bodies of higher magnitude; suitable for model testing according to NCASI (see text for more explanation)										
39	Westvaco Corp, Wickliffe Second fish listing	3.53	0.124	34	321.3	129	1.9 7.4	0.001 0.004	1.4 4.8	967

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Table 7-10. (cont'd)

Number	Company/City	Plant flow L/hr*10^6	TCDD mg/hr	TSSe mg/L	River flow L/hr*10^8	TSSu mg/L	Lipid %	Fish concentrations pg/g (ppt) whole wt		Multiple Discharges Mill Numbers
								Predicted	Observed	
40	Int Paper Co, Natchez	5.99	0.228	115	407.2	221	22.6	0.01	3.1	92633394167
41	Potlatch Corp, Mcghee Second fish listing	1.92	0.077	21	375.2	130	3.5 5.8	0.001 0.002	1.4 4.7	92633394067
42	James Riv C, St. Francis Second fish listing Third fish listing	4.46	0.366	36	355.3	107	2.3 2.3 10.8	0.004 0.004 0.017	1.8 0.8 6.0	9.31333439404e+18
43	Georgia Pac, Zachery Second fish listing	4.1	0.718	130	355.3	13	2.0 8.7	0.035 0.15	1.4 1.8	9.26333439404e+18
44	Boise Cac C., St. Helens Second fish listing Third fish listing	5.54	0.122	59	183.5	22	2.0 9.6 3.2	0.008 0.04 0.01	1.3 2.6 1.1	373846
45	Wayerh Co, Longview Second fish listing	8.36	0.071	46	191.6	22	3.0 11.4	0.007 0.026	1.5 5.2	37384446
46	Boise Casc, Wallula Second fish listing Third fish listing Fourth fish listing	3.15	1.1	157	145.8	14	3.9 10.9 25.1 0.7	0.2 0.7 1.6 0.04	5.2 7.9 56.0 0.4	37
47	James River, Clat Second fish listing	6.43	0.097	40	191.6	46	7.0 2.9	0.01 0.005	2.8 1.73	3738444546
SIMPLE MEANS		4.83	0.32	71	280.8	78	7	0.14	5.7	9 mills / 21 fish

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Table 7-10. (cont'd)

Number	Company/City	Plant flow L/hr*10^6	TCDD mg/hr	TSSe mg/L	River flow L/hr*10^8	TSSu mg/L	Lipid %	Fish concentrations pg/g (ppt) whole wt		Multiple Discharges Mill Numbers
								Predicted	Observed	
III. No fish in NCSRF according to NCASI										
48	Georgia-Pac., Woodland									
49	Lincoln Pulp and Pap, Lincoln									
50	Scott Paper, Westbrook									
51	Scott Paper, Hinckley									
52	Int. Paper Co., Mobile									
53	Scott Paper									
54	Potlatch Corp., Cloquet									
IV. Mill already considered as multiple source										
55	Boise Cas. Corp, Rumford									
56	Gulf St Pap Co, Demopolis									
57	International Paper Co, Selma									
58	James River Corp, Butler									
59	Georgia-Pac Corp, Crosset									
V. Effluent discharge at ND										
60	Finch & P. & Co, Glen F.									
61	Appleton Pap, Roaring Sp.									
62	P.H. Glat. Co, Spring Gr.									
63	Proc & Gam, Mehoopany									
64	Champion Int., Cantonment									
65	Gilman Paper Co, St. Marys									
66	Buckeye Cell, Oglethorpe									
67	Wilamette Ind, Hawesville									
68	Bowater Corp., Calhoun									
69	Mead Corp, Escanaba									
70	Pentair, Inc., Park Falls									
71	Wausau P Mills Co, Brokaw									
72	Longv. Fiber C, Longview									
VI. Mill discharges into estuary, not suitable for model testing										
73	ITT-Ray, Inc., Fernandina B.									
74	Stone Cont Corp, Pan C.									
75	Bruns P. & Paper, Bruns									
76	Int. Paper Co, Georgetown									
77	Alaska Pulp Corp, Sitka									
78	Ketch Pulp & Pap 1, Ketch									
79	ITT-Ray, Inc., Port Angeles									
80	Wayerh Co., Cosmopolis									
81	Wayerh Co., Everett									
82	ITT-Rayonier, Inc., Hoquiam									

Table Headings:

Number:	mill number, established for this table only	River flow:	receiving water body flow rate
Company, city:	abbreviated name and city location	TSSe,u:	effluent, upstream suspended solids
Plant flow:	effluent flow rate	Fish conc:	concentrations as measured in NCSRF
TCDD:	2,3,7,8-TCDD discharge rate	Multiple discharges:	other mills assumed to influence fish concentrations
Lipid:	measured fish lipid, percent		

Table 7-11. ISCST3 and soil model input assumptions and parameters.

Description	Parameter Value and Comments				
I. ISCST3 Model Inputs					
Source Characterization	1992 stack test: 6799 ng/m^3 total; 136 ng/m^3 TEQ emission concentration from tested stack; *extrapolated to:* 3.12*10^{-5} g TEQ/sec emission rate considering three stacks, equal to 985 g TEQ/yr				
	1994 stack test: 3685 ng/m^3 total; 64 ng/m^3 TEQ emission concentration from tested stacks; *extrapolated to:* 8.47 *10^{-6} g TEQ/sec emission rate, equal to 267 g TEQ/yr				
Dispersion Coefficients Terrain Regulatory Default Option - Stack tip downwash - Final Plume Rise - Buoyancy induced dispersion - Wind profile exponents - Calm winds processing - Vertical potential temp. gradient - Decay coefficient - Building wake effects Wind Speed/Stability Category Wet/dry particle-phase deposition Wet/dry vapor-phase deposition Plume depletion by deposition	rural flat yes yes yes yes regulatory defaults calm hours not included in conc. calculations regulatory defaults 0 (no decay of contaminant in plume) Building dimensions were input to the model regulatory defaults yes no yes				
Building height/stack height Stack temperature Exit velocity	36 m, 83 m 434 °K 5.5 m/sec				
For Deposition Modeling Only	Diam. µm	Mass fraction	Density g/cm^3	Scav. Coef. (liq) 1/(s-mm/hr)	Scav. Coef (ice) 1/(s-mm/hr)
Particle Category 1 Category 2 Category 3	1.00 6.78 20.0	0.88 0.09 0.03	1.4 1.4 1.4	0.00043 0.0046 0.0066	0.00014 0.0016 0.0022
II. Soil Modeling Inputs					
Soil half-live, yrs	All homologue groups assume 25 year half-life				
Particle Fraction (vapor fraction = 1 - particle fraction)	TCDD: 0.49; PCDD: 0.87; HxCDD: 0.97; HpCDD: 0.99; OCDD: 0.998 TCDF: 0.53; PCDF: 0.80; HxCDF: 0.945; HpCDF: 0.985; OCDF: 0.998				

Table 7-12. Comparison of observed and modeled total CDD/F concentration increments at the urban monitoring stations (total = sum of homologue group concentrations; on-site, airport = model results generated using on-site and airport meteorological data; NA = not available).

Station	March 94 Sampling, fg/m^3			April 94 Sampling, fg/m^3	
	Observed	On-site	Airport	Observed	On-site
SN-2	1321	6606	20833	0	0
SE-3	6368	8181	2388	16105	8994
SNW-1	0	8943	1270	557	0
SSW-4	0	0	0	3682	8638
HSCNE	NA	NA	NA	1493	8028

Table 7-13. Comparison of observed and modeled homologue and TEQ concentrations at station SE-3 using on-site meteorological data for model input.

Homologue Group	Stack Emission Rate, ng/dscm	SE - 3, March 94, fg/m^3		SE - 3, April 94, fg/m^3	
		Observed	Modeled	Observed	Modeled
TCDD	32	490	71	851	78
PCDD	97	594	215	1144	236
HxCDD	300	543	666	1402	732
HpCDD	508	424	1126	1378	1237
OCDD	578	384	1281	1575	1408
TCDF	293	904	651	1976	716
PCDF	439	1226	977	2982	1074
HxCDF	648	951	1439	2518	1582
HpCDF	616	718	1366	1846	1502
OCDF	170	134	391	433	429
Total	**3681**	**6368**	**8181**	**16105**	**8994**
TEQ	**64**	**125**	**144**	**309**	**156**

Table 7-14. Results of ISCST3 deposition and soil prediction modeling, comparing measured concentrations for clusters of soil samples with modeled concentrations assuming either the 1992 or the 1994 stack tests.

Cluster–>	On-site			Off-site			Urban			Urban		
Description of Cluster–>	n = 3; on incinerator property			n = 5; just outside property, downwind within 500 m			n = 14; all directions within about 3 km.			n = 12; all directions from 3 to 8 km.		
Homologue	Obs	'92	'94	Obs	'92	'94	Obs	'92	'94	Obs	'92	'94
TCDD	1118	265	19	98	93	7	19	38	3	<1	9	<1
PCDD	1820	815	102	64	286	35	13	117	15	2	29	4
HxCDD	1885	1202	351	150	421	123	43	173	51	4	43	13
HpCDD	1666	781	606	654	273	212	154	112	87	20	28	21
OCDD	1431	445	696	2901	156	243	613	64	100	150	16	25
TCDF	2147	1304	187	153	457	66	35	188	27	2	47	7
PCDF	255	2335	425	194	818	149	33	336	61	5	83	15
HxCDF	1195	2769	740	116	970	259	22	399	107	3	99	26
HpCDF	1183	1079	732	193	378	256	37	155	105	5	39	26
OCDF	222	274	212	88	96	74	15	40	31	3	10	8
TOTAL	**1292**	**11269**	**4070**	**4611**	**394**	**142**	**984**	**162**	**587**	**194**	**403**	**146**
TEQ	**466**	**236**	**69**	**45**	**83**	**24**	**9**	**34**	**10**	**<1**	**8**	**2**

notes: soil concentrations in pg/g, obs = observed; '92, '94 = ISCST3 results using 1992 and 1994 stack test data; "on-site" observed data not expected to represent deposition trends - see text for more details.

Table 7-15. Results of the air-to-soil and soil-to-air model testing

Congener	Observed Soil pg/g	Predicted Soil pg/g	Observed Air pg/m^3	Predicted Air pg/m^3
2378-TCDD	0.39	0.03	$1.4*10^{-3}$	$1.8*10^{-5}$
12378-PCDD	0.14	0.19	$5.2*10^{-3}$	$2.5*10^{-6}$
123478-HxCDD	0.35	0.31	$7.9*10^{-3}$	$4.0*10^{-6}$
123678-HxCDD	0.82	0.36	$9.3*10^{-3}$	$1.4*10^{-5}$
123789-HxCDD	1.23	0.54	$1.4*10^{-2}$	$2.1*10^{-5}$
1234678-HpCDD	17.7	9.1	$2.3*10^{-1}$	$1.9*10^{-4}$
OCDD	161.0	36.2	$9.0*10^{-1}$	$1.3*10^{-3}$
2378-TCDF	0.64	0.06	$2.8*10^{-3}$	$4.2*10^{-5}$
12378-PCDF	0.17	0.20	$6.5*10^{-3}$	$3.5*10^{-6}$
23478-PCDF	0.21	0.26	$7.4*10^{-3}$	$5.1*10^{-6}$
123478-HxCDF	0.16	0.50	$1.3*10^{-3}$	$3.8*10^{-6}$
123678-HxCDF	0.11	0.59	$1.6*10^{-2}$	$2.1*10^{-6}$
123789-HxCDF	0.15	0.11	$2.8*10^{-3}$	$3.4*10^{-6}$
234678-HxCDF	0.67	0.36	$9.2*10^{-3}$	$1.5*10^{-5}$
1234678-HpCDF	4.06	2.74	$6.9*10^{-2}$	$7.0*10^{-5}$
1234789-HpCDF	0.27	0.58	$1.4*10^{-3}$	$3.0*10^{-6}$
OCDF	10.7	2.70	$6.7*10^{-3}$	$8.0*10^{-5}$
TEQ	**1.37**	**0.70**	**$1.9*10^{-2}$**	**$3.6*10^{-5}$**

Table 7-16. Data and results of the soil to below ground vegetable validation exercise.

Congener group	Koc, L/kg	RCF	Control Soil			Contaminated Soil		
			Soil, ppt	Observed Peel, ppt dry	Predicted Peel, ppt dry	Soil, ppt	Observed Peel, ppt dry	Predicted Peel, ppt dry
TCDD	$3.98*10^{6}$	5200	11.0	1.7	1.2	24.3	2.9	2.6
PCDD	$2.69*10^{6}$	3900	6.8	1.2	0.8	80.5	5.6	9.6
HxCDD	$2.12*10^{7}$	18600	23.5	1.6	1.7	176.7	7.3	12.7
HpCDD	$6.17*10^{7}$	43700	45.6	1.6	2.7	238.6	5.4	13.9
OCDD	$9.77*10^{7}$	62200	85.4	3.0	4.5	297.4	6.3	15.6
TCDF	$7.76*10^{5}$	1500	21.8	11.9	3.5	270.7	36.7	43.0
PCDF	$2.88*10^{6}$	4080	34.8	5.9	4.1	361.9	24.8	42.1
HxCDF	$6.17*10^{6}$	7410	38.5	3.2	3.8	418.4	22.0	41.0
HpCDF	$3.86*10^{7}$	29400	49.0	1.2	3.1	667.2	12.2	41.8
OCDF	$3.89*10^{8}$	180000	46.6	0.4	1.8	687.3	5.0	26.2

Table 7-17. Summary of plant concentration versus soil concentration data for 2,3,7,8-TCDD.

Plant:soil Concentrations	Contaminant Ratio	Reference and Comments
I. Below-Ground Vegetation		
54-167 ppt/ 1-5 ppb	0.01-0.17	Wipf, et al., 1982; results are for 2,3,7,8-TCDD and greenhouse carrots grown in Seveso contaminated soil; the 54 ppt concentration listed was for carrot peels and inner portions; the 167 ppt listed includes the 54 ppt plus additional residues found in wash water and can be described as "unwashed" concentration; 96% of 167 ppt unwashed concentration includes that found in wash water (67%) and peels (29%).
0.8-9.2 ppb/ 2.7-8.3 ppb	0.24-1.73	Coccusi, et al., 1979; results are for 2,3,7,8-TCDD and carrots, potatoes, narcissus, and onions grown on contaminated soil the spring following the Seveso contamination; aerial plant part ratios were 0.25-0.40 - underground part ratios were 0.23-1.73; residues in contaminated plants were found to dissipate when contaminated plants transplanted to unpolluted soils; results show higher ratios than the Wipf, et al. (1982) noted above; results were expressed in fresh plant weight and fresh soil basis; very high ratios and plant impacts render these data suspect.
156-1807 ppt/ 160-752 ppt	1.00-2.40	Facchetti, et al., 1986; results are for 2,3,7,8-TCDD and bean and maize roots grown in indoor greenhouse pots and outdoor pots; unclear whether plant concentrations are fresh or dry weights. Data considered highly suspect due to very high ratios found and also reporting 16 and 37 ppt in roots when "blank" soil had 1.5 ppt (ratios of 10.7 and 24.7).
735 ppt/ 411 ppt	1.8	Young, 1983; results are for 2,3,7,8-TCDD and roots of grass and broadleaf plants at Eglin Air Force Base; unclear whether root concentrations are fresh or dry weight.
0.5-40.2 ppt/ 2-6000	0.001-0.3	Hulster and Marschner, 1991; results at right are for unpeeled potato tubers, in TEQ and dry weight basis. Plant:soil ratio decreased as soil concentrations increased; highest ratios were at the 2.4 ppt low soil concentration. Peeled tuber concentration stayed below 0.5 ppt over all soil concentrations, indicating insignificant within plant translocation. Plant concentrations given in dry weight basis.
0.1-15 ppt/ 6-690 ppt	0.001-0.5	Muller, et al. 1994; results at right describe the range of concentrations and ratios for data on ten congener groups, in two soils (a control and a contaminated soil), and for carrots. For the control soil, which had a TEQ concentration of 5 ppt, typical of background soils, the average plant:soil ratio was 0.10; for the contaminated soil with a TEQ concentration of 56 ppt, the plant:soil ratio was 0.02.

Table 7-17. (cont'd).

Plant:soil Concentrations	Contaminant Ratio	Reference and Comments
I. Below-Ground Vegetation (cont'd)		
0.2-6.0 ppt/ 328-12,800 ppt	0.00001-0.009	Hulster and Marschner, 1993. Results are for potato tubers, peeled and unpeeled, and for potato shoots, results for TEQ and in dry matter terms. Concentrations for peeled potato tubers stayed consistently less than 0.5 ppt, despite soil concentrations, while shoots and unpeeled tubers increased as concentration increased. Plant:soil ratios remained relatively constant for tubers and shoots with soil concentration increases, leading authors to conclude that a soil/plant relationship exists for plants growing in the soil. Less transfer was noted for higher chlorination.
II. Above-Ground Vegetations		
9-42 ppt/ 10 ppb	0.0009-0.0042	Wipf, et al., 1982; analysis of apples, pears, plums, figs, peaches, and apricots grown in Seveso, Italy year following contamination; apples, pears, and peaches showed >95% of whole fruit concentrations listed here was in the peels; analysis of vegetative samples in less contaminated areas showed non-detections at 1 ppt detection limit; reference was unclear as to whether reported concentrations in fruit was based on fresh or dry weight.
8-9 ppt/ 10 ppb	0.0008	Wipf, et al., 1982; concentrations listed were those found in sheaths of corn grown year following Seveso contamination; none found in cobs and kernels at 1 ppt detection limit.
1-63 ppt/ 12-3300 ppt	0.003-0.35	Sacchi, et al., 1986; data was for: "aerial parts" of bean and maize plants, tritiated TCDD amended soil with concentrations ranging as noted, taken at different intervals including 7, 34 and 57 days (one test), 17, 34, and 57 days (another test), 8 and 77 days, and 8 and 49 days, and in tests where soil was and was not amended with peat. Results showed increasing plant concentrations with increasing soil concentrations, but the ratio of plant to soil concentrations was inversely related to increasing soil concentrations (lowest ratios at highest soil concentrations). Soils without peat had higher ratios than soils with peat. Plant concentrations were fresh weight basis; high plant impact and trend for increasing impact over time renders these results suspect.

Table 7-17. (cont'd).

Plant:soil Concentrations	Contaminant Ratio	Reference and Comments
I. Above-Ground Vegetation (cont'd)		
ND (DL=1 ppb)/60 ppt	<0.017	Isensee and Jones, 1971; results are for mature oat and soybean tops, and oat grain and the bean of soybean, in soil treated with [^{14}C]TCDD to achieve a concentration of 60 ppb - no residues of TCDD were found; ratios of 0.14 and 0.28 were found for 2,4,-dichlorophenol (DCP) in oat and soybean tops, and 0.20 for 2,7-dichlorodibenzo-p-dioxin (DCDD) in oat tops; trace amounts of DCP and DCDD were found in the bean of soybean.
10-270 ppt/ 411 ppt	0.02-0.66	Young, 1983; data was for 2,3,7,8-TCDD and above ground plant parts of perennial grasses and broadleaf plants grown on 2,4,5,-T treated soils. Unclear whether plant concentrations are fresh or dry weight basis. Soil concentration was average over 3 depth increments to 15 cm. Crown near soil surface at 270 ppt and 0.66 ratio was highest; plant tops had ratios of 0.02-0.17.
0.3, 0.1 ppt/ 8750,5215 ppt	0.00003, 0.00002	Muller, et al, 1993. Result at right are for whole pear (0.3) and whole apple (0.1) dry weight concentrations (article presented TEQs for two pears from one tree which were averaged, and one apple, and for fresh weight; dry weight was estimated assuming 12% dry matter in pears/apples) and the average concentration over 70 cm (article supplied concentrations for the 0-30 and 30-70 cm depths). Article also provided peel and pulp results and results for congener groups. Article concluded: soil levels were not correlated to fruit concentrations and therefore fruits were impacted by airborne contamination, and that concentrations were higher in peel than in pulp.
0.1-0.6 ppt/ 326-5752 ppt	0.00002-0.0008	Hulster and Marschner, 1993. Results are for inner and outer leaves of lettuce, expressed as dry matter, and in TEQs. Results indicate a drop in ratio as soil concentration increases, and unexpected small differences between inner and outer leaves.
4-38 ppt/ 326-12,800 ppt	0.001-0.01	Hulster and Marschner, 1993. Results are for hay, dry matter, and TEQs. Results indicate a drop in ratio as soil concentrations increase.

Table 7-17. (cont'd).

Plant:soil Concentrations	Contaminant Ratio	Reference and Comments
I. Above-Ground Vegetation (cont'd)		
< 1 ppt/ 326-5752 ppt	0.0001-0.0003	Hulster and Marschner, 1993. Results are for grass and herbs, dry matter, and TEQs. Results indicate a drop in ratio as soil concentrations increase. For above three entries, results are also given for congener groups. Authors conclude that: little correlation between soil and above ground plant concentrations, and that contamination is by atmospheric deposition.
<0.01, 0.04/ 5, 56 ppt	<0.002	Muller, et al., 1994. Results are for peas at soil concentrations of 5 and 56 ppt; pea concentrations in TEQ and dry weight. Results for pods indicated more impact with ratios at 0.002-0.026. Ratios decreased as soil concentration increased.
0.32, 0.21 ppt/5, 56 ppt	0.004-0.064	Muller, et al., 1994. Results are for lettuce at soil concentrations of 5 and 56 ppt; lettuce concentrations in TEQ and dry weight. Little difference seen between inner and outer leaves, which was unexpected - outer leaves expected to be more impacted. Ratios decreased as soil concentration increased.
0.5-22.6 ppt/ 0.4, 148	0.14-2.5	Hulster, et al., 1994. Results are for zucchini fruit at two soil concentrations of 0.4 and 148 ppt TEQ, fruit results are TEQ and dry weight. Results contradict conventional wisdom that above ground vegetation impact is from air only and mainly an outer surface phenomena; zucchini contamination was uniform throughout plant and plant:soil ratios highest ever found for above ground bulky fruits.
0.6 ppt/ 148 ppt	0.004	Hulster, et al., 1994 Results are for cucumber grown in soil at 147 ppt TEQ; cucumber results in TEQ and dry weight. Results are more in line with most other studies for above ground bulky fruit plant:soil ratios.
7.5 ppt/ 148 ppt	0.05	Hulster, et al., 1994. Results are for pumpkin grown in soil at 148 ppt TEQ; pumpkin results in TEQ and dry weight. Results not as dramatic as for zucchini, but plant concentrations are ratio are still high.
0.4-1.9 ppt/ 2.4-6000 ppt	0.0003-0.3	Hulster and Marschner, 1991. Results are for lettuce, in TEQ and dry weight. Experiments were conducted outdoors with soil covered by a water permeable polypropylene fleece. Plant concentrations showed little variation with large increases in soil concentration, and given the soil covering, this would strongly indicate little root to shoot translocation and that lettuce concentrations were the result of air to plant transfers

Table 7-18. Parameters for the empirical relationship relating the sub-cooled liquid vapor pressure, $p°_L$, to the particle/gas partition coefficient, K_p, of semivolatile organic compounds (SOC).

Setting/SOC	Location	m	b	Reference
I. Urban				
PAHs	Portland, Oregon	-0.882	-5.38	1
PAHs	Portland, Oregon	-0.890	-4.75	2
PAHs	Denver, Colorado	-0.760	-5.10	3
PCBs	Denver, Colorado	-0.946	-5.86	3
PAHs	Chicago, Illinois	-0.694	-4.61	4
PCBs	Chicago, Illinois	-0.726	-5.18	4
PAHs	London, U.K.	-0.631	-4.61	5
PAHs	Osaka, Japan	-1.04	-5.95	6
PAHs	Brazzaville, Congo	-0.810	-5.31	7
OC pesticides	Brazzaville, Congo	-0.740	-5.76	7
II. Rural				
PAHs	Coastal Oregon	-0.724	-4.94	1
PAHs	Lake Superior	-0.586	-3.83	8
PAHs	Lake Superior	-0.614	-4.25	9
PAHs	Green Bay	-1.00	-5.47	4
PCBs, OC pesticides	Bayreuth, Germany	-0.610	-4.74	10

References:
1. Ligocki and Pankow (1989);
2. Hart (1989);
3. Foreman and Bidleman (1990);
4. Cotham and Bidleman (1995);
5. Baek, et al. (1991);
6. Yamasaki, et al. (1982);
7. Ngabe and Bidleman (1992);
8. McVeety and Hites (1988);
9. Baker and Eisenreich (1990);
10. Kaupp and Umlauf (1992)

Table 7-19. Summary of modeling changes from the 1994 air-to-beef model validation exercise to the present update.

Congener	B_{vpa}, unitless		Vapor/Particle Partitioning		BCF, unitless		Cs, pg/g	
	1994	1996	1994	1996	1994	1996	1994	1996
2378-TCDD	$1.0*10^5$	$6.55*10^4$	55/45	51/49	4.32	5.76	0.1	0.4
12378-PCDD	$6.3*10^5$	$2.39*10^5$	26/74	13/87	4.16	5.55	0.6	0.1
123478-HxCDD	$2.3*10^6$	$5.20*10^5$	7/93	3/97	2.02	2.69	0.6	0.4
123678-HxCDD	$6.9*10^5$	$5.20*10^5$	4/96	3/97	1.74	2.32	0.9	0.8
123789-HxCDD	$6.9*10^5$	$5.20*10^5$	2/98	3/97	2.24	2.99	1.2	1.2
1234678-HpCDD	$1.0*10^7$	$9.10*10^5$	2/98	1/99	0.36	0.48	13.9	17.7
OCDD	$2.4*10^9$	$2.36*10^5$	0/100	0.2/99.8	0.52	0.69	69.3	160.9
2378-TCDF	$1.5*10^5$	$4.57*10^4$	71/29	47/53	0.94	1.25	0.8	0.6
12378-PCDF	$3.8*10^5$	$9.75*10^4$	42/58	25/75	0.73	0.97	0.7	0.2
23478-PCDF	$5.3*10^5$	$9.75*10^4$	30/70	16/84	3.10	4.13	0.5	0.2
123478-HxCDF	$5.9*10^5$	$1.62*10^5$	6/94	7/93	2.34	3.12	1.4	0.2
123678-HxCDF	$1.4*10^6$	$1.62*10^5$	6/94	7/93	2.00	2.67	1.3	0.1
123789-HxCDF	$8.3*10^5$	$1.62*10^5$	11/89	4/96	2.00	2.67	0.3	0.2
234678-HxCDF	$8.3*10^5$	$1.62*10^5$	7/93	4/96	1.78	2.37	1.0	0.6
1234678-HpCDF	$6.8*10^5$	$8.30*10^5$	4/96	2/98	0.41	0.55	4.9	4.1
1234789-HpCDF	$6.8*10^5$	$8.30*10^5$	3/97	1/99	0.99	1.32	0.7	0.3
OCDF	$1.7*10^8$	$2.28*10^6$	0/100	0.2/99.8	0.20	0.27	4.1	10.7

B_{vpa}: air-to-leaf vapor transfer factor, unitless
BCF: beef bioconcentration factor, unitless
Vapor/Particle: vapor phase/particle phase percentages
Cs: soil concentration, pg/g

Table 7-20. Comparison of air concentration profiles used in the 1994 air-to-beef model validation compared against the current air profiles.

Congener	1994 urban air profile, pg/m^3	Columbus urban air profile, pg/m^3	1994 rural air profile, pg/m^3	Columbus rural air profile, pg/m^3	Ratio, Col urban/Col rural
2378-TCDD	0.010	0.0065	0.002	0.0014	4.6
12378-PCDD	0.030	0.017	0.006	0.005	3.4
123478-HxCDD	0.025	0.022	0.005	0.008	2.8
123678-HxCDD	0.035	0.035	0.007	0.009	3.9
123789-HxCDD	0.050	0.033	0.010	0.014	2.4
1234678-HpCDD	0.580	0.280	0.116	0.227	1.2
OCDD	2.930	1.053	0.586	0.904	1.2
2378-TCDF	0.115	0.019	0.023	0.003	6.3
12378-PCDF	0.050	0.036	0.010	0.007	5.1
23478-PCDF	0.030	0.030	0.006	0.007	4.3
123478-HxCDF	0.060	0.068	0.012	0.013	5.2
123678-HxCDF	0.060	0.087	0.012	0.016	5.4
123789-HxCDF	0.015	0.003	0.003	0.003	1.0
234678-HxCDF	0.045	0.050	0.009	0.009	5.6
1234678-HpCDF	0.210	0.262	0.042	0.069	3.8
1234789-HpCDF	0-.030	0.044	0.006	0.014	3.1
OCDF	0.173	0.173	0.034	0.067	2.6
TOTAL	**4.448**	**2.220**	**0.890**	**1.380**	---
I-TEQ	**0.095**	**0.070**	**0.019**	**0.019**	---

Table 7-21. Comparison of predicted leafy vegetation samples of the current, revised validation exercise with the previous predictions of leafy vegetations and several observations in the literature (units are pg/g dry weight).

Congener	Predicted 1994	Predicted 1996	US alfalfa[1], 1994	UK grass[2], 1979-1988	UK grass[3], 1996	UK grass[4], 1997	US hay[5], 1989
2378-TCDD	0.1	0.05	0.11	0.03	0.12	0.72	ND
12378-PCDD	0.9	0.18	0.16	0.14	0.07	1.3	ND
123478-HxCDD	0.7	0.18	0.29	0.14	0.10	0.93	ND
123678-HxCDD	0.2	0.22	0.25	3.00	0.17	2.3	1.2
123789-HxCDD	0.2	0.32	0.23	1.40	0.08	1.8	ND
1234678-HpCDD	21.0	4.12	0.85	7.10	2.80	22	30.0
OCDD	6.0	13.20	6.21	24.0	15.60	94	285.0
2378-TCDF	7.2	0.07	0.06	0.46	1.28	14	ND
12378-PCDF	1.4	0.19	0.21	0.18	0.29	1.8	ND
23478-PCDF	0.8	0.16	0.08	0.20	0.28	2.2	ND
123478-HxCDF	0.5	0.26	0.19	0.32	0.21	5.6	ND
123678-HxCDF	0.9	0.31	0.30	0.16	0.09	2.2	ND
123789-HxCDF	0.3	0.04	0.24	0.02	0.02	0.61	ND
234678-HxCDF	0.5	0.14	0.20	0.15	0.09	2.6	ND
1234678-HpCDF	1.4	1.68	0.31	1.90	1.02	12	5.4
1234789-HpCDF	0.1	0.25	0.45	0.14	0.13	1.1	ND
OCDF	0.4	0.96	0.96	2.00	0.98	13	7.5
TOTAL	**42.6**	**22.3**	**11.1**	**41.34**	**32.2**	**178.2**	**---**
I-TEQ	**3.2**	**0.46**	**0.44**	**0.89**	**0.57**	**6.0**	**---**

[1] From an unpublished data set for alfalfa supplied by V. Fiel, United States Department of Agriculture, for a beef feeding study which is currently underway. For these results, all but the hepta dioxin and the two octa congeners were not detected - results above are ½ detection for the two alfalfa samples taken.
[2] Kjeller, et al., (1991); [3] Kjeller (1996); [4]Jones and Duarte-Davidson (1997); [5] Reed, et al. (1990) - detection limits not supplied for non-detects, but described as between 0.31 and 6.5 ppt.

Table 7-22. Results of the 1994 air-to-beef model validation exercise compared against results from the current air-to-beef model validation exercises (all beef concentrations in terms of pg/g lipid; values in parentheses are observations calculated assuming non-detects equal 0.0; values not in parenthesis assume non-detects equal ½ detection limit).

Congener	1994 Validation Results		Current Validation Results	
	Observed beef	Predicted beef	Observed beef	Predicted beef
2378-TCDD	0.13 (0.06)	0.16	0.05 (0.03)	0.13
12378-PCDD	1.17 (0.13)	1.42	0.35 (0.04)	0.37
123478-HxCDD	1.38 (0.74)	0.53	0.64 (0.18)	0.19
123678-HxCDD	4.40 (4.40)	0.16	1.42 (1.21)	0.20
123789-HxCDD	1.08 (0.34	0.21	0.53 (0.26)	0.38
1234678-HpCDD	10.13 (9.99)	1.53	4.48 (4.39)	0.79
OCDD	15.32 (14.84)	1.53	4.78 (3.21)	4.54
2378-TCDF	0.30 (0.25)	2.42	0.03 (0)	0.04
12378-PCDF	0.23 (0.005)	0.37	0.31 (0)	0.07
23478-PCDF	1.11 (0.90)	0.89	0.36 (0.06)	0.25
123478-HxCDF	2.68 (2.44)	0.42	0.55 (0.27)	0.29
123678-HxCDF	0.33 (0.10)	0.68	0.40 (0.12)	0.28
123789-HxCDF	0.30 (0)	0.21	0.31 (0)	0.05
234678-HxCDF	0.38 (0.11)	0.37	0.39 (0.10)	0.14
1234678-HpCDF	2.08 (1.74)	0.21	1.00 (0.75)	0.35
1234789-HpCDF	0.68 (0.07)	0.05	0.31 (0)	0.11
OCDF	1.18 (0.55)	0.05	1.88 (0)	0.13
TOTAL	**42.9 (36.7)**	**11.21**	**17.8 (10.7)**	**8.29**
I-TEQ	**2.51 (1.55)**	**1.85**	**0.93 (0.35)**	**0.61**

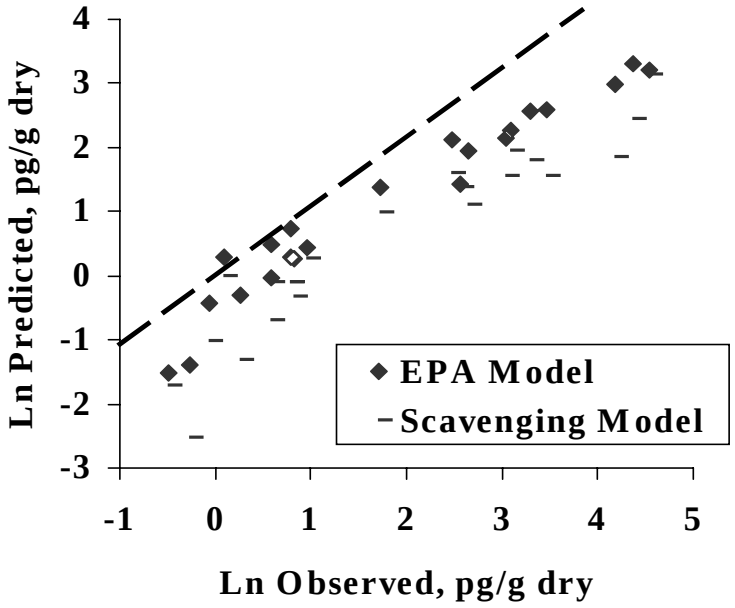


Figure 7-1. Comparison of observed and predicted grass concentrations of dioxin and furan congeners for the EPA and the scavenging models at the rural site. The perfect match of observed and predicted is shown in the dashed observed = predicted line.

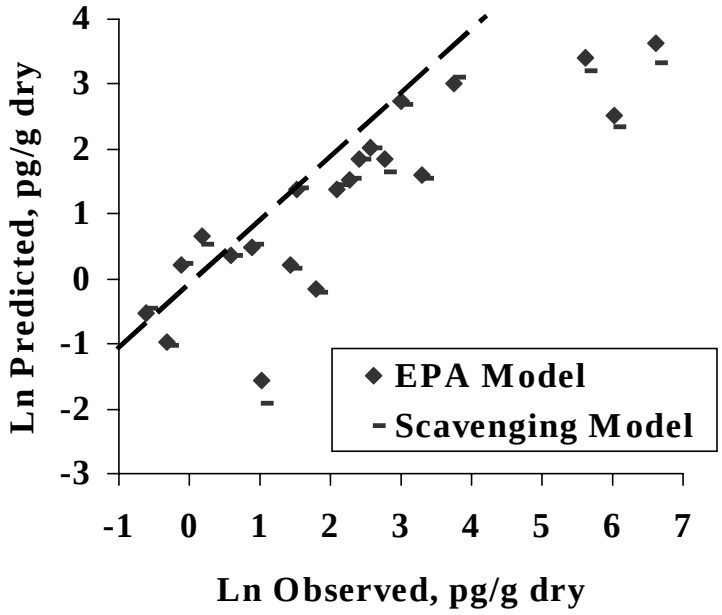


Figure 7-2. Comparison of observed and predicted grass concentrations of dioxin and furan congeners for the EPA and the scavenging models at the industrial site. The perfect match of observed and predicted is shown in the dashed observed = predicted line.

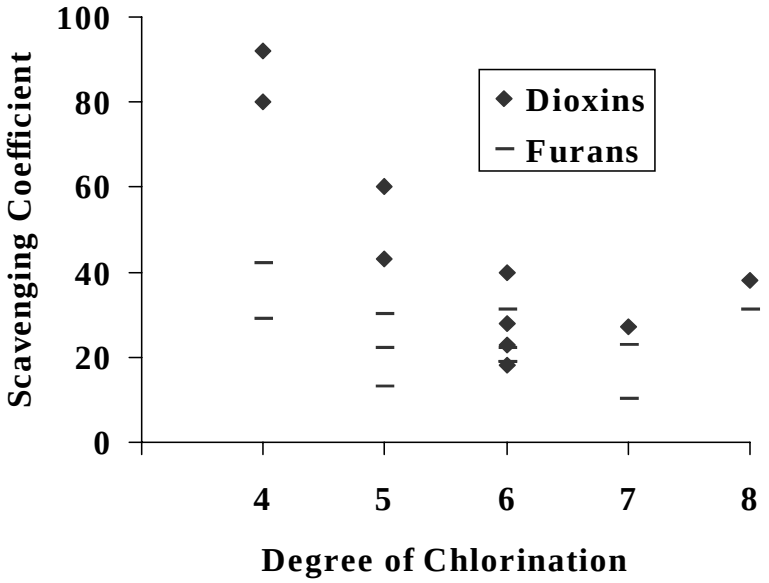


Figure 7-3. The observed scavenging coefficient (grass concentration over air concentration) calculated from the rural site data.

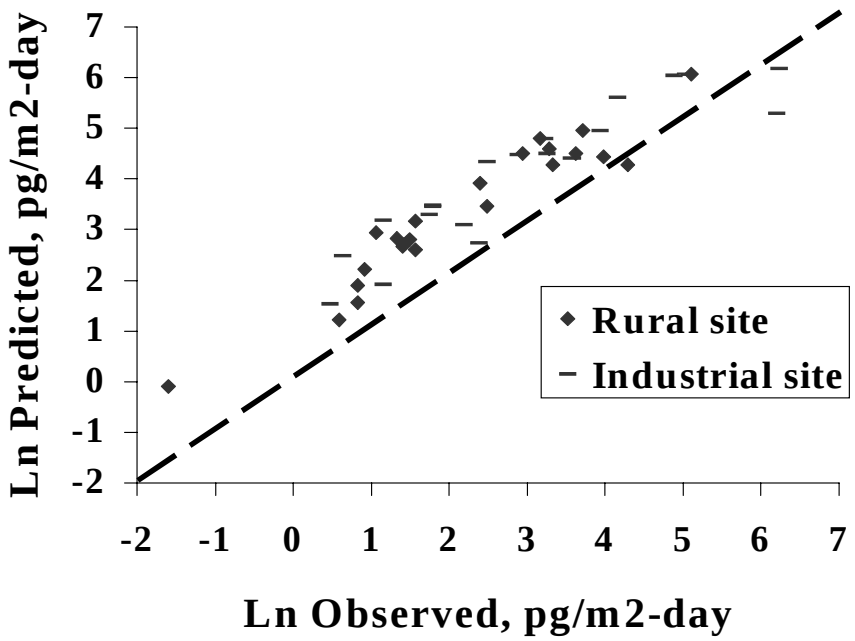


Figure 7-4. Comparison of observed and predicted deposition at the rural and industrial sites. The perfect match of observed and predicted is shown in the dashed observed = predicted line.

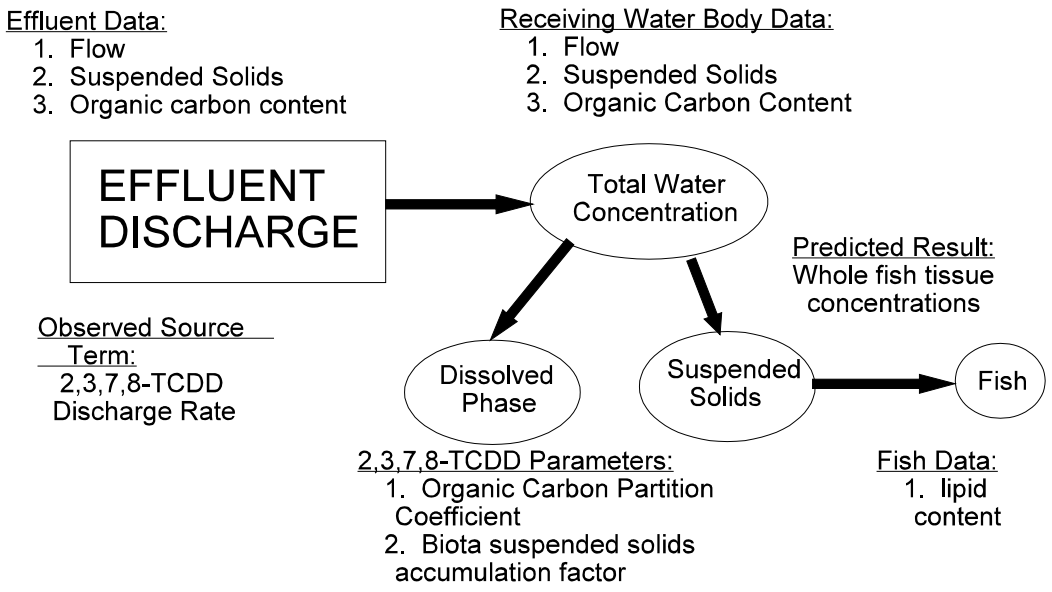


Figure 7-5. Schematic of effluent discharge model showing all parameter inputs and observed fish concentrations.

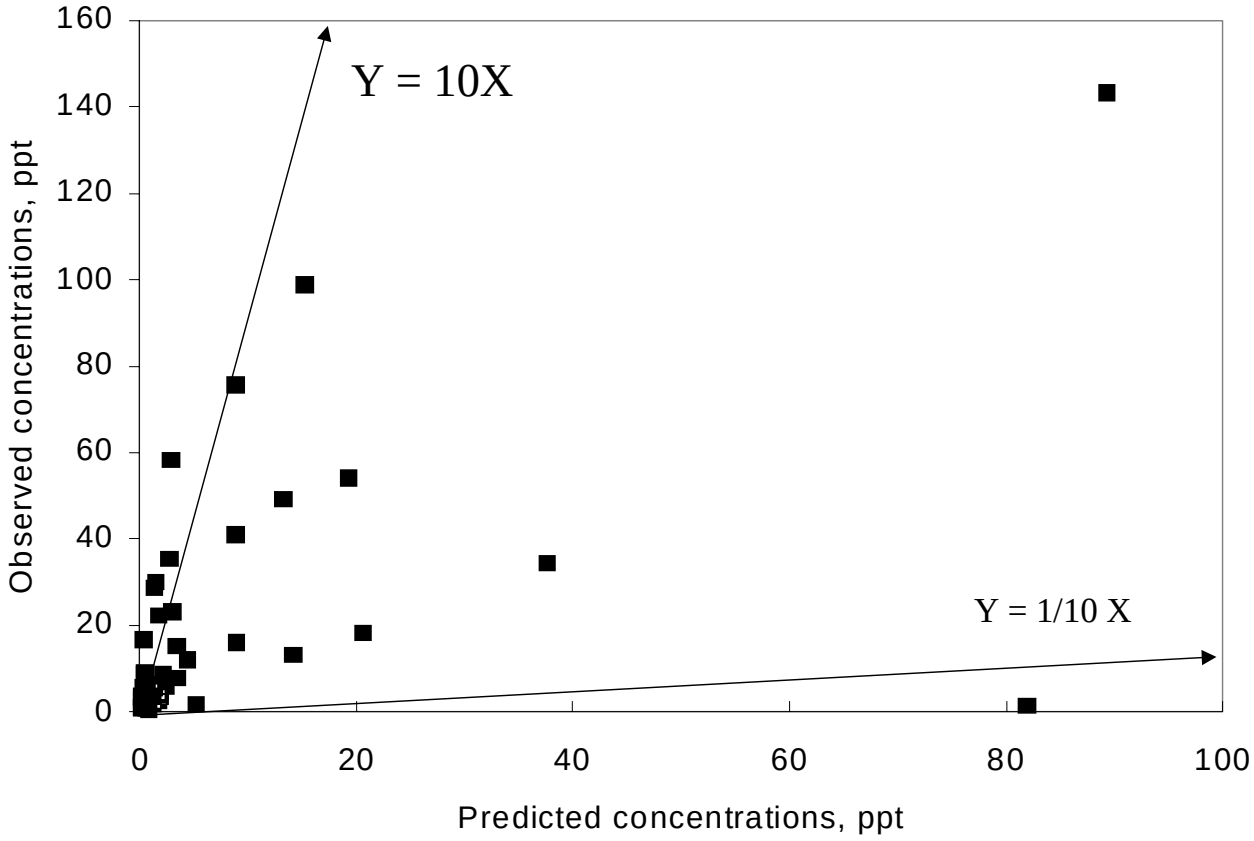


Figure 7-6. Comparison of predicted and observed fish tissue concentrations for validation of the effluent discharge model.

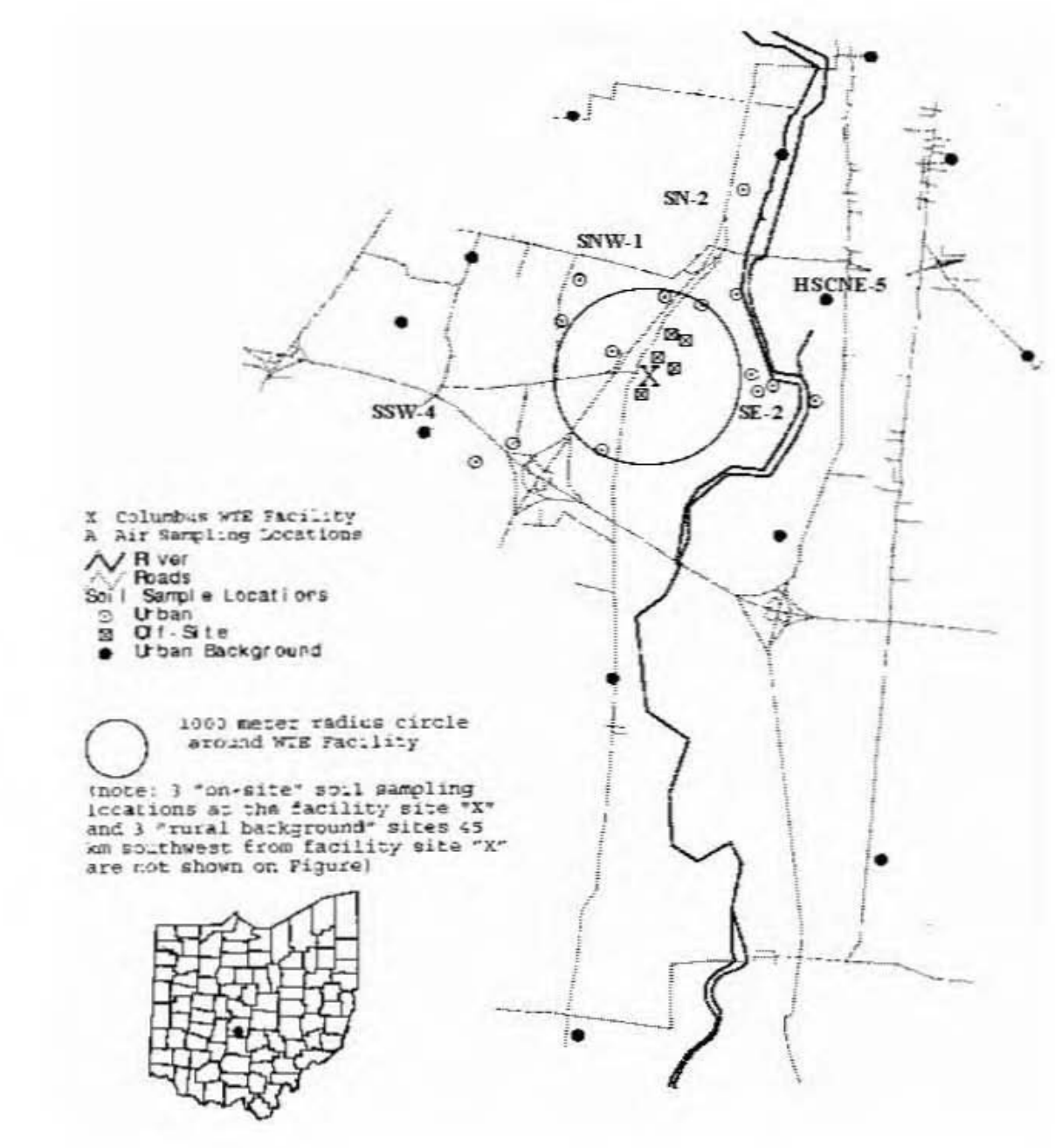
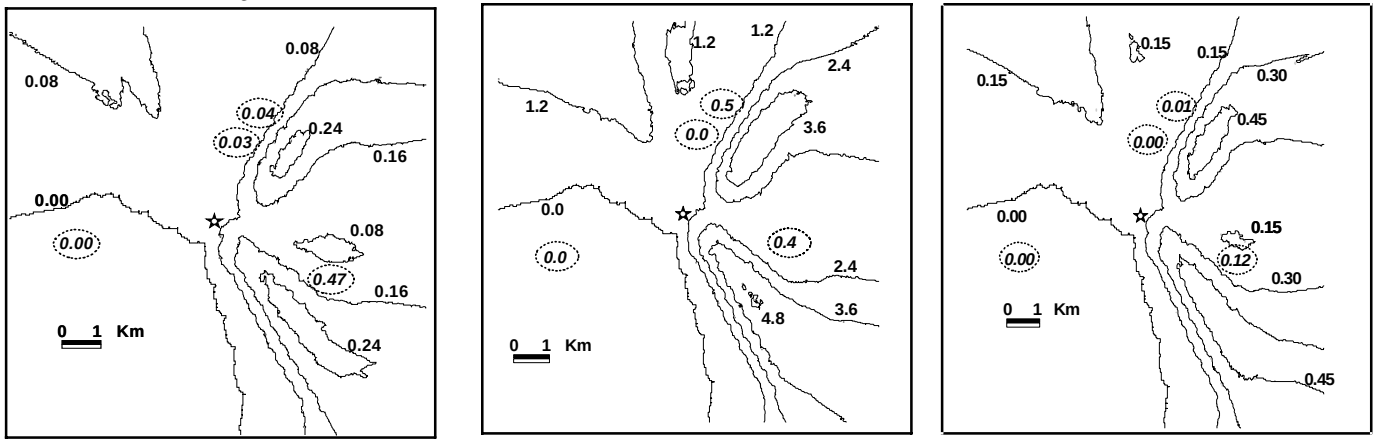
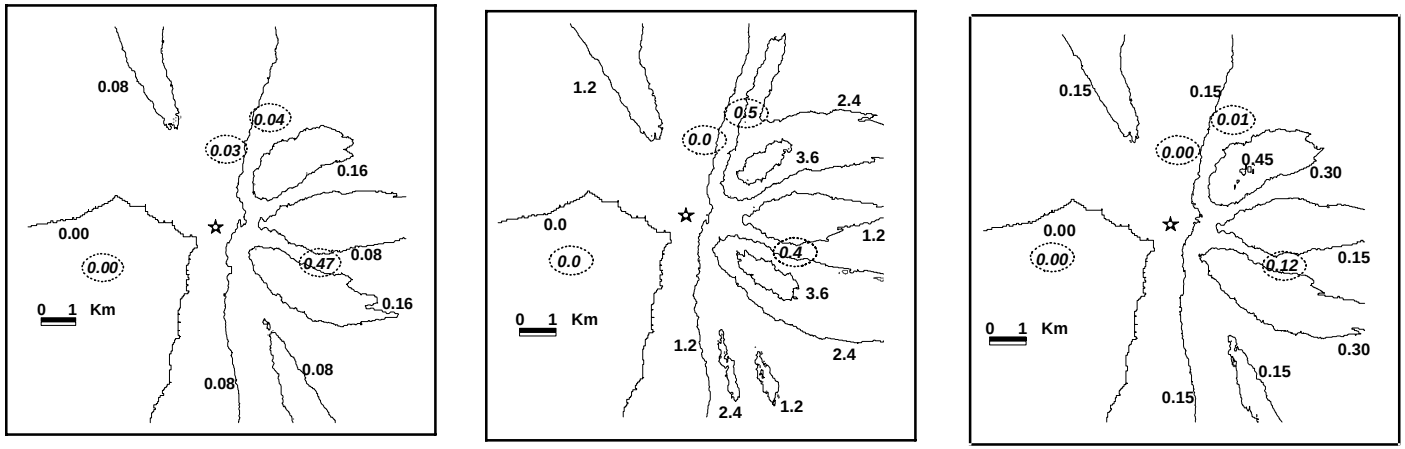


Figure 7-7. Site map showing locations of soil and air samples in the vicinity of the Columbus Municipal Solid Waste-To-Energy (CMWSTE, abbreviated WTE above) Facility.



(a) TCDD, March, On-site (b) OCDD, March, On-site (c) TEQ, March, On-site



(d) TCDD, March, Airport (e) OCDD, March, Airport (f) TEQ, March, Airport

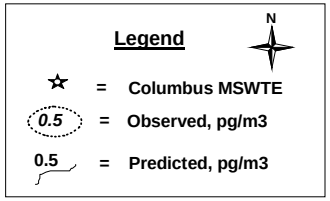
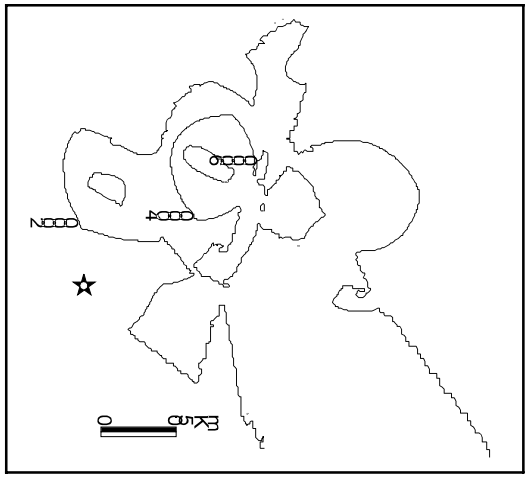
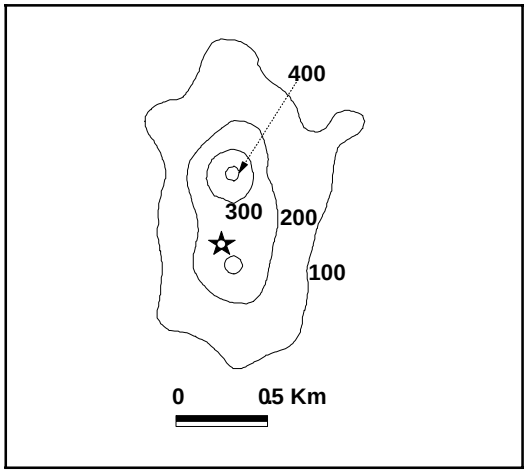


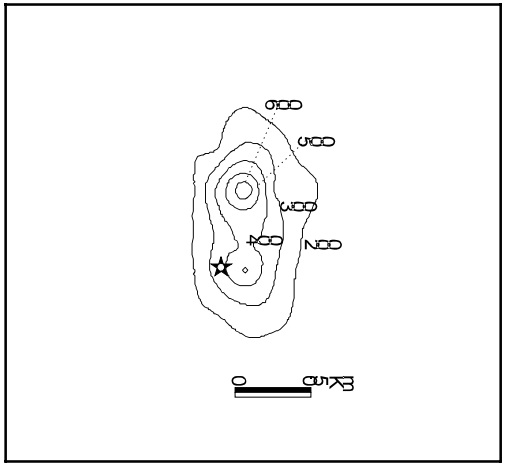
Figure 7-8. Isoline figures of predicted air concentrations overlain by measured air concentrations of TCDD, OCDD, and TEQ (pg/m^3) when using the "on-site" meteorological data set (sub-figures a, b, and c) and when using the "airport" meteorological data set (sub-figures d, e, and f).



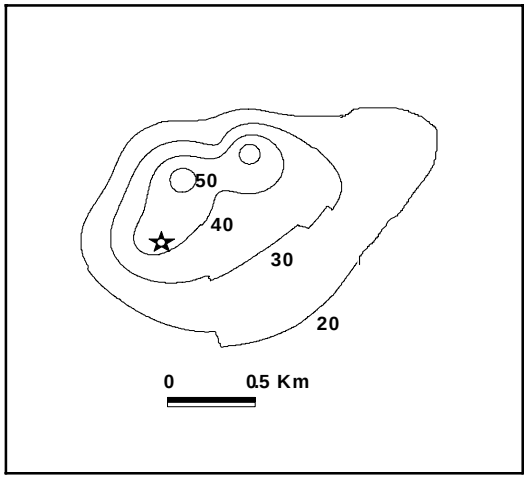
(a) TCDD, Observed



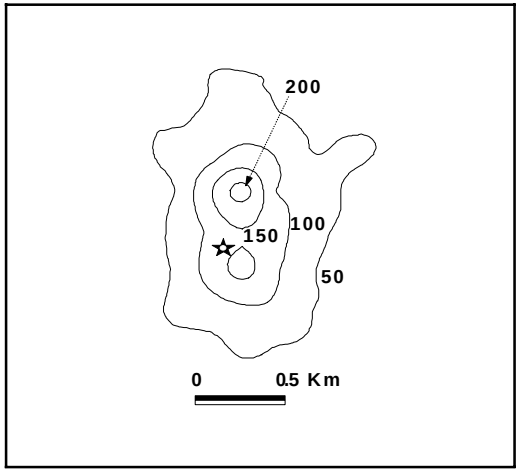
(b) TCDD, '92 Stack Test



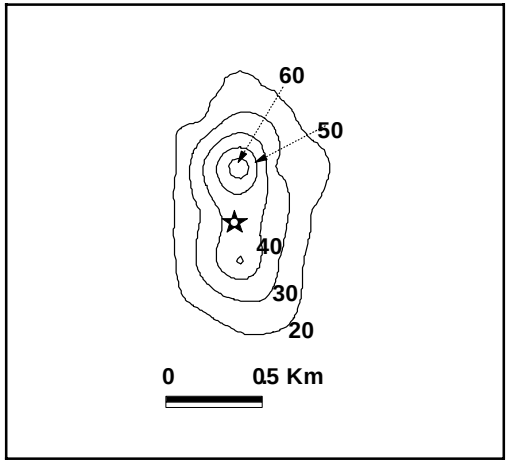
(c) TCDD, '94 Stack Test



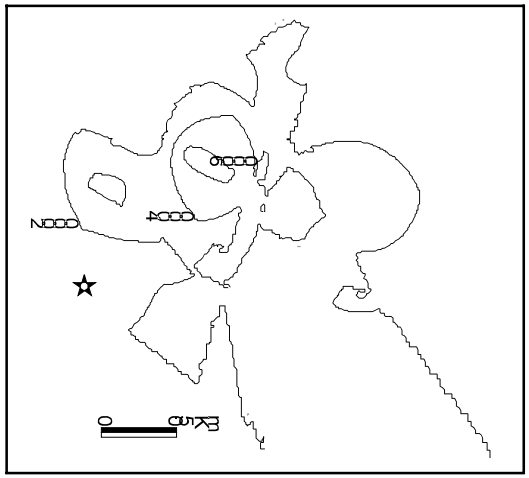
(d) OCDD, Observed

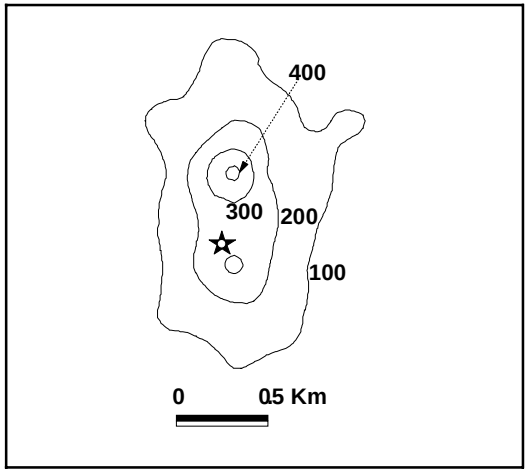


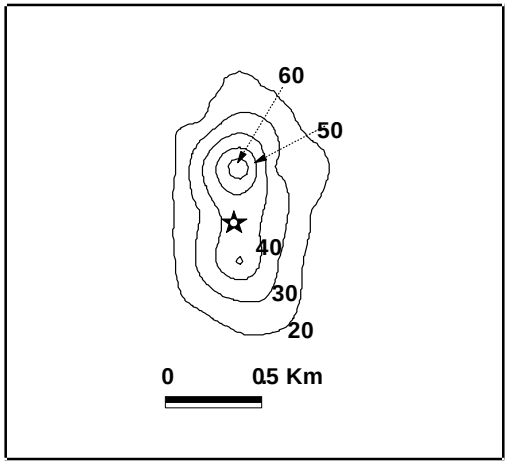
(e) OCDD, '92 Stack Test



(f) OCDD, '94 Stack Test







. (h) TEQ, Observed (i) TEQ, '92 Stack Test (j) TEQ, '94 Stack Test

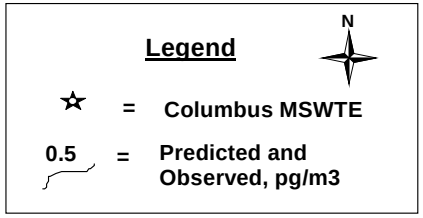
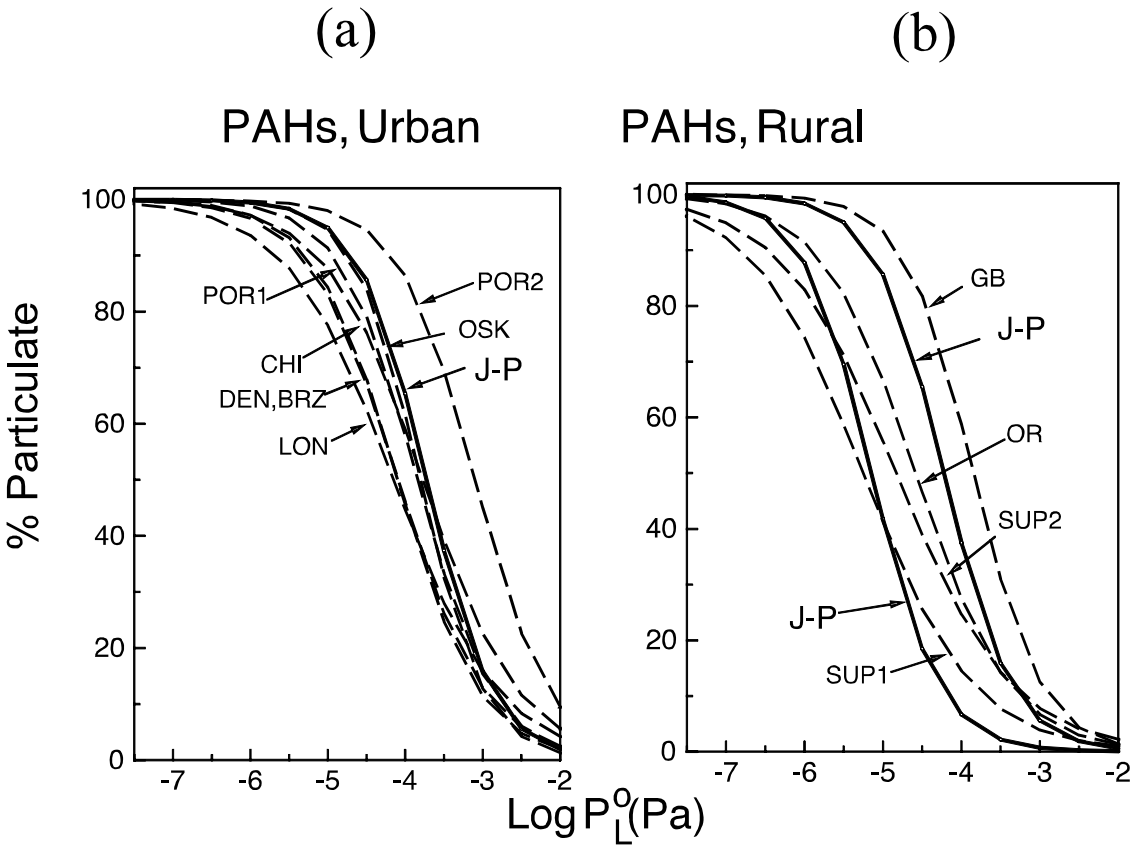
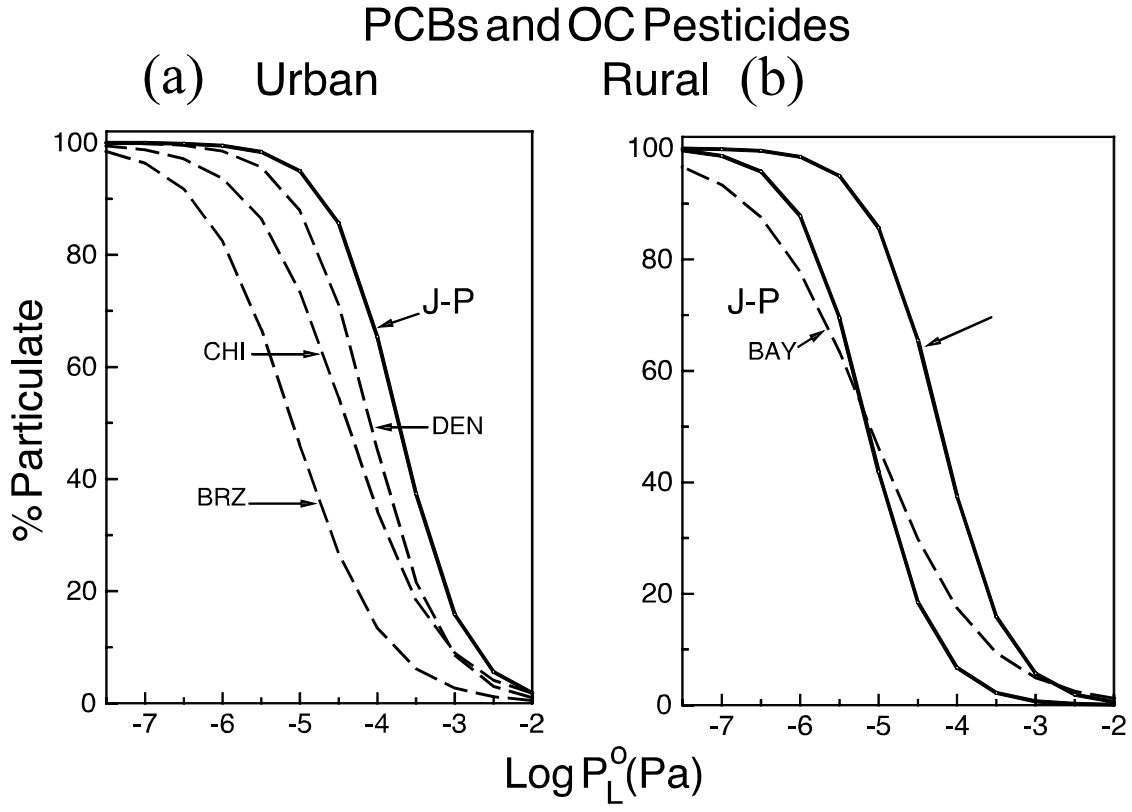


Figure 7-9. Isoline figures of predicted soil concentrations of TCDD, OCDD, and TEQ (sub-figures a, d, g) compared against isoline figures of measured soil concentrations using the 1992 stack emission test (sub-figures b, e, and h) and the 1994 stack emission test (sub-figures c, f, and i).



Key: J-P: Junge - Pankow model; the two solid lines in the rural setting represent clean continental background and background + local sources regimes.
DEN = study in Denver (Foreman and Bidleman, 1990)
POR1 and POR2 = two studies in Portland (Ligocki and Pankow, 1989; Hart, 1989)
CHI = study in Chicago (Cotham and Bidleman, 1995)
SUP1 and SUP2 = two studies in Lake Superior (McVeety & Hites, 1988;Baker & Eisenreich, 1990)
BRZ = study in Brazzaville, Congo (Ngabe and Bidleman, 1992)
LON = study in London (Baek, et al., 1991)
OSK = study in Osaka, Japan (Yamasaki, et al., 1982)
GB = study in Green Bay (Cotham and Bidleman, 1995)

Figure 7-10. Comparison of measured and predicted particulate percentages of PAHs in urban and rural air.



Key: J-P: Junge - Pankow model; the two solid lines in the rural setting represent clean continental background and background + local sources regimes.
DEN = study in Denver (Foreman and Bidleman, 1990)
CHI = study in Chicago (Cotham and Bidleman, 1995)
BRZ = study in Brazzaville, Congo (Ngabe and Bidleman, 1992)
BAY = study in Bayreuth, Germany (Kaupp and Umlauf, 1992)

Figure 7-11. Comparison of measured and predicted particulate percentages of PCBs and organochlorine pesticides in urban and rural air.

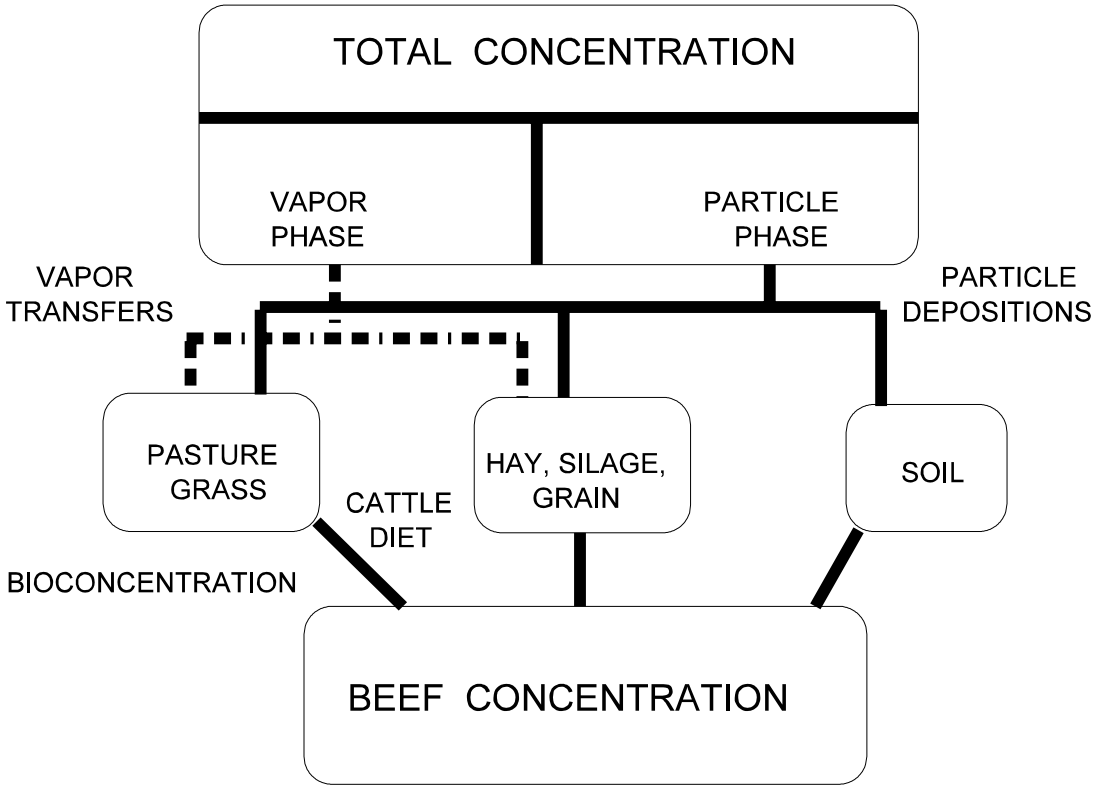


Figure 7-12. Overview of model to predict beef concentrations from air concentrations.

8. UNCERTAINTY

8.1. INTRODUCTION

This chapter addresses uncertainty in dioxin exposure assessment performed with the methodologies presented in this document. Some discussion of the issues commonly lumped into the term "uncertainty" is needed at the outset. The following questions capture the range of issues typically involved in uncertainty evaluations:

(1) How certain are site specific exposure predictions that can be made with the methods?
(2) How variable are the levels of exposure among different members of an exposed local population?
(3) How variable are exposures associated with different sources of contamination?

The emphasis in this document is in providing the technical tools needed to perform site-specific exposure assessments. For the assessor focusing on a particular site, question (1) will be of preeminent importance. Therefore, the emphasis of this Chapter is to elucidate those uncertainties inherent to the exposure assessment tools presented in this document. This chapter examines the uncertainties associated with estimating exposure media concentrations of the dioxin-like compounds using the fate, transport, and transfer algorithms, and also identifies and discusses uncertain parameters associated with human exposure patterns (contact rates and fractions, exposure durations, etc.).

Section 8.2 focuses on uncertainty issues associated with the use of the ISCST3 model for air transport modeling for the stack emission source category. The ISCST3 model and its application in this assessment are presented in detail in Chapter 3. Section 8.3 discusses the variability and uncertainty with chemical-specific parameters which are required for all source categories of this assessment methodology. Section 8.4 provides a general overview of all key uncertainties with each pathway.

A site specific assessment will also need to address the variability of risks among different members of the exposed population, the second key question above. The level of detail with which this can be done depends on the assessors knowledge about the actual or likely activities of these residents. In this document, one approach to evaluating this variability is demonstrated. Separate "central" and "high end" scenario calculations are presented to reflect different patterns of human activities within an exposed population. "Central" scenarios are constructed to represent typical behavior patterns for residential exposures in a hypothetical rural

setting. "High end" calculations focus on a farming scenario where individuals raise food for their own consumption, in the same rural area. It should be emphasized that high end calculations could also have been developed for residential exposures by making, for example, higher range assumptions about the duration of residence or contact rates with the contaminated media. Indeed, this would be recommended for an assessment where considerable emphasis was placed on residential exposures. The key issue with regard to intra-population variability is that it is best (if not only) addressed within the context of a specifically identified population. If such information is available, a powerful tool that can be used to evaluate the variability within a population is Monte Carlo Analysis. Section 8.5. reviews recent Monte Carlo studies which have been done for exposure to 2,3,7,8-TCDD. Assumptions on distributions of exposure patterns and fate and transport parameter distributions are described, as are the results of their analyses. Aside from this review, this chapter does not address question (2) in any further manner.

With regard to question (3), this document does not present a detailed evaluation of how exposure levels will vary between different sources of release of dioxin-like compounds into the environment. Volume I of this assessment examines sources of release of dioxin-like compounds into the environment. This document, Volume III, presents methodologies for three types of sources - soil, stack emissions, and effluent discharges into surface water bodies. While this document demonstrates the methodologies developed for these sources with source strengths and environments crafted to be plausible and meaningful, there is still a great deal of variability on both the source strengths and on the environments into which the releases occur. For example, the frequency with which farms and rural residences are near stack emissions of dioxin-like compounds is not addressed. The scenario calculations in Chapter 5 are intended to be illustrative; the exposure levels that are obtained there are not intended to be typical of actual exposures for the sources and pathways assessed.

Nonetheless, some readers might ideally wish information on both the magnitude of actual exposures and the variability of these exposures associated with different sources of dioxin-like compound releases into the environment. However, the analysis presented in this chapter cannot support so broad a goal. Representative data to address the variation of dioxin exposures are becoming available for sources as well as exposure media. Volume I discusses and quantifies releases from known sources in the US, and the compilation of environmental and exposure media concentrations presented in Chapter 3 of Volume II of this assessment displays the range of measured concentrations in the environment. The careful selection of certain literature reports on concentrations of dioxin-like compounds to represent background conditions, described in Chapter 4 of Volume II, is one way such environmental measurements

can be used. References to EPA and other assessments on dioxin-like compounds have been made throughout this document, such as those related to soil exposures (Paustenbach, et al., 1992a), exposures to contaminated fish (EPA, 1991a), exposures resulting from land disposal of sludges from pulp and paper mills (EPA, 1990), just to name a few. Still, studies comparing and ranking different sources and exposure patterns, and elaborations on ranges of source strengths and exposures, are generally not available. Information in Volumes I and II of this assessment, and procedures for source specific evaluations in Volume III, can provide others with information and tools to begin such analysis.

8.2. A DISCUSSION OF UNCERTAINTY ISSUES ASSOCIATED WITH THE USE OF ISCST3 FOR TRANSPORT AND DISPERSION OF STACK EMITTED CONTAMINANTS

Air dispersion and deposition analysis was performed using the ISCST3 Model. The model is intended to provide long term average air concentrations and wet and dry deposition flux. This section discusses some of the uncertainties and critical parameters associated with the general modeling approach used in ISCST3, and reviews some of the literature on model testing and validation.

Atmospheric dispersion in ISCST3 is modeled using the common Gaussian plume model. Downwind concentrations of the dioxin-like chemicals are calculated as a function of stack height, the mass emission rate, the wind speed, and general atmospheric conditions. The Gaussian model assumes that the emission concentrations predicted by the model will fit a normal distribution. The principal assumptions in the Gaussian model are (Kapahi, 1991):

- The air concentration of the chemical at a fixed distance from the source is directly proportional to the emission rate from the source;
- The air concentration of a given chemical is inversely proportional to the wind speed corresponding to the effective height of release of the chemical into the air;
- The predicted ground-level concentration of the chemical approaches zero at large distances from the initial point of release.
- The model is steady-state.
- The model assumes constant wind speed, wind direction, and atmospheric stability over time and space for a given time period.

In general, the Gaussian plume model has been shown to predict annual average ambient air concentrations of a chemical emission from an industrial source to within a factor of one-order of magnitude of measured values, and in some cases, within a factor of 3 to 4-fold of field

measurements (Cohrssen and Covello, 1989). This modeling error spans both sides of the predicted concentration, that is, the actual concentration may be plus or minus this amount of the predicted value. Even more assertive, an early position paper on the application of gaussian short-term dispersion models claimed an approximate factor-of-two accuracy in the absence of complicating factors (complex terrain, building wake effects) (AMS, 1978).

The most sensitive aspects to variability in modeled predictions of ambient air impacts, if emissions are held constant, are stack height (height of the release), and terrain (flat verses complex topography). To investigate modeling variability, EPA placed a prototype hypothetical hazardous waste incinerator in flat terrain and elevated terrain in geographical areas around the U.S. (EPA, 1991b; analysis conducted with the Industrial Source Complex, or ISC, model). Then the stack height was varied at these particular locations. Numerous runs were made at twelve specific sites to compare and contrast the influence of stack height and terrain on predicted ambient air concentrations of various mass emission rates of specific inorganic pollutants. A series of tables were developed from this sensitivity analysis from which the numerical estimation of the variability as a function of stack height and terrain can be inferred. When the hypothetical hazardous waste incinerator was modeled in flat terrain, e.g., topography within a distance of 5 km is not above the height of the stack, and the stack height was varied from 4 meters to 120 meters, the variability in the predicted ambient air concentration spanned two orders of magnitude (100). The lower stack height resulted in a predicted ambient air concentration that was 100 times greater than the concentration predicted using the tallest stack height. When the hypothetical hazardous waste incinerator was located in complex terrain over the same range of physical stack heights, the variability in estimated groundlevel concentration of the subject pollutant spanned two orders of magnitude (100-fold). In the latter case the stack height was computed as the terrain-adjusted stack height by subtracting from the physical stack height the influence of terrain on plume rise. From the limited sensitivity analysis of hazardous waste incinerators, it can be assumed that the predictions of spacial ground-level ambient air concentrations of dioxin-like compounds could differ from values in Tables 3-17 and 3-18 by two-orders of magnitude in consideration of changes in stack height or changes in terrain. For example, Tables 3-17 and 3-18 show that the maximum annual average ambient air concentration of 2,3,7,8-TCDD predicted near the hypothetical incinerator is approximately 10^{-11} $\mu g/m^3$ for the stack height of 30.5 meters, and assuming flat terrain. If only the stack height is varied from 20 meters to 120 meters, and all other modeling parameters are held constant, then the predicted ambient air concentration would be approximately 10 times greater and 10 times less than the estimated concentration, respectively. The uncertainty is broader when considering the influence

of topography on predictability of the ground-level concentrations from the model. If only terrain elevation is varied at a distance of 5 km from the hypothetical incinerator from zero elevation to 30.5 meters, e.g., the height of the stack, then the predicted ambient air concentration of 2,3,7,8-TCDD would be approximately ten times greater. The tables derived in the hazardous waste incineration analysis have a limitation of elevation of terrain to the height of the stack.

The most uncertain aspect to the modeling is the estimation of dry and wet deposition flux of dioxin-like compounds on the vicinity of a hypothetical incinerator. Contributing most to this uncertainty seems to be the settling velocities and scavenging coefficients estimated for specific particle size diameters (Cohrssen and Covello, 1989; Doran and Horst, 1985). Seinfeld (1986) found that particles over 20 microns in diameter settle primarily by gravity, whereas smaller particles deposit primarily by atmospheric turbulence and molecular diffusion. Considerable, but non-quantifiable, uncertainty exists with respect to deposition velocities of particles 0.1 to 1.0 microns in diameter (Seinfeld, 1986). The uncertainty is difficult to define. The wide variation of predicted deposition velocities as a function of particle size, atmospheric turbulence and terrain adds to this uncertainty (Sehmel, 1980). However, Gaussian plume dispersion models have been field validated for their ability to spatially predict dry deposition flux over some specified distance (Doran and Horst, 1985). In a series of field experiments conducted by Pacific Northwest Laboratory (Doran and Horst, 1985), zinc sulfide was used as a depositing tracer gas, and sulfur hexafluoride was used as a non-depositing tracer gas to compare and contrast modeling results with field measurements of dry deposition and atmospheric diffusion of the gases. The tracer was released from a height of 2 meters, and all releases were made under relatively stable atmospheric conditions. Five sampling stations were located downwind of the release from 100 to 3200 meters. The results of these experiments showed good agreement with the predicted verses the measured deposition of the tracer ZnS. The overall correlation coefficient between predicted and measured deposition concentration was found to be 0.82 (Doran and Horst, 1985), but the models marginally over-predicted deposition flux near the source of release, and under-predicted deposition flux at 3200 meters.

Travis and Yambert (1991) have evaluated the uncertainty in modeling the dry deposition flux of particulates using four standard Gaussian plume dispersion models. Since deposition flux is dependent on deposition velocity for a given particle mass and diameter, comparisons were made between model-generated deposition velocities and measured values found in the open literature for particles ranging from 0.01 to 30 microns in diameter. It was found that measured deposition velocities for a given particle size in the scientific literature exhibit variability spanning roughly two orders of magnitude. The analysis of the mean predicted deposition

velocities to mean measured values showed that most measured data exceeded the predicted data for all four models. Moreover, the models underestimated the mean deposition velocities for particles in the range of diameters from 0.05 to 1.0 microns.

Similar uncertainty probably exists with regard to scavenging of various diameter particles by various intensity of rainfall. Seinfeld (1986) has calculated scavenging coefficients in terms of the removal efficiency of particles of a given size by rain droplets having a given momentum. Seinfeld (1986) found that the scavenging coefficient of a given particle diameter corresponding to a given rainfall intensity can be calculated based on physical laws, but there is a complete absence of research data to verify these calculations. Hence it is not possible to address the accuracy nor uncertainty of the wet deposition flux estimated in Table 3-19.

There have been some limited validation work done with ISCST3 and its ISC predecessors. Chapter 7 described a model validation exercise for air dispersion and deposition/soil concentration modeling done for dioxins in the vicinity of a municipal solid waste incinerator known to be emitting large amounts of dioxins. The predicted concentrations were mostly within a factor of 10 of observations, higher or lower, for both air and soil. There was evidence that the profile of dioxins in both the air and the soil were distinct from the profile of dioxins being emitted from the incinerator. This observation suggests transformations in the dioxin profile in either, or both, the air and soil environments. In clearly impacted ambient air samples that were downwind of the incinerator during sampling events, for example, the measured profile suggested a more predominance of lower chlorinated dioxins than was seen in the stack emission. Two explanations were offered to explain this observation: the higher chlorinated dioxins deposited much more so than the lower chlorinated dioxins, which lessened their predominance in the profile and/or higher chlorinated dioxins dechlorinated to form lower chlorinated dioxins. When testing air dispersion alone (no deposition, no atmospheric decay or transformation of emitted dioxins), the air concentration profile perfectly matched the stack emission profile, as it should, so neither of these possibilities could be tested. However, when testing the deposition/soil concentration capabilities of ISCST3, evidence did strongly suggest that the model was underpredicting the deposition rate of OCDD, at least. Even with this possible finding, the disparity between the soil concentration profile and the stack emission profile continued to suggest that transformations may be taking place in soils and/or the air which were not captured in the model testing at this site. In general, the model was able to duplicate the trend of elevations in both air and soil near the facility, to within a factor of 10 of these elevations.

Early ISC (the predecessor to ISCST3) model validation work was conducted by Bowers, et al. (1981). They tested the gravitational dry particle deposition algorithms, new at that time, and showed that the model predicted deposition rates generally within a factor of two of measured depositions of glass microspheres of 50 to 200 μm measured in an experimental setting. They also tested the capabilities of building wake effects using data from diffusion experiments conducted at a Nuclear Power Station in which the tracer SF_6 was released from the reactor building main vent and the tracer Freon 12B2 was simultaneously released from three vents on the adjacent turbine building. They then predicted concentrations of these tracers with and without building wake effects, and found that the inclusion of building wake effects improved the average correspondence between modeled and observed concentrations by almost a factor of 2.

8.3. UNCERTAINTIES AND VARIABILITIES WITH CHEMICAL-SPECIFIC MODEL PARAMETERS AND ASSUMPTIONS

This assessment assumed that levels of dioxin-like compounds in soil and sediment were constant over the period of exposure, with two exceptions. One circumstance was when contaminated soil eroded from one site and deposited on a site of exposure nearby - the soil contamination source category. The other was when stack emitted particulates deposited onto a site of exposure - the stack emission source category. In both these instances, it is assumed that only a relatively thin layer of surface soil at the site of exposure would be impacted, and that this thin layer is subject to dissipation processes - erosion, volatilization, possibly degradation. Data in Young (1983) implied a soil half-life of 10 years for surficial 2,3,7,8-TCDD residues, although the circumstances of the soil contamination were not analogous. Specifically, a 37 ha test area at the site had received an estimated 2.6 kg of 2,3,7,8-TCDD over a two year period. Soil sampling which occurred over 9 years from the last application suggested that less than 1 percent remained at the test area. Although Young hypothesized that photodegradation at the time of application was principally responsible for the dissipation of residues, other mechanisms of dissipation including volatilization, erosion, and biological removal may also have contributed to the loss of residues. Soil sampling over time after application implied a dissipation half-life of 10 years for soil residues of 2,3,7,8-TCDD. Mclachlan, et al. (1996) reported on an analysis of soil taken from experimental plots which had been amended with sewage sludge in 1968 and sampled in 1972, 76, 81, 85, and 90. These archived samples were analyzed for all 17 dioxin-like CDD/Fs, and based on an analysis of results, McLachlan and coworkers concluded that half-lives were on the order of 20 years, with dioxin removal from the plots being mainly physical removal

processes (overland runoff, wind erosion). Furthermore, their results suggested that all congeners had been removed at roughly the same rate, which is why they concluded that removal processes were mainly physical and very little in-situ degradation appeared to be occurring. Paustenbach, et al. (1992a) reviewed several reports of the soil dissipation of 2,3,7,8-TCDD, including Young (1983), and concluded that the half-life of 2,3,7,8-TCDD residues below the surface varied from 25-100 years. A half-life of 25 years ($k = 0.0277\ yr^{-1}$) was assumed to apply to all dioxin-like compounds in this assessment.

Section 2.6.1, Chapter 2 in Volume II of this assessment, reviewed the literature on degradation of dioxin-like compounds. As discussed, biological transformations as well as chemical processes (oxidation, hydrolysis, and reduction) do not appear to result in substantial degradation of these compounds. There is evidence of photolysis, particularly when dissolved in solution and when organic solvents are present. Most of these data are specific to 2,3,7,8-TCDD. Uncertainty is introduced into parameter assignment when information specific to one congener is assumed to apply to all dioxin-like congeners. However, it is judged that there is no good data available to assign different soil dissipation rates to different dioxin congeners in this assessment, and McLachlan's (1996) data is judged to be reasonably strong to support an assumption that all dioxin congeners dissipate with roughly the same half-life.

Dissipation of surficial residues could translate to lower soil-related exposures including particulate inhalations, soil ingestion, and soil dermal contact. However, it is not clear that reductions in exposure would, in fact, occur, particularly if the soil is contaminated below the surface. Processes such as wind erosion, soil erosion, or volatilization originating from deeper in the soil profile, could serve, in a sense, to replenish reservoirs at the soil surface. Depositions back onto soils from other soils, or depositions from distant sources, also replenish soils. Given very low rates of degradation (for all degradation processes except photolysis), the assumption of no degradation for the soil contamination source category is reasonable with moderate, but unquantifiable uncertainty.

In evaluating an assumption of no degradation, another issue to consider is the depletion of the original source of contamination. For the stack emission and effluent discharge source categories, the assumption is made that steady releases occur while the source is active. Therefore, depletion of the original source is not an issue. For the soil contamination source category, it is assumed that the reservoir of contaminant is constant throughout the duration of exposure. If such a duration is assumed to be very long, then degradation or dissipation of soil residues would be more critical than if the duration were relatively short. Uncertainties associated with the duration of exposure are discussed in Section 8.4 below. Also, Section 6.4 in

Chapter 6 evaluated the assumption of a constant soil concentration by estimating the time it would take for a 15-cm reservoir of soil contamination to be depleted, using the dissipation algorithms of this assessment. These algorithms include volatilization, soil erosion, and wind erosion, with lesser releases due to biological uptake, and leaching and runoff. It was found that it would take over 90 years to deplete a 15-cm reservoir, lending some credibility to a non-degradation assumption if the exposure duration were in the range assumed for the demonstration scenarios of this assessment, 30 years.

A critical contaminant parameter required for the procedures in this assessment is the octanol water partition coefficient, Kow, although none of the fate and transport algorithms directly require a Kow. One of the empirical biota transfer parameters is, however, a function of Kow. This is the RCF, or Root Concentration Factor, which estimates the transfer of contaminant from soil water to root. Log Kow estimates for dioxin-like compounds range from 6.00 to 8.5, with higher log Kow associated with higher chlorination. However, this is not a certain parameter. Estimates in literature for 2,3,7,8-TCDD, for example, range from 6.15 to 8.5. The uncertainty of the RCF is addressed in Chapter 7, Section 7.3.9, where experimental data on the transfer of dioxins from soil to carrots was used in a validation exercise. It was found that the RCF allowed for the reasonably accurate simulation of the transfer of dioxins to the carrot peel, with the model able to predict peel concentrations within a factor of 2 for 15 of 20 observations, and for the other five observations, predictions and observations differed by a factor of 5 or less.

Two biota transfer coefficients are used to estimate fish tissue concentrations based on water body sediment concentrations: the Biota Sediment Accumulation Factor, BSAF, and the Biota Suspended Solids Accumulation Factor, BSSAF. There are no empirical relationships which estimate these as a function of the more common Kow for dioxin-like compounds. Rather, values were assigned based only on experimental and field data. Needless to say, most of the data available was for 2,3,7,8-TCDD, leaving large gaps for other compounds. Also, there is no data available for estimating the BSSAF, a parameter proposed in EPA (1993) which was used in the effluent discharge source category. The BSSAF was set equal to the BSAF for this assessment. Field data including bottom sediment concentrations and concurrent fish concentrations were used to determine values for BSAF. The limited field data available for BSAF suggests values in the range of 0.03 to 0.30 for 2,3,7,8-TCDD, with higher values approaching 1.00 indicated for bottom feeders (catfish, carp, etc.), and decreasing values as the degree of chlorination increases - limited information suggests values in the 10^{-3} to 10^{-2} range for hexa- through octa- CDDs and CDFs. EPA (1995) used available data to develop the "bioequivalency factors", BEFs, or multipliers to the BSAF or BSSAF to assign values for

congeners other than 2,3,7,8-TCDD, when data on only 2,3,7,8-TCDD is available. The BEF concept and the BEFs are described further in Chapter 4. They were used to assign values for the BSAF/BSSAF for other dioxin-like congeners assuming a BSAF/BSSAF of 0.09 for 2,3,7,8-TCDD. Data on PCBs suggest that BSAFs are higher than those of CDDs and CDFs by an order of magnitude and more, and that the trend with increasing degrees of chlorination is not the same. The data indicates that BSAFs for PCBs increase from dichloro- through hexa- or perhaps hepta-chloro PCBs, and decrease thereafter.

A bioconcentration factor, BCF, translates the average contaminant in the diet of the cattle into a beef or milk fat concentration. Experimental rather than field data was available for estimates of BCF for dioxin-like compounds. Farm animals were fed known quantities of these compounds and their body tissues and milk were monitored over time to arrive at BCFs. Data showed that the BCF decreased to below 1.0 as the degree of chlorination increased. An experimental data set, including analysis of 16 of the 17 dioxin-like congeners, described in McLachlan, et al (1990), was used to assign BCF values for this assessment. A more recent study, by Fries, et al. (1999), developed BCFs for 14 of 17 congeners in a feeding experiment where four cows were fed PCP-contaminated wood. Results showed a good agreement between these BCFs and those developed from the data of McLachlan, et al. (1990), although the BCF for 2,3,7,8-TCDD was highest in this experiment at 7.1 as compared to the BCF of 5.76 developed from McLachlan's data and used in this assessment. Limited data showed PCB BCFs to be the same order of magnitude, although trend data for increasing degrees of chlorination was not available.

Similar bioconcentration factors, also termed BCF in Chapter 4, were described for chicken fat. Like the beef/milk fat BCF, they were developed from experimental data on chickens and eggs (Stephens, et al., 1995). The transfer of vapor-phase dioxins from air to plant is also modeled with a simple biotransfer factor, termed B_{vpa}, is also developed from field data.

Obviously, a degree of uncertainty is introduced when relying on these empirical bioconcentration or biotransfer coefficients to estimate concentrations in fish, beef, milk, chicken, eggs, and terrestrial vegetation. The variability in the data suggests up to an order of magnitude range of variation may result from use of these parameters. All but one of these factors (the RCF) were developed from field or experimental data on dioxin-like congeners or homolog groups. This, by definition, will lend a degree of credibility to their assignment. Also, a validation exercise described in Chapter 7 testing the air-to-beef algorithm is a test of two of these biotransfer/bioconcentration factors, the B_{vpa} and the BCF, and both appear to be supported by this exercise. It appears likely, therefore, that the actual variation in these

biotransfer/bioconcentration factors, is less than an order of magnitude, perhaps less than a factor of five.

Another important chemical-specific parameter that can be estimated from Kow or estimated experimentally is the organic carbon partition coefficient, Koc. Koc describes the steady state partitioning between soil or sediment organic carbon and water; it impacts the volatilization flux from soils, and the partitioning between suspended sediment and water in the water column. Koc is used to estimate in-situ partitioning using a fraction organic carbon in the soil or sediment, OC_{sl}, OC_{sed}, and OC_{ssed}, as $Koc*OC_{sl}$, etc. The resulting chemical-specific parameter is termed the soil (or sediment) partition coefficient, Kd_s (or Kd_{sed}, Kd_{ssed}). The empirical equation used to estimate Koc from Kow in this assessment was derived by Karickhoff (1979). This equation was chosen over others available (Lyman, 1982) because it was derived from laboratory testing of 10 hydrophobic contaminants. Others available would have led to lower estimates of Koc. The Koc for 2,3,7,8-TCDD estimated for this assessment using Karickhoff's relationship was 3,980,000. Some data implies that this estimate itself may be low for 2,3,7,8-TCDD. Studies reviewed in Section 2.4.5., Chapter 2 of Volume II of this assessment, particularly those Jackson, et al. (1986) and Lodge (1989), indicate 2,3,7,8-TCDD Koc estimates in the range of 20,000,000 to greater than 30,000,000.

Another contaminant parameter is the Henry's Constant. Volume II, Chapter 2, provides the values of the Henry's Constants, H, for dioxin-like compounds, some of which were estimated given vapor pressure and water solubility data. The CDD/F Henry's Constants were in the 10^{-6} to 10^{-5} atm-m^3/mol range, while coplanar PCBs were in the 10^{-5} to 10^{-4} range, with one high value at $3x10^{-3}$ atm-m^3/mol.

Finally, the contaminant molecular diffusivity in air is required for estimates of volatilization flux from soils. The molecular diffusivity in air is set at 0.05 cm^2/sec for all dioxin-like compounds. Molecular diffusivity is a property of both the chemical and the medium. It represents the propensity of a chemical to move through a medium. It is recognized to be largely a function of molecular weight. The values selected are evaluated as reasonable for all dioxin-like compounds, since the molecular weight for these compounds are similar.

8.4. UNCERTAINTIES ASSOCIATED WITH EXPOSURE PATHWAYS

The purpose of this section is to qualitatively describe the uncertainties associated with exposure estimates for the exposure pathways that are included in this methodology. The principal focus is on the exposure parameters - the contact rates and fractions, exposure durations, and so on. A brief summary is also presented on some of the findings pertaining to the

fate, transport, and transfer algorithms used to estimate the exposure media concentrations. This summary will highlight findings that have been included in other sections of this chapter, Chapter 7 on model comparisons and model validations, as well as a section in Chapter 6 on User Considerations. Each section below includes a table summarizing key points of uncertainty. Section 8.4.1 looks at three key exposure parameters which are common among all pathways - lifetime, body weights, and exposure durations. Sections 8.4.2. to 8.4.11 are pathway-by-pathway discussions.

8.4.1. Lifetime, Body Weights, and Exposure Durations

Values for lifetime of 70 years and adult body weight of 70 kg are traditionally used for risk assessment purposes, although data in the Exposure Factors Handbook (EPA, 1997) suggest that the current average body weights may be lower and the lifetime may be longer. The deviations are small and more precise numbers would not change exposure estimates by a meaningful amount. The uncertainty regarding body weight is reduced in the ingestion pathways of fruit/vegetables and the terrestrial animal food products including beef, milk, chicken, and eggs. This is because the consumption rates used in these pathways for the demonstration does in this assessment are in units of g/kg/day and were derived from survey data which incorporated the amount consumed with the individual body weight. Specifically, these rates originated from the household portion of the National Food Consumption Survey conducted by USDA (USDA, 1992). Chapter 2 describes the use of this survey data in detail and Section 8.4.7 below summarizes some of the uncertainties in using it. The assumed child body weight of 17 kg (for ages 2-6) is well founded and not expected to introduce uncertainty into soil ingestion exposure estimates.

Assumptions on exposure durations are the most uncertain of the three parameters discussed here. A value of 9 years assumed for central exposure scenarios was the 50th percentile of time living at one residence derived from census survey data (EPA, 1997). Such mobility surveys typically ask respondents how much time they are living at one residence, so a result such as this one will likely be an underestimate because respondents are likely to continue to live at their residence beyond the time they answered the survey question. The estimate of 30 years for the average residence time of farming families (used to define high end exposure scenarios) was also based on survey data which showed that the 90th percentile time spent in one residence was 32.7 years. For the high end scenarios of this assessment, this 90th percentile is justified based on the definition of high end. Also, however, it is supported based on a

qualitative judgement that farming families may tend to live longer in one spot as compared to non-farming families.

Exposure durations are also tied to assumptions about source strength over time. Assuming 30 years of exposure to stack emissions, for example, assumes that the source of stack emissions will be (or has been) in operation for this length of time with the same stack emission controls in place. The same is noted for the effluent discharge source category. If the source is contaminated soil, assumptions include whether or not the soil will be removed, the site will be capped, and so on. Another consideration is the dissipation of soil residues. Section 8.3 discussed uncertainties with the assumption of non-degradation of dioxin-like compounds in soil when the soil itself is contaminated. A 25-year dissipation half-life is applied to residues which migrate to an exposure site to impact only a thin layer of surface soil. Specifically, a simple soil mixing model incorporating the 25-year dissipation half-life is used to calculate steady state soil concentrations of dioxin in a thin surface layer resulting from atmospheric depositing dioxins, from the stack emission source, or from soil eroding from a nearby site of soil contamination. As discussed above in Section 8.3., an assumption of non-degradation during periods of exposure in the range of 30 years is reasonable, since degradation/dissipation pathways lead to very slow decline of dioxin concentrations in soil.

Exposure estimates are linearly related to all three exposure parameters - increasing body weight and lifetime decreases exposures in an inverse linear fashion, while increasing exposure durations increase estimates in a direct linear fashion.

Uncertainties associated with body weight, lifetime, and exposure durations are summarized in Table 8-1.

8.4.2. Soil Ingestion Exposure

This exposure is directly a function of the concentration of contaminants in surface soil layers. For example Scenarios 1 and 2, demonstrating background conditions, soil concentrations at the site of exposure were set at levels corresponding to an actual setting which can described as, “background”. For example Scenario 3, demonstrating the soil contamination source category, erosion onto the site of exposure deposited residues into a thin, no-till, surface layer of 2 cm, and a thicker, 20-cm, till layer of soil. Soil ingestion exposures were based on concentrations in the 2-cm layer. In Scenarios 4 and 5 demonstrating the stack emission source category, contaminated particles deposited onto the exposure site, also creating a till and a no-till concentration. The no-till depth for this category was also 2 cm.

Discussions on the methodology to estimate exposure site soil concentrations resulting from erosion of contaminated soil from a nearby site are contained in Section 6.3.3.2, Chapter 6, which was on sensitivity analysis and the impact of different parameter values on estimated exposure site soil concentrations, and in Chapter 7, Section 7.3. discussing literature reports of off-site impacts from soil contamination. While off-site impacts were noted in the literature, no data could be found that was directly amenable to comparison with the scenarios of Chapter 5. The closest site for which data was available was the Dow Site in Midland, Michigan. The ratio of soil concentrations of 2,3,7,8-TCDD in areas described as "background" in the 600 ha site to soil concentrations in the contaminated areas was 1/8 to ½ as much (depending on how the contaminated area soil concentration was interpreted) as the ratio modeled in the off-site demonstration scenario. This might imply that the model overpredicts off-site soil impacts, except that the "background" areas in the Dow Site appear substantially further away than the 150 meters in the off-site demonstration scenario. Also, data was unavailable to determine the erodibility of soil at the Dow Site. Had this and other site-specific information been available, a more precise test of the off-site soil impact algorithms of this assessment may have been possible. Still, a key finding in the sensitivity analysis exercises was that the erosion algorithms may be overestimating off-site impacts. No information is available on estimating how much of an overestimation may have resulted, and this finding is not a definite conclusion.

If, in fact, an overestimation is occurring, it could be due to a few different factors: 1) an uncertain dissipation rate - increasing it could reduce soil concentrations, 2) assumed depth of mixing for untilled situations - increasing it could also reduce soil concentrations, and 3) the steady state simplification. These factors were examined in the sensitivity analyses conducted in Chapter 6.

In contrast to the possible overprediction of soil concentrations for the soil contamination source category, an exercise described in Chapter 7, Section 7.3.8 suggested that the stack emission source category may be underpredicting soil concentrations. Measured air concentration in an actual rural setting were used in a model validation exercise which attempted to duplicate measured soil concentrations at that same setting. It was seen that modeled soil concentrations were slightly lower than measured soil concentrations. Two possible causes for this underprediction were offered: 1) the model does not account for deposition of vapor-phase dioxins, either through direct deposition or by detritus production, and 2) the representative air profile was derived from samples in March, April, and June, and the average may not have represented typically higher wintertime air concentrations.

In the stack emission source category and the soil contamination source category where the site of exposure is distant from the site of contamination, the two key uncertain parameters are the depth of mixing and the soil half-life for dioxins depositing onto the site of exposure. The mixing depth is a theoretical parameter for which little data is available. The data of Brzuzy and Hites (1995) on soil profiles of dioxins for undisturbed soils does show that dioxins migrate below the surface, in some cases under sandy conditions, to depths greater than 30 cm. However, their non-sandy soil profiles showed most of the dioxins within 5 cm of the surface, and considering that their undisturbed soil cores reflect depositions of dioxins which were speculated to have occurred 50 years or more, the assumption of 2 cm is felt to be reasonably justified. Others have assumed depths of mixing of 1 cm for analogous applications. Evidence from radioactive fallout suggests depths no deeper than 5 cm. Sensitivity analysis on the erosion algorithms showed that assuming a depth of 1 cm instead of 2 cm would have increased soil concentrations by a factor of 2.5, while decreasing the mixing depth to 10 cm decreases soil concentrations by 60%. Very little data is available on dioxin soil half-lives, but the assumption of a half-life of 25 years is within the range of 25-100 years hypothesized by Paustenbach, et al. (1992a) for surface and buried residues based on their survey of the available literature. The analysis by McLachlan, et al. (1996) on data on dioxin concentrations in a plot of soil amended with sewage sludge over 20 years earlier showed half-lives consistently around 20 years for the suite of dioxin congeners, and this is probably the best support for the use of a constant half-life for all dioxin congeners.

Another issue is whether children should be assumed to be exposed to tilled soils - tilled by home gardening, farming, etc. - or untilled soils. It is feasible that children would be exposed to tilled soils in farming or home garden settings. If the soil was impacted by stack emission depositions or erosion from a nearby site of soil contamination, then tilling would reduce soil concentrations. However, it is more reasonable to assume that they generally play outside in areas that are not mechanically tilled.

The estimated soil ingestion quantity is based on field measurements, using trace elements, of soil ingested by relatively small groups of children over brief periods. Methodological issues in these studies remain to be addressed. In particular, ingestion estimates may have been lower if dietary intake of the trace elements was taken into account. Research is underway to refine soil ingestion estimates obtained through trace element measurements. Given the available data, EPA (1997) suggests that 100 mg/day is a reasonable central estimate for children under 6 years of age, and that value is used in this assessment in the central scenarios. Due to the behavior known as pica, some children are known to ingest high amounts of various

non-food materials. Estimates of pica ingestion of soil by children have ranged as high as 5000 mg/day. The high end estimate of 600 mg/day is not characterized as pica. It was determined from studies evaluated in EPA (1997) which showed upper percentile estimates ranging from 106 mg/day to 1,432 mg/day with an average of 587 mg/day for soil and dust ingestion.

Soil ingestion exposure estimates also depend on the duration of the period over which children are assumed to ingest soil. Data on soil ingestion by age are not available, and the estimate that significant ingestion occurs between ages 2 and 6 is broadly supportable on behavioral grounds.

No measurement data are available on soil ingestion in infants (0-2 yrs. old) or in older children or adults, and no ingestion is assumed for these groups. While some soil ingestion will occur in these groups, e.g., through contact of soiled hands with food, it is plausible that such ingestion is of a lesser degree than occurs in early childhood. If Hawley's (1985) estimate that an adult ingests an average 60 mg/d of soil is used, after accounting for differences in exposure duration (9-20 yrs versus 5 yr) and body weight (70 kg versus 17 kg), the adult soil ingestion exposure is close to the estimated exposure for children (at 200 mg/d). The high end example scenarios in Chapter 5 assumed that the exposed family was involved in farming operations. One implication is that individuals on the farm would be working closely with the soil, which may result in some soil or dust ingestion (dust ingestion is distinct from the particulate inhalation exposure pathway). The other implication is that, should this be the case, they might be in contact with tilled or otherwise well mixed soil, whose concentration could be as much as 10 times less than the no-till soil for which children are assumed to be exposed.

Considering these uncertainties, the soil ingestion exposure estimates presented for children are plausible. Further consideration may be warranted for considering adult soil ingestion, particularly in farming situations. Uncertainties associated with the soil ingestion pathway are summarized in Table 8-2.

8.4.3. Soil Dermal Contact Pathway

Estimates of dermal exposure to soil rely largely on four factors unique to this pathway: exposed skin area, soil adherence (also termed soil contact), frequency of soil contact and fraction of contaminant absorbed. The uncertainty in these three terms are discussed below.

Before that discussion, a brief note is made on uncertainties associated with soil concentrations. Discussions above on the soil ingestion pathway addressed uncertainties associated with soil concentrations which result from migration of residues from a distant source to the site of exposure. Distant sources in this assessment include off-site soil contamination and

stack emissions. Discussions in the soil ingestion pathway section above pertain to this exposure pathway and are not repeated here. However, there is one key difference in the soil dermal and soil ingestion pathways. Soil ingestion exposures are assumed to occur only from surficial soil layers and from untilled soils, which translates to the 2-cm mixing depth for both the "central" (residential) and "high end" (farming properties) scenarios. Soil dermal contact, on the other hand, is assumed to occur in association with both tilled and untilled soils . "Indoor" soil is assumed to have concentrations equal to that of untilled soils, while "outdoor" dermal contact events are assumed to occur in association with gardening or farming activities, where the concentrations are the more dilute tilled concentrations.

The range of possible estimates of exposure via dermal contact is probably more a function of variability in the population than uncertainty in the dermal contact methodology and assignment of exposure parameters. Relatively accurate measurements have yielded a good data base on total skin area. Thus the uncertainty in this factor is derived more from the assumptions of how much of the total skin area is exposed. EPA (1992b) recommends approaching this issue by determining the coverage of normal apparel in the exposed population and assuming exposure is limited to the uncovered skin. As discussed in EPA (1992b), this assumption could lead to underestimates of exposure since studies have shown that some exposure can occur under clothing, especially in the case of vapors or fine particulates. Assignment of skin surface areas in this assessment have assumed estimates for various combination of areas for hands, arms, and legs. The extent to which individuals where short or long sleeve shirts and trousers is part of the variability in skin surface area assignment.

The potential for soil contact and subsequent adherence probably varies little across the population, but few actual measurements have been made. A wide range of from <0.002 to >20 mg/cm^2-event has been identified in EPA (1997). The very high adherence rates were found for the scenario described as, "kids-in-mud", and was from data on children playing by a lakeshore. The lower range was found for an indoor Tae Kwon Do setting. Adherences for a day-care setting ranged from 0.03 for arms and legs to 0.1 for hands. Outdoor adherences for gardeners ranged from 0.005 for legs to 0.02 for arms to 0.2 for hands. The uncertainty in these estimates reflect primarily the lack of measurement data rather than population variability. Site variability is probably important as well since soil properties such as moisture content, clay content and particle size distribution are likely to affect adherence.

Exposure frequency to soil reflects largely personal habits and thus the range in values for this parameter is primarily based on population variability. Seasonal and climate conditions can also affect this behavior introducing site variability as well. Indoor contact events were assumed

to occur daily, gardening events were assumed to occur 100 times per year and farming events 350 times per year. These values were assigned based on judgement, and not any particular studies.

The dermal absorption fraction of compounds varies widely across chemicals, whereas skin properties that affect absorption, i.e. thickness and composition vary little across the population. Thus the uncertainty in this factor is derived primarily from measurement error rather than population variability. Soil properties, such as organic carbon content, can also affect the extent of dermal absorption and thus create site variability as well. EPA (1992b) reports two studies which measured dermal absorption of 2,3,7,8-TCDD from soil. Testing included human skin in vitro, rat skin in vitro and rat skin in vivo. On the basis of these tests, a range of 0.1 - 3.0% was recommended in EPA (1992b). Dermal absorption testing, especially for soils, is a relatively new field and many uncertainty issues are involved. These include extrapolation of animal tests to humans, extrapolation of in vitro to in vivo conditions, and extrapolation of experimental conditions to expected exposure conditions. Extrapolation of the tests on 2,3,7,8-TCDD to the other dioxin like compounds (which have not been tested) introduces further uncertainties. A dermal absorption fraction of 3.0% was adopted here for application to all the dioxin like compounds. Based on the observed range of values for 2,3,7,8-TCDD this assumption may lead to overestimates of a factor of 30. Considering all possible uncertainties, under estimates are also possible, though judged less likely.

In summary, dermal exposure estimations rely on a number of parameters whose values are not well established. The range of possible dermal contact estimations is judged to be mainly a function of population variability, rather than parameter uncertainty. One parameter that is uncertain is the absorption fraction. The value selected for this assessment. 0.03 (3% absorption) is on the upper end of the range of suggested values, so its selection is likely to result in overestimating, rather than underestimating, the exposure due to this pathway. Although it is difficult to estimate the overall variability and uncertainty with this pathway, it is judged to be plus or minus one to two orders of magnitude. A summary of the uncertainties associated with the dermal absorption pathway is given in Table 8-3.

8.4.4 Water Ingestion

The strong sorptive tendencies of the dioxin-like compounds result in very low water concentrations. Monitoring for CDD/Fs mostly have not found these compounds at a detection limit around 1 pg/L (ppq), and when found, have generally been very near this concentration. The one exception is an upstate New York community water system, where tetra through octa-

CDFs were found at concentrations ranging from 2 pg/L (tetra) to over 200 pg/L (octa). The surface water concentrations predicted by the algorithms of this assessment for all source categories are 10^{-2} pg/L and lower, which is consistent with the sparse monitoring data. Although there was no data found that could be directly applicable to the source categories, it does not appear that the models estimating water concentrations will introduce significant uncertainty into water ingestion exposure estimates.

The classically assumed water ingestion rate of 2.0 L/day was examined in EPA (1997). The conclusion was that this estimate is more appropriately described as an upper percentile consumption rate for adults, and recommended 1.4 L/day for use as an average. This value was used for water ingestion in the central scenarios. EPA (1997) cautions that data on consumption rate for sensitive subpopulations such as manual laborers are unavailable. As such, the 1.4 L/day rate for individuals in farming families who work the field may be low. For this reason, a 2.0 L/day was assumed in the high end, farming, scenarios.

The contact fraction is defined as the fraction of total contact with an exposure media that is contact with contaminated media. For drinking water, this translates to the fraction of water ingestion that comes from the contaminated water source. In the example scenarios, it was assumed that the impacted water was a river which supplied water to the exposed individuals, perhaps through a public water system. The contact fraction of 0.70 for central scenarios is based on time use surveys which showed roughly this fraction of time spent in and around the home environment on the average (EPA, 1997). The upper limit is, by definition, 1.00; this was felt to be unrealistic even for high end scenarios. EPA (1997) recommends an upper end value for time at residence at 0.90, and this value was used for the high end scenarios.

The uncertainties associated with the water ingestion pathway are summarized in Table 8-4.

8.4.5. Fish Ingestion Exposure

Chapter 7, Sections 7.3.5 and 7.3.6 addressed the capabilities of the models of this assessment to estimate fish tissue concentrations, by comparing measured fish concentrations with modeled concentrations. In general, it was concluded that modeled fish tissue concentrations in background settings are consistent with those found in the literature for similar settings. Also, impacts of point source discharges into surface water appear to have been appropriately modeled.

Chapter 7, Section 7.3.2. looked at a comprehensive data set developed and supplied by the Connecticut Department of Environmental Protection which included soil concentrations,

sediment concentrations of water bodies near where soil samples were taken, and fish concentrations from the same water bodies. Data on 2,3,7,8-TCDD, 2,3,7,8-TCDF, 2,3,4,7,8-PCDF, and total TEQ were examined. Soil concentrations of 2,3,7,8-TCDD were found to be in the low ppt range, which has been described in various places in this document as a range for "background" soil conditions. Sediment concentrations of the three congeners and total TEQ were generally in range of 2-3 times higher than soil concentrations, which was consistent with the demonstration of background conditions. This demonstration scenario had a basin-wide 2,3,7,8-TCDD soil concentration of 0.37 ppt, and the sediment concentration was estimated at 0.99 ppt. The Biota Sediment Accumulation Factor, BSAF, from this field data was estimated to be 0.86 for 2,3,7,8-TCDD. This was higher than the assumed 0.09 in the demonstration scenarios. Two explanations were offered for this difference. One was that the fish sampled were bottom feeders, which would put them in more contact with contaminated sediments compared to column feeders, and the 0.09 value was based on data from column feeders; higher impact from contaminated sediments is expected from bottom feeders as compared to column feeders. Two, the 0.86 may have been skewed from two (of seven) sites in the Connecticut data which had high BSAFs at greater than 1 and 3. Although the soil sampling in this data set was generally sparse, the result that bottom sediment concentrations exceeded surface soil concentrations by 1.6-3.9 times generally supports the model's algorithms for estimating sediment concentrations in areas with low basin-wide concentrations.

Chapter 7, Section 7.3.5 looked at fish concentrations in background areas and where point source impacts to water bodies were identified. A principal source of information was EPA's National Study of Chemical Residues in Fish (EPA, 1992a; abbreviated NSCRF). The range of fish tissue concentrations of 2,3,7,8-TCDD measured for (perhaps) background conditions in this study, 0.56 - 1.02 ppt, were comparable to the fish tissue concentration estimated assuming the low (perhaps) background soil concentration of 0.37 ppt soil concentration, 0.2 ppt. It may not be appropriate, however, to make the same observation for the source categories assuming higher soil concentrations as compared to measured concentrations. In this case, the range of measured concentrations, 1.4 - 30.02 ppt, does not compare with the modeled 0.3 ppt. It was noted that the soil contamination source category was demonstrated with a setting that had four hectares of contaminated soil at 1 ppb surrounded by a watershed of 100,000 hectares with a 0.0 soil concentration, which may explain partly why the results did not compare with the concentrations in the NSCRF that were taken near contaminated sites. Specific field data were not available for more detailed analysis. In general, it would appear that the magnitude of concentrations appears to have been captured for background situations.

While the modeled PCDD/PCDF fish concentrations seem reasonably in line with measured concentrations, this assessment may have underestimated concentrations of 2,3,3',4,4',5,5'-HPCB in the demonstration scenarios. Concentrations for fish in the Great Lakes Region were in the tens to hundreds of ppb range, while this assessment derived estimates all under 1 ppb. However, an examination of bottom sediment concentrations of PCBs in the literature showed them to be roughly three orders of magnitude higher than estimated with the algorithms of this assessment. This mirrors the difference in observed versus estimated fish tissue concentrations. The Biota Sediment Accumulation Factors, BSAFs, for PCBs also was noted to be variable, with values below 1.0 to values over 20.0 (see Chapter 4, Section 4.3.4.1). The BSAF for the example PCB congener in this assessment was 2.0. Higher BSAFs would also increase PCB concentrations estimated for fish.

Chapter 7, Section 7.3.6 evaluated the model for estimating fish tissue concentrations for the effluent discharge source category, using data from the 104-mill study. Comparing model predictions of fish tissue concentrations with observed concentrations, it was found that there was generally an underprediction of observed fish tissue concentrations, although the average predicted concentration 7 ppt cannot be considered significantly different then the observed average concentration of 15 ppt. An important qualifier is that this exercise assumed that the effluent discharges were the sole source of contaminants which may have impacted the water bodies. Also, the maximum "observed" fish tissue concentration of 143 ppt was matched by a predicted concentration of 89 ppt, which was also the maximum predicted concentration. Finally, there was discussion that the BSSAF (biota suspended sediment accumulation factor) assigned value of 0.09 for 2,3,7,8-TCDD, the same value used for the BSAF, might be low for the effluent discharge source category. The justification for this hypothesis concerns the differences between past and ongoing water body impacts, and the fact that the 0.09 value was based on field data for a water body where impacts are speculated as principally occurring in the past (see Section 7.2.3.6 for a further discussion of this issue). When the BSSAF was "calibrated" to 0.20, the average predicted fish concentration of 15 ppt for 2,3,7,8-TCDD now matched the observed average fish tissue concentration.

The model did not perform as well for pulp and paper mills discharging into the largest receiving water bodies. The average fish tissue concentration observed for 21 fish was about 7 times higher than predicted concentration. No precise conclusion can be reached with this result, although modeling lower fish concentrations in a large receiving water body than are measured does not appear unexpected. Large water bodies are likely to be ones having multiple sources of dioxin release in comparison with small water bodies. Therefore, the assumption that one or

more proximate mills are solely responsible for observed fish concentrations is most likely to be flawed for large water bodies.

In summary, the evaluations for model performance regarding fish tissue concentration estimation seem to lend credibility to the approaches taken, despite the simplicity of the of dilution models chosen. The sensitivity analyses exercises on the algorithms to estimate fish tissue concentration discussed the variability and uncertainty with the parameters required for the algorithms. Generally, the most sensitive input was the source strength characteristics - soil concentrations, contaminant discharge rates in effluents, and so on. A single order of magnitude or less range in predicted concentrations would result with singular changes in all other model parameters.

An exposure parameter of paramount importance in estimating exposure to contaminated fish is the fish ingestion rate. Available fish consumption surveys are discussed in EPA (1997). They were divided into five subsets of surveys, one of which was titled, "freshwater recreational anglers". Three surveys in this subset were deemed appropriate for generation of consumption rates, and EPA (1997) recommended a mean and a 95^{th} percentile consumption rates of recreationally caught fish of 8 and 25 g/day, respectively. Another possible approach is described in EPA (1989) and was used in a previous version of this dioxin reassessment document (EPA, 1994). Briefly, this approach assumes a meal size and then determines, on a site-specific basis, the number of meals an individual would consume from fish obtained from the impacted water body. EPA (1994) assumed meal sizes of 150 g/meal, and 3 and 10 meals/year for the central and high end assumptions, respectively, which led to daily consumption rates of 1.2 and 4.1 g/day. Assessors should also be cognizant of situations where subsistence fishing can lead to much higher rates of fish consumption. EPA (1997) summarizes studies where subsistence patterns of fish consumption can lead to consumption rates in the hundreds of grams per day. Like other food consumption pathways, which have the highest exposure estimates for dioxin-like compounds, obtaining site-specific information for fish ingestion is critical for this pathway.

A summary of the uncertainties associated with the fish ingestion pathway is given in Table 8-5.

8.4.6. Vapor and Particle Phase Inhalation Exposures

This section will address the uncertainty associated with vapor and particulate phase inhalation exposures. Sources addressed in this assessment include stack emissions and contaminated soils; this section will only address contaminated soils. The fate and transport of

dioxin-like compounds from stack emissions to exposure sites, and the resulting air concentrations, are discussed in Chapter 3.

The respiration rates of 13 and 20 m^3/day used for inhalation exposures is based on data described in EPA (1997). The contact fraction is 0.70 for central scenarios and 0.90 for high end scenarios. Like the water ingestion contact fractions, these were based on time at home surveys. The inhalation rate and contact fractions are not expected to introduce much uncertainty into inhalation exposure estimates.

Another exposure parameter critical for the inhalation pathway is exposure durations, which is 9 years for central and 30 years for high end exposures. The uncertainties associated with this parameter in its use as an exposure parameter are discussed above in Section 8.4.1. However, exposure duration is additionally critical for the inhalation pathway for the soil contamination source category, as estimated volatilization flux is a function of the time during which volatilization is occurring. Essentially, the model assumes that contamination is at the soil surface at time zero, and over time, residues which volatilize originate from deeper in the profile leading to lower volatilization fluxes after time, and also lower average volatilization flux as the averaging time increases. The sensitivity analyses exercises in Chapter 6, Section 6.3.3.1., evaluated the sensitivity of air concentration predictions to changes in exposure duration. It was shown that there is roughly a factor of four difference between concentrations predicted over one year duration to a seventy year duration. Therefore, there is both a direct and an indirect impact from changing the exposure duration in these procedures. The direct impact from changing exposure duration is in the exposure equation - increasing the exposure duration increases the exposure estimate. What is seen also with increases in exposure, however, is a decrease in the estimated average air concentrations to which individuals are exposed. The impact in the exposure estimates is more driven by having more years of exposure rather than being exposed to a lower average air concentration, as expected.

Vapor-phase emissions from soils are estimated with a volatilization flux algorithm. The procedures were developed in Hwang, et al. (1986). A near-field dispersion model estimates air concentrations for the circumstance where the soil contamination is at the site of exposure. Where the site of contamination is located distant from the site of exposure, the same volatilization flux model is used, but exposure site concentrations for these sources are estimated using a far-field dispersion model.

Sensitivity analyses in Chapter 6 showed that the air concentration varied roughly over an order of magnitude with testing of key contaminant parameters, the organic carbon partition coefficient, Koc, and the Henry's Constant, H. Air concentration predictions are also sensitive to

other key parameters, including those associated with source strength (area of contamination, concentration), geometry, (distance to receptor in off-site source category), and climate (average windspeed). However, these might be expected to be known with a reasonable degree of certainty for a site-specific application. If they are, it can be concluded that the most uncertainty associated with the vapor phase algorithm is in the contaminant parameters, and it would appear that a range of about an order of magnitude difference in predicted air concentrations might be expected with different pairs of these parameters.

A model validation exercise described in Chapter 7, Section 7.3.8 tested the algorithms modeling air concentrations above a soil of known concentrations. Using measured soil concentrations at a site near Columbus, Ohio, and measured air concentrations at this same site, it was shown that the model predictions of air concentrations were orders of magnitude lower than measured air concentrations. While this suggests that the model is underpredicting the release of dioxins from soil into the air and/or underpredicting the dispersion of released residues, it may be true, on the other hand, that the measured air concentrations in the rural setting near Columbus are the result of long range transport of air-borne dioxins from distant sources of release.

Another piece of evidence came in an examination of above ground plant:soil ratios as generated by the models and found in experimental testing. The models underestimated these ratios by 1 to 2 orders of magnitude as compared to the literature when vegetation in the field studies described in the literature were grown in soils with concentrations in the ppt range, a range typical of background settings. Two explanations were offered for this trend: the experiments were impacted by sources of dioxins other than the soil in which the plant was growing, and/or, the soil-to-air models may be underestimating air concentrations. Like the model validation exercise described above, it is unclear which explanation dominates the observed trend.

An alternate model for volatilization flux and an alternate model for air dispersion were evaluated in Chapter 7, Section 7.2.4. It was found that the alternate volatilization model predicted about a third as much volatilization as the Hwang model, but that the alternate dispersion model predicted air concentrations that may be up to an order of magnitude higher than the models predicted in this assessment.

There was no data on concentrations of air-borne contaminants in the particle phase only. The procedures used to estimate the suspension of particles were developed from information on highly erodible soils. As such, fluxes and hence concentrations may be higher than expected. However, with no data to compare, this cannot be ascertained. It was seen that vapor phase concentrations exceeded particle phase concentrations by over an order of magnitude. The

sensitivity analysis exercises in Chapter 6 did indicate a two order of magnitude range in estimated concentrations depending on the assumptions concerning wind erodibility of the soil. Also, several issues of uncertainty concerning the suspension of contaminated particles and relationship between air-borne vapor and particle phases were examined. It was noted that the total reservoir of suspended contaminated particulates was likely to be underestimated because the algorithm for wind erosion was developed only for inhalable size, < 10 μm, particles, which is appropriate for inhalation exposures but would lead to an underestimate of the depositions onto vegetation, including fruits/vegetables for consumption and grass/feed for the beef/milk bioconcentration algorithm. Vegetation concentrations might also be low because the impact of rainsplash on transferring soil to the lower parts of vegetation was not considered.

A critical assumption made was that volatilized residues remained in the vapor phase and did not sorb to airborne particles. This led to a dominance of vapor phase contaminants - 90% and more of the total airborne reservoirs (vapor + particle phases) estimated for the on-site and off-site soil source categories were in the vapor phase. Even though only three contaminants were modeled for the soil source category, this trend would be repeated for essentially all the dioxins (except not as much for the octa dioxins since the models would predict much less vapor phase release than the other dioxins). Having much more vapor phase dioxins than particle phase dioxins is inconsistent with the vapor/particle partitioning models used to partition ambient air dioxins into vapor and particle phases, and also inconsistent with monitored vapor/particle partitioning. For example, the vapor/particle partitioning model resulted in a prediction that 51% of the total airborne 2,3,7,8-TCDD would exist in the vapor phase, not over 90%. For the other dioxins, the particle phase is predicted to dominate the air concentrations. This suggests that the soil models of this assessment are deficient in that they do not repartition soil emitted dioxins. Specifically, a portion of the vapor-emitted dioxins are unlikely to remain as vapor, but are likely to sorb to particles. Transferring portions of the vapor phase contaminants to the particulate reservoir to get balances suggested by the vapor/particle partitioning models of this assessment would not change total inhalation exposures, but would impact concentrations in above ground vegetation. Currently and even with transfers such as these, vapor phase transfers dominate plant concentrations. Because vapor phase reservoirs would be reduced after transferring a portion to the particle phase, such transfers translate to reductions in plant concentrations, and for grass and feed, subsequent reductions in beef and milk concentrations and exposure estimates.

Perhaps the most critical assumption which could be questioned is that airborne vapor and particle phase contaminants at the site of exposure originate only from the site of contamination when the site of contamination is distant from the site of exposure. Meanwhile,

soils at the exposure site are impacted - concentrations in the air at the exposure site do not consider possible fluxes from exposure site soils, or from soils between the contaminated and exposure sites.

A test was conducted for this assumption using the demonstration scenario for the soil contamination source category, which had a 4-ha site at 1 ppb 2,3,7,8-TCDD 150 meters from an exposure site of the same size. The soil concentrations at the exposure site were 0.36 ppb for a 2-cm notill mixing depth and 0.06 ppb for a 20-cm tilled mixing depth. These concentrations were then input as soil concentrations for the soil contamination source algorithms to determine what air concentrations would result above the soil. For this test, the "near field" dispersion algorithms described in Chapter 4 were used instead of the "far field" algorithms used in the demonstration of that source category in Chapter 5. These near field exposure site air concentrations, generated with a starting soil concentration of 0.36 ppb, were compared with exposure site air concentrations generated when using the far field dispersion algorithms, starting with the soil concentration of 1 ppb. It was found that on-site air concentrations with soil concentrations at 0.36 ppb exceeded exposure site vapor and particle air concentrations estimated for a 1 ppb contaminated site 150 meters away by a factor of about 5. When the same test was run using a tilled concentration of 0.06 ppb, concentrations predicted using the near field algorithms and this concentration were similar to the concentrations predicted using far field algorithms and a starting concentration of 1 ppb.

Several uncertainties were discussed, but a lack of data and a complete understanding of atmospheric processes for dioxin-like compounds precludes any final quantitative judgements on uncertainties in the air concentration algorithms. Some of the uncertainties imply that procedures and assumptions adopted overestimate pertinent environmental media, and others imply that such media concentrations were underestimated. The assumption that air-borne reservoirs of contaminant originate only at an off-site area of contamination and not from other soils should be examined further.

A summary of the uncertainties associated with the vapor and particle inhalation routes is given in Table 8-6.

8.4.7. Fruit and Vegetable Ingestion

Consumption rates of 1.49, 1.52, and 1.16 g/kg/day were derived in EPA (1997) from the household portion of the National Food Consumption Survey (NFCS; USDA, 1992). Contact fractions of 0.101 for fruits and 0.173 for vegetables were also obtained from an analysis of NFCS data. Briefly, the household portion of the NFCS was a survey filled out by the head of a

household and includes the amount of food product brought into the house for consumption. The data includes the number, age, and weight of all household members, in addition to critical questions concerning home production of foods. Further details on this survey and the use of the data is described in Chapter 2.

Use of this portion of the NFCS has its benefits and drawbacks. One major benefit is that it reduces uncertainty by the calculation of rates which include body weights. The earlier version of the dioxin reassessment document (EPA, 1994) had the consumption of all food items in terms of g/day. In this assessment, fish ingestion is still handled this way, but all other foods considered (vegetables/fruits, terrestrial animal food products) more appropriately consider the interaction between rate of consumption and body weight. Another major benefit is that it allows one to estimate how much of a food product is consumed in a household which was produced by the household, which is precisely what is desired for the demonstration scenarios of this assessment. This estimation includes a reported consumption rate and also a contact fraction ascertained from survey data. Another part of the NFCS was called the "1-day individual consumption survey". One cannot ascertain consumption rates for home-produced foods from the 1-day survey. However, the individual survey does ascertain the consumption rate for foods "as eaten" by the individual. In contrast, the household survey asked for total food product brought into the house for consumption that week. That necessitates assumptions on the meal size per individual in the household, and in addition to data on the weight of the household individuals, EPA (1997) derived estimates of g/kg/day consumption rates, which were used in this assessment. That also necessitates a consideration of the amount of the total food product brought into the house which is not eaten by individuals in the house, since the "total food product" is not a quantity analogous to, "as eaten". Reductions in this total would include losses such as from cooking, discarding part of the food product, such as bones or uneaten portions, or portions given to guests. This is one disadvantage to the household survey, in contrast to the "as eaten" data from the 1-day consumption survey. In Chapter 2, reduction factors are described and used in this assessment to describe cooking (weight reduction) and post cooking (bones, etc) for beef and chicken, as well as other meats not considered in this assessment.

EPA (1997) also ascertained, from questions on specific fruits/vegetables from the household survey, consumption rates for "exposed above ground vegetables/fruits" and "root vegetables". Protected vegetables/fruits, as opposed to exposed, were defined as vegetables/fruits which have outer protective coverings which are removed prior to consumption such as peas or oranges. No root vegetables were considered to be protected although, of course, it is common to consume some below ground vegetables such as carrots or potatoes after removal

of the skin. Consumption rates for exposed fruits and vegetables are desired because the evidence is fairly clear that dioxin-like compounds will not penetrate through thick skins which are peeled prior to consumption. This assessment does consider, however, the peeling of skins off exposed vegetables. This consideration is in the form of a "VG" parameter. The VG parameter, which includes separate assignments for above ground vegetables/fruits, VG_{ag}, and for below ground vegetables, VG_{bg}, considers the following: evidence that little translocation from the surface of bulky vegetation, below or above ground, to the inner portions of these vegetation, and any additional consideration of the peeling of the skin (carrots, potatoes, e.g) prior to consumption. In this assessment, values of 0.01 and 0.25 were assigned to VG_{ag} and VG_{bg}, respectively.

All these assumptions discussed: total consumption rates, protected or unprotected, above or below ground, and fraction home grown, are probably reasonable for general assessment purposes as long as exposures are to the broad categories of fruits or vegetables, and not for individual fruits or vegetables. For a site specific assessment, there will likely be wide variability on the types of produce grown at home, what percentage of that is unprotected, and so on. Finally, and as is also true for beef and milk exposures, this assessment only considers the impact of home-grown fruits and vegetables. In rural settings, it is plausible that a large percentage of an individual's total fruit and vegetable intake comes from nearby and impacted sources, more than the 10-20% assumed in this assessment. If all of the consumption of fruit and vegetables is from local sources, and adjustments are made to correctly predict concentrations in local fruits and vegetables, than contact fractions should be set at 1.0, and exposures could increase up to 10 times compared to the demonstration scenarios depending on concentration estimation.

Several issues of uncertainty pertinent to the estimation of concentrations in below and above ground vegetation have been examined in other parts of this document and are not repeated here. Key issues include: 1) the uncertainty associated with empirical parameters, VG_{ag} and VG_{bg}, 2) the assumption that residues which volatilize from contaminated soils remain in the vapor phase and not partially partition into the vapor phase, 3) the possible underestimation of total particle reservoirs of contaminant in the air resulting from wind erosion of contaminated soils because the wind erosion algorithm only estimated suspension of inhalable size and not all particulates, and also because the possible effect of rainsplash onto vegetables low to the ground such as lettuce, was not considered, 4) for the stack emission source, uncertainties associated with air dispersion and deposition modeling using the ISCST3 model as discussed earlier in Section 8.2, and therefore the subsequent impacts of air-to-plant and soil-to-plant transfers, 5) for the stack emission and off-site soil source categories, air borne concentrations in the vapor and

particle phases at the exposure site are assumed to only originate at the source of contamination (the off-site contaminated soil and stack emissions) and not on impacted soil at the exposure site - considering additional fluxes from impacted soils other than exposure site soils could lead to up to an order of magnitude higher concentrations in the vapor and particle phases, which in turn affect above ground vegetation, and 6) also for the stack emission and off-site soil source categories where garden soil concentrations are predicted and then used to predict concentrations in underground vegetables, there are uncertainties for the soil concentration algorithm, particularly in the assignment of half-life, mixing depths, and lack of consideration of detritus production and vapor impacts to soils.

Quantitative judgements as the uncertainties associated with these issues are difficult to make. An examination of experimental data in Chapter 7, Section 7.3.10, where most of the vegetation were grown in well characterized conditions implied that the soil contamination models may be underestimating concentrations in above ground vegetables. The evidence examined was plant:soil ratios for experimental conditions versus what the models would predict. This could be due to underestimation of air concentrations of dioxins originating from soils, and there was some suggestion of that. However, it could also be due to the fact that the residues affecting the plants in the experiments were not only from soil releases but from other sources leading to air-borne residues. The models of this assessment only consider air concentrations from the source in question. Therefore, it is hard to ascertain whether the models underpredict, overpredict, or adequately predict above ground vegetation concentrations resulting from soil contamination.

Chapter 7, Section 7.2.1 did look at three modeling approaches for the air-to-plant pathway for leafy vegetation (grass, in particular), including the EPA model. That did section did suggest that the EPA model led to reasonable matches between predictions and observations, with just about a factor of two separating predictions and observations. Also, the air-to-beef model exercise described in Chapter 7, Section 7.3.12 also included an examination of the capability of the air-to-plant model. Although there wasn't a good data set for validation - i.e., measured air concentrations above measured grass concentrations, the examination in that section did support the model's algorithms. In the same vein, it is noted that the vapor phase air-to-leaf transfer algorithm was developed from actual field data. By definition, therefore, it would appear that the air-to-plant modeling are going to predict reasonable plant concentrations. This discussion is put forth only to suggest that the air-to-plant modeling would not be an issue for uncertainty regarding the impact of contaminated soils on above ground plants.

A summary of uncertainties associated with the fruit and vegetable ingestion exposure pathway is provided in Table 8-7.

8.4.8. Ingestion of Terrestrial Animal Food Products Including Beef, Milk, Chicken, and Eggs

The algorithms for the calculation of dioxin concentrations in all these animal food products is the same: they are a function of the weighted average concentration in the diet of the cattle (dairy or beef) and chicken, which is a function of the proportion of the diet in soil and animal vegetation, and a bioconcentration factor. Therefore, previous sections on soil contamination, soil transport algorithms, and plant concentration estimation, are relevant to estimating terrestrial animal food concentrations.

The most critical and uncertain parameters in these algorithms are the bioconcentration factors. The multiplication of the weighted average dietary concentrations of the chicken and cattle by the bioconcentration factors yields a product fat concentration (beef fat, chicken meat fat, milk fat, and egg fat). A set of bioconcentration factors were developed from laboratory feeding experiments for chicken meat, specifically from data on chicken thighs, and a separate set from eggs. There is uncertainty in applying these laboratory derived BCFs to field situations. Data is being developed by these same researchers from chickens which are raised in the field. One purpose of these additional experiments is to verify the laboratory derived BCFs (M. Petreas, Department of Toxic Substances Control, California EPA, personal communication). The bioconcentration factors used for calculation of beef and milk fat were less certain. They were derived from one experiment on one cow and on milk. Besides the sparsity of data, there is obviously uncertainty in applying bioconcentration factors developed from milk fat to beef fat. However, researchers have noted that the dioxin concentrations in beef and milk fat tend to be similar, and this they attribute to the fact that most cattle are slaughtered within 2 years of life while they are still growing. Therefore, the body fat pool is expanding which provides dilution to dioxins taken in by the beef cattle, and as a result, body fat concentrations are found to be similar to milk fat concentrations.

What also strengthens the use of the milk fat BCF to beef fat is the air-to-beef model validation exercise described in Chapter 7, Section 7.3.12. That section described a validation exercise where air concentrations of dioxin-like compounds were routed through the food chain model to estimate concentrations in beef. Generally, that section showed that an air concentration of 0.019 pg I-TEQ/m^3, speculated to be an appropriate air concentration for rural environments where cattle are raised for beef, translates to a beef fat I-TEQ concentration of 0.61

ppt, using the models and parameters of this assessment. The observed beef fat concentration of 0.89 ppt I-TEQ (assuming non-detects were equal to ½ detection limit) was the average from a national, statistically design, monitoring study of dioxins in beef back fat conducted jointly by EPA and USDA. Besides a very reasonable match between observed and predicted I-TEQ beef fat concentration, Section 7.3.12 also describes a reasonable match in the concentrations of the individual congeners.

Other than the critical bioconcentration factors, there is uncertainty with the soil bioavailability factor, B_s, and the parameters describing the chicken and cattle diet which include dietary fractions in soil, grass, and feed (the sum of the three adding to 1.00). The B_s was assigned a value of 0.65 for the beef and chicken algorithms, and reflects an assumption that dioxins are less bioavailable to the animals when the vehicles are soil rather than vegetative feeds. This is a critical assumption for chickens, particularly, since the algorithm for free range chicken impact assumes 10% of the diet in soil, and no exposure through their other diet. This was based on analysis of the chicken feed showing non-detects for dioxins at low detection limits done by the researchers who developed the BCFs, who also developed the rationale for the 10% soil assumption (Stephens, et al., 1995b). The beef cattle diet differs from the dairy cattle diet in that the beef cattle diet is dominated by leafy vegetation (i.e., pasture grass) and partially protected vegetation (a combination category which would include barn feeds such as hay or silage), with 8% in soil. The dairy cattle diet is assumed to be dominated by grains, which are assumed to be protected and residue-free. Only 10% of the dairy cattle diet is assumed to originate from soil (4%) and leafy vegetation (6%).

Section 6.2.3., Chapter 6, described the results of sensitivity analysis of these parameters applied to the beef and milk algorithms. It was shown that there is a small range of possible values for B_s and a small impact on results, for beef and milk at least. The impact, as noted above, would be greater for chickens. Data indicates that range of values for BCF for 2,3,7,8-TCDD is 1 to 10, with a concurrent order of magnitude difference between the upper and lower values. The parameters describing cattle exposure to soils and vegetation at the site are also critical, with up to an order of magnitude difference in concentrations for the example exposure situations examined in Section 6.2.3. It is expected that cattle exposure assumptions can be reasonably described for a specific site. Therefore, the most uncertainty in the bioconcentration algorithm itself lies with the bioconcentration factor, BCF.

Besides the air-to-beef model validation exercise, there was one other literature comparison that was made was comparing beef fat:soil and milk fat:soil concentration ratios derived for PBBs with those estimated for 2,3,7,8-TCDD in the soil contamination demonstration

scenario. Such a comparison is thought to be valid since PBBs are similar in fate and bioconcentration tendencies to the dioxin-like compounds. The field data was from an experiment where the cattle were raised in soils very high in PBB concentration. This provided some evaluation of the beef bioconcentration algorithm as applied to soil contamination. In this comparison, differences in beef and milk bioconcentration tendencies appear to be captured. Fries (1985) found body fat:soil PPB and milk fat:soil PBB concentration ratios for dairy heifers to range from 0.10 to 0.37, and from 0.02 and 0.06, respectively. For body fat of beef cows, these ratios were 0.27 and 0.39. Analogous ratios were derived for the contaminated soil scenario, and for beef and milk fat. For the contaminated soil demonstration scenario, Scenarios 3, beef fat:soil and milk fat:soil ratios were 0.15 and 0.08, respectively. These appear a bit lower than the PBB ratios derived by Fries (1985). The interpretation of this result was that, again here was some evidence that models may be underestimating the impacts of soil contamination to air, and hence air to plants and plants to animals.

Chapter 7, Section 7.2.6 evaluated other beef and milk bioconcentration models; none were found for chickens. It was found that most efforts are quite similar to the model of this assessment, with simple mathematical transformations. Other efforts had considered cattle inhalation exposures and cattle ingestion of impacted water, and found them to be of minimal importance in estimating beef and milk concentrations. They were not considered in this assessment. Two efforts, that of Stevens and Gerbec (1988) and Fries and Paustenbach (1990), evaluated the practice of placing beef cattle on a grain-only diet for fattening prior to slaughter. Both assumed that the reduction in beef concentrations could be modeled as a first-order process with a half-life of around 115 days. With grain only diet periods of 120-130 days, they showed beef concentrations to be reduced by about 50%. The models of this assessment allow for the incorporation of an empirical reduction factor to account for a fattening program prior to slaughter. In the demonstration scenarios, it was assumed that the beef cattle slaughtered by the farmer for his home use were not fattened, and a value of 1.00 was assumed. For the air-to-beef model validation exercise, however, a value of 0.50 was applied, as suggested by these two research efforts.

The air-to-soil algorithms of the stack emission source category, and the soil-to-air algorithms of the soil contamination source categories have both been highlighted as algorithms which may have uncertainties. These uncertainties are detailed in Section 8.4.7. Generally, it was found that the air-to-soil algorithms may be slightly underestimating soil concentrations, while the soil-to-air algorithms may be underestimating air concentrations by an order of magnitude (although this speculation may not even be warranted, given that appropriate

experiments were not available to test the soil-to-air models). As a result, an examination of model trends show a key dichotomy in the way the stack emission source category performed as compared to the soil contamination source categories. Specifically, soil alone accounted for about 90% of the milk and beef impacts for the soil source category, whereas soil accounted for only about 5% of the milk and beef impacts for the stack emission source category. Refinements to the model algorithms or the model parameters which would increase air concentrations resulting from soils, and increase soil concentrations resulting from depositions would narrow this gap.

Data on rates of consumption of these food products, as well as the contact fractions used in the demonstration scenarios, were from the household component of the National Food Consumption Survey conducted by the USDA (USDA, 1992). A review of the uncertainties inherent in the use of this data is included in Section 8.4.7 above on fruit and vegetable ingestion, and will not be repeated here. One additional factor considered for meats of the terrestrial food pathways is the pre- and post-cooking losses, including factors such as weight loss by cooking, weight of bones, and so on. Based on data on such losses, consumption are reduced by about one-half based on these considerations.

A summary of uncertainties associated with the terrestrial animal food pathways is given in Table 8-8.

8.5. USE OF PROBABILISTIC TECHNIQUES FOR ASSESSING EXPOSURE TO DIOXIN-LIKE COMPOUNDS

The purpose of this discussion is to 1) briefly discuss how probabilistic techniques, such as Monte Carlo or Latin Hypercube simulations, work and could be applied in exposure assessments and 2) summarize recent efforts by five investigators to apply probabilistic procedures to assessments involving dioxin-like compounds.

Basically, Monte Carlo and Latin Hypercube assessments are generic statistical methods which generate a distribution for an output of a mathematical model using the distributions of the input variables. Computer simulations are used to repeatedly generate outputs based on parameter inputs, where values for parameters are selected from their distributions. The outputs are compiled and expressed as a frequency distribution. In the context of exposure assessment, for example, a Monte Carlo application could involve developing distributions for each of the parameters in the exposure equation and generating a distribution showing how the exposure levels vary in the exposed population. The final distribution can be interpreted as the probabilities of one individual (randomly selected from the exposed population) experiencing

various exposures. Since exposure levels are not only a function of the exposure parameters but also of the concentration in exposure media, another application of the Monte Carlo method would be to estimate the distribution of exposure media concentrations using mathematical models for fate and transport.

Probabilistic techniques can be a powerful tool for expressing variability and evaluating scenarios in exposure assessments. However, their use requires detailed input data which are frequently unavailable. Although the procedure may make an analysis look more elegant, it may actually yield misleading results if based on poor data. Accordingly, exposure assessors should be very cautious when trying to apply Monte Carlo techniques or interpreting the results.

Generally, Monte Carlo procedures should be applied only when credible distribution data are available for most of the key variables. Distribution data refers to empirical information on the statistical variation of the variable that is relevant to the site assessed. Usually this data should be obtained from surveys conducted at the site of interest. However, data on human behavioral characteristics could be obtained from survey information based on populations distant from the site, if comparability can be established.

Paustenbach et. al. (1992b) used Monte Carlo procedures to develop soil cleanup levels for 2,3,7,8-TCDD at residential and industrial sites. The following exposure pathways were included: dermal contact, soil ingestion, dust inhalation and fish ingestion. For each parameter a range of values was identified (on the basis of reported values in the literature) and a uniform distribution assumed. These assumptions are summarized in Table 8-9. For the residential scenario, the soil level corresponding to the 50th percentile (defined as 50% of the population being exposed below a risk of 10^{-5}) was 17 ppb and the 95th percentile was 7 ppb. For the industrial scenario (outdoors), the soil level corresponding to the 50th percentile was 160 ppb and the 95th percentile was 50 ppb.

Anderson et. al. (1992) used Monte Carlo procedures to describe the distribution of exposures to 2,3,7,8-TCDD occurring in various U.S. population segments as a result of ingesting fish caught near pulp and paper mills. The populations considered were all U.S. residents, all sport fishermen, U.S. residents living near (within 50 km) mills, and sport fishermen living near mills. The distributions for the various parameters were derived by either fitting idealized curves to empirical data or using personal judgement. These distributions are summarized in Table 8-10. The distribution of 2,3,7,8-TCDD concentrations in fish was derived from data collected in EPA's National Study of Chemical as exposure parameters. Distributions were developed for input factors and Monte Carlo Residues in Fish (EPA, 1992a). The following 50th and 95th percentile risks were estimated (using EPA cancer potency values):

all US residents - 1×10^{-9} & 3×10^{-7}
near mill residents - 4×10^{-8} & 2×10^{-6}
all sportfishermen - 2×10^{-8} & 3×10^{-6}
near mill sportfishermen - 6×10^{-7} & 2×10^{-5}

McKone and Ryan (1989) developed an exposure assessment procedure based on simple steady state transfer factors called PEFs or pathway exposure factors. These factors were applied to two paths: air/plant/food and soil/plant/food. This is an example of Monte Carlo techniques being applied to estimate exposure media concentrations as well as describe the variability in the distribution of exposure behaviors such as ingestion rates. The procedure was demonstrated using 2,3,7,8-TCDD and four pathways: ingestion of fruit/vegetables, grains, meat and dairy products. The distributions used for the various input parameters are summarized in Table 8-11.

Two recent assessments (Cullen, 1995; Keenen, et al., 1995) looked at the modeling of the impacts of dioxin-like compounds on indirect pathways from combustor emissions. Cullen (1995) looked the exposure to 2,3,7,8-TCDD through consumption of produce grown near a municipal solid waste incinerator. She included several parameters used to model the concentration of 2,3,7,8-TCDD in vegetables, and through a decomposition analysis, attempted to evaluate which parameters are most uncertain with regard to the modeling of vegetation concentration. Table 8-12 looks at the various parameters which Cullen (1995) evaluated to model vegetation concentrations.

Keenen, et al. (1995) evaluated another indirect pathway for 2,3,7,8-TCDD, also from an incinerator. The pathway they evaluated was the beef ingestion pathway, and the modeled incinerator type was a hazardous waste incinerator. They conducted a two-dimensional Monte Carlo exercise which separately characterized uncertainty and variation using a nested loop approach. They characterized the modeling of beef concentrations, including the modeling of the transfer of 2,3,7,8-TCDD from air to plant to animal, as uncertain, and characterized various exposure related quantities as variable. The “variable” considerations included locations of farms in relation to the incinerator (which was important because the air dispersion model predicted different concentrations and depositions of dioxins at sites of exposure), the individuals’ body weights, their beef consumption rates, and their exposure durations. In the nested approach, a beef concentration was estimated using the food chain model and parameter selections from probability density functions of the uncertain parameters. Then, a second nested procedure modeled a distribution of dose rates associated with the uncertainty calculation of the beef concentration. They results of their analysis suggest that exposures to 2,3,7,8-TCDD via

consumption of beef produced near a hazardous waste incinerator could have a total uncertainty spanning three orders of magnitude, and that the uncertainty was dominated by interindividual variability.

The five articles discussed above differ widely in how they have applied Monte Carlo methods, particularly in the selection of input parameter distributions. In some cases, it appears that uniform distributions were assumed due to the lack of data needed to support more complex distributions. The central values in these ranges probably occur more often than those near the ends, so the uniform distribution assumption probably underestimates the occurrence of central values and overestimates the occurrence of values near the ends of the distribution. Clearly more data are needed to better support input parameter distributions.

Also, the benefit of conducting Monte Carlo or other numerical methods to evaluate the uncertainty of model predictions of exposure media concentrations that result from a source of contamination is unclear. If attempting such an exercise, assessors must be aware of the following: 1) the relationship between contaminant fate parameters which are included in the same modeling exercise - high log Kow is associated with lower bioconcentration, lower volatility, etc.; and 2) the certainty in the range of parameters reported upon which a distribution is to be based - old literature, different and/or inappropriate experimental conditions, and so on. The authors of this assessment are of the opinion that the following exercises are far preferable in understanding and using fate and transport models for dioxins: 1) gaining confidence in a single set of dioxin fate parameters through model validation exercises, 2) checking the "validity" of predicted exposure media concentrations by comparing them with existing known concentrations, such as background concentrations or concentrations found in known settings of contamination, as a regular part of any fate modeling exercise, 3) understanding what optional models are available and, when possible, seeing if they result in a substantially different exposure media prediction, 4) identifying parameters of most uncertainty, and then determining how final predicted exposure media concentrations could vary as a result of varying that single parameters (as in the sensitivity analyses exercises in Chapter 6), and 5) compiling field data to assign and check on the all-important biotransfer/bioaccumulation parameters for the models of this assessment. These are exactly the exercises that have been undertaken in support of all the fate and transport models promoted in this document.

The five articles are just a small set of the growing body of literature on the topic of applying Monte Carlo methods to exposure and risk assessments. For example, the application of Monte Carlo methods to problems involving contaminated groundwater and related exposure pathways such as ingestion, indoor air inhalation and dermal contact with water has been

examined (McKone and Bogen, 1991). Although this work does not deal specifically with dioxin, it may be informative to readers generally interested in Monte Carlo procedures. Similarly, Paustenbach has published additional articles dealing with the application of Monte Carlo methods to exposure problems involving other chemicals (Paustenbach et al. 1991; Paustenbach, et al., 1992). Burmaster has also published numerous articles on this topic which may be of general interest to readers (ie. Burmaster and Stackelberg, 1991).

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Table 8-1. Uncertainties associated with the lifetime, body weight, and exposure duration parameters.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Lifetime	70 yrs	Standard EPA assumption.	Actuary data indicate that lifetime may be increasing	Not a major source of uncertainty
Body weight	70 kg	Standard EPA assumption. Not needed for food pathways of fruit/vegetables, beef, milk, chicken and eggs because consumption rates are units of g/kg/day and hence incorporate body weight	Not much uncertainty. Current data suggests average body weights are lower and are different for men or women - averages above 60 kg for both.	Not a major source of uncertainty.
Exposure duration	9 and 30 years	Assumptions for central and high end exposure scenarios. Estimates are 50th and 90th percentile mobility survey results; higher estimate also justified based on the assumption that rural farming families live in one location longer than non-farming families in rural settings.	Can vary for site-specific applications. Source strength dissipation not a consideration for effluent discharge or stack emission sources assuming discharges/emissions continue for duration of exposure. However, source strength dissipation may be a consideration for soil contamination source.	The 30 year duration for high end farming families assumes such families are less transient than non-farming families.
Overall: Of these three parameters, the exposure duration is the most uncertain. The values used in this assessment were from mobility studies and they also considered that farming families may tend to live in one location longer than non-farming families. Evidence in the literature and a sensitivity analysis exercise in Chapter 6 suggest that soil concentrations of dioxins dissipate slowly, such that the assumption of non-reduction of the soil concentration over the duration of exposure for the soil contamination source category is a reasonable assumption.				

Table 8-2. Uncertainties associated with the soil ingestion pathway.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Exposure site soil concentrations estimated when source is not at exposure site	Air dispersion and deposition modeled for stack emission source category; erosion modeled for soil contamination source category; for both, soil mixing depths of 2 and 20 cm, and 25 year half-lives assumed	Algorithms assume steady state; limited research suggests that the selected parameters are reasonable estimates for dioxin-like compounds.	A model validation exercise suggests that the deposition model is underestimating soil concentrations, most likely due to lack of consideration of vapor deposition and detritus additions. On the other hand, the soil erosion algorithm may be overestimating off-site impacts.	Future refinements should focus on improvements to air-to-soil modeling which add vapor impacts and detritus production.
Soil ingestion exposure assumptions	Ingestion occurs between 2-6 years old; central and high end rates of 100 and 600 mg/day; adult ingestion not considered	Soil ingestion is most likely to occur for this age range; ingestion rates selected from a review of studies in EPA (1997).	Adult soil ingestion could be important for farming situations where soil contact is frequent. Proper soil ingestion rates is an ongoing issue of research.	Ingestion rates do not consider pica behavior, which could lead to ingestion rates significantly higher than selected here. Adult soil ingestion should be considered for site specific application.
Overall: The modeling algorithms which are used to predict soil concentrations at a site of exposure when the source is distant from the site of exposure can result, in one case, an overprediction of soil concentrations, and in the other case, an underprediction of soil concentrations. The air-to-soil algorithm of the stack emission may be underestimating soil concentrations because of a lack of consideration of vapor phase impacts and a lack of consideration of detritus production. On the other hand, the erosion algorithm may be overestimating soil concentrations, based on a comparison of off-site impacts noted at an industrial site in Midland, MI, with the modeled off-site impacts. Uncertain parameters identified for soil concentration modeling include the soil dissipation rate (half-life of 25 years), the soil erosion and transport algorithm, the mixing depths, and for the stack emission source category, the uncertainties associated with the ISCST3 model. Soil ingestion for older children and adults was not considered. Assessors may wish to consider these pathways if soil concentrations at a site (modeled or measured) are high. Otherwise, soil exposure parameters are expected to be reasonable for general assessment purposes.				

Table 8-3. Uncertainties associated with the dermal exposure pathway.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Soil concentration modeling	See Section 8.4.2 and Table 8-2 for a summary of the uncertainties in soil concentration modeling.			
Use of tillled vs. untilled concentrations	used "tilled" concentration for all outdoor dermal exposures and "untilled" for indoor dermal exposures	Soil dermal contact assumed to occur while farming/gardening outdoors; indoor dust assumed to originate from untilled soils.	Tilled concentrations are lower than untilled concentrations; no data available to show relationship between outdoor and indoor dioxin concentrations in soil/dust.	Assessors should consider site-specific behaviors to determine patterns of behavior leading to soil dermal contact
Contact/ adherence rate	0.005 mg/cm^2-event for indoor contact; 0.03 and 0.1 mg/cm^2-event for residential gardening and farming, respectively.	Based on data suggesting a much larger range from <0.002 to >20 (for "kids-in-mud"); measurement data available described in EPA, 1997	measurement data may have uncertainties; variability expected due to behaviors, soil type, and so on.	Should be considered an uncertain parameter, but little data is available to make better parameter assignments.
Contact frequency	365 events/yr for indoor; 350 events/yr for farming; 100 events/yr for gardening.	based on judgement and assumption that farmers spend more time in soil than non-farmers; indoor events judged to occur daily.	uncertainty judged to be relatively small given assumptions for behaviors	climatic conditions, behaviors, other site-specific factors could be important
Surface area	1,000 cm^2 for indoor events; 10,000 for residential gardening (central scenario) and 3600 for farming (high end scenario)	Based on total body surface area data and clothing assumptions: bare hands indoors; hands and arms for farmers; hands, arms, and legs for gardeners	Good data and small variability on body surface area; clothing assumptions based on judgement and site-specific conditiosn.	Studies have shown that fine particulates can deposit under clothing. Different behaviors can lead to different assumptions regarding exposed body areas.
Absorption fraction	0.03 for all compounds	Data in EPA (1992c) suggested a range of 0.001 to 0.03 based on data for 2,3,7,8-TCDD.	Value chosen was upper end of range, so refinements would appear to lead to lower estimates of dermal exposure.	Soil properties may also affect absorption.
Overall: The uncertainties and variabilities in the soil contact/adherence and absorption fraction parameters make the overall exposure estimates highly uncertain; judged to be plus or minus 1 to 2 orders of magnitude. Assessors should also be aware of uncertainties associated with prediction of soil concentration if source is distant from site of exposure.				

Table 8-4. Uncertainties associated with the water ingestion pathway.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Water Concentrations	See modeling approaches for the soil, stack emission, and effluent discharge source categories in Chapter 4		literature data show few occurrences of dioxin-like compounds at 1 pg/L detection; models estimate 0.01 pg/L range and lower; cannot therefore ascertain uncertainty due to modeling, although little uncertainty expected due to low concentrations both found and predicted; and suitability of model predictions of sediment concentrations.	No major uncertainty expected due to modeling of water concentrations
Water Ingestion Rate	1.4 L/day central; 2.0 L/day high end	The classically assumed 2.0 L/day was evaluated as upper end rather than central value; 1.4 L/day recommended instead for central value.	EPA (1997) also noted that information on sensitive subpopulations such as laborers was unavailable; still, their analysis indicated that 2 L/day corresponds to high end value; hence it is appropriate for high end settings	Not expected to be a critical factor for uncertainty.
Contact Rate	0.70 central; 0.90 high end	values correspond to central and high end values for time at residence from several time use studies reviewed in EPA (1997).	The major uncertainty has to do with the extent to which exposed individuals rely on impacted water body for drinking water consumption. By using contact rates based on time at home, the assumption is that 100% of drinking water at home comes from impacted water body (which is assumed to supply water to household).	Exposure could be less if exposed individuals rely on water supply for drinking water other than impacted water body.
Overall: Data in the literature suggests concentrations mostly below 1 pg/L, which is consistent with modeling of concentrations 0.01 pg/L and lower in demonstration of all source categories. With this evidence, uncertainty with modeling is unknown, but the uncertainty is expected to be low because there is evidence that sediment predictions are consistent with field information. In general, water exposure is essentially the lowest exposure pathway.				

Table 8-5. Uncertainties associated with the fish ingestion pathway.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Bioaccumulation approaches for fish tissue concentration estimation	Modeled bottom and suspended concentrations multiplied by BSAF or BSSAF	Bioaccumulation approaches rather than bioconcentration approaches are appropriate for lipophilic persistent organic compounds; water-based rather than sediment based approaches could be used, but sediment based approaches offer two advantages: 1) sediment data can and has been measured to derive field-based BSAF/BSSAFs - water concentrations for dioxins are too low, and 2) models for predicting sediment concentrations can likewise be tested.	Strictly speaking, BSAFs developed from one set of data are not transportable to other water bodies, and/or to other fish species; uncertainty exists with sediment concentration modeling; range of measured BSAF from selected value of 0.09 to greater than 1.00.	Model validations and comparisons of predicted with measured fish concentrations speak well for fate and transport algorithms
Fish ingestion rate	8 and 25 g/day for central and high end	Based on a review of recreational angler surveys in EPA (1997)	Assignment of this parameter should be based on site-specific considerations; subsistence behaviors leading to much higher fish ingestion rates should be ascertained.	Example settings were defined as rural/agricultural, but with a major river used as drinking water supply and suitable for fishing; hence, freshwater recreational fishing data was used.
Overall: Comparison of fish concentrations generated in the demonstration scenarios with literature values of fish concentrations of dioxin-like compounds shows them to be comparable. The validation using 104-mill data and testing the effluent discharge algorithms showed that fish concentrations were low by about one-half, but two important considerations for that test include: the discharging mill was assumed to be the only source of 2,3,7,8-TCDD, and uncertainties with the field data and the BSSAF lead to a conclusion that the model behaves quite adequately. Fish concentrations of PCBs may have been underestimated, but this conclusion is tempered by the fact that the modeled PCB sediment concentrations are similarly lower than has been measured. Alternate modeling approaches based on water column factors show comparable fish concentrations than sediment-based methods. Assignment of the fish ingestion rates was based on data from “recreational angler surveys”; “general population” and “subsistence” ingestion rates would be lower and higher, respectively, than selected for this assessment.				

Table 8-6. Uncertainties and sensitivities associated with estimating vapor and particle-phase air concentrations from contaminated soils.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Exposure parameters	13 and 20 m^3/day for central and high end; 0.70 and 0.90 contact fractions for central and high end.	Central and high end estimates as described in EPA (1997)	not much uncertainty or variability expected for inhalation rates and contact fractions	uncertainty introduced by exposure durations of 9 and 30 years because of their role in the volatilization algorithm; otherwise uncertainty more an issue for methodologies estimating air concentrations.
Volatilization followed by near or far field dispersion for vapor phase concentrations	Used model developed by Hwang, et al (1986) for volatilization of PCBs; standard area source modeling for dispersion	Like PCBs, dioxin-like compounds are highly sorbed and persistent. Hwang (1986) model also has the advantage that the solutions were simplified using assumptions deemed reasonable for soils contaminated with dioxins.	Chemical parameters H and Koc are most uncertain with an order of magnitude range in estimated concentrations; estimations also sensitive to area, distance, and frequency wind blows to receptor.	An analysis of model performance suggests that the soil to air algorithms may be underestimating air concentrations, although this cannot be ascertained for certain because measured air concentrations are due to distant sources as well as soils.
Wind erosion followed by same dispersion algorithms	Used model based on highly erodible soils for dust flux to estimate fluxes for particle sizes < 10 μm	Assuming highly erodible soils may tend to overestimate flux, but not considering particles of size >10 μm would underestimate total airborne reservoir.	Parameters associated with the erodibility of soils can lead to a 2 order of magnitude range for estimated concentrations; much less sensitivity noted for other parameters.	No data to evaluate model results; however, particle concentrations are over 1 order of magnitude lower than vapor concentrations. Considering that the model was based on erodible soils, dust flux concentrations may be generally unimportant.

Table 8-6. (cont'd).

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Volatilization or resuspension of eroded contaminants not considered	Contaminants eroding to exposure site assumed not to volatilize or resuspend to contribute to exposure site concentrations	Traditionally, evaluation of the off-site impacts from a site of soil contamination considered only the impacts from the contaminated site.	If delivered contaminants volatilize or resuspend at site of exposure, exposure site air concentrations would increase by a factor of 2 to over 10.	More consideration of the fate of delivered contaminants is warranted.
Overall: The results of a model validation exercise showed that model predictions of air concentrations of dioxins resulting only from soil emissions were less than observed air concentrations by 2-3 orders of magnitude. The fact that they are lower is to be expected, since observed air concentrations over soils in an actual setting are very likely to be due mostly to long range air-borne transport from distant sources. Still, an analysis of data of plants growing in soils of known concentrations also suggests that the air-to-soil model may be underpredicting air concentrations. Ultimately, no data could be found on air concentrations over soils where it is definitely known that the soil is the only source of the dioxin-like compounds, so a degree of underprediction, if that is in fact occurring, could not be ascertained. Sensitivity analysis showed estimations of vapor phase air concentrations to be sensitive to Koc and H, and also to key source strength and delivery terms such as areas of contamination and wind speed. Assuming these non-chemical specific parameters can be known with reasonable certainty for site-specific applications, the most uncertainty lies with chemical specific data. Alternate approaches for volatilization and air dispersion generally estimate comparable air concentrations (within an order of magnitude or lower). Approaches to estimate particulate phase concentrations are empirical and based on field data. They are based on highly erodible soils but are specific to inhalable size particles, those less than 10 μm. As such, they may overestimate inhalation exposures, but may underestimate the total reservoir of particulates, which becomes critical for the particle deposition to vegetation algorithms. Another area of uncertainty is the assumption that volatilized contaminants do not become sorbed to airborne particles - this is also critical because vapor phase transfers dominate plant concentration estimation. A final key area of uncertainty is that transported contaminants from a contaminated to an exposure site via erosion are assumed not to volatilize or resuspend at the exposure site - air borne exposure site concentrations may be underestimated as a result.				

Table 8-7. Uncertainties associated with vegetable/ fruit ingestion exposure algorithms.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Ingestion Rates and Contact Fractions	1.16, 1.52, and 1.47 g/kg/day root/above veg, and fruit; 0.101 and 0.173 for fruit and veg contact fractions	Derived from National Food Consumption Survey (NFCS) of 1987-88; Household portion. Available data allows for most appropriate estimates of homegrown rates and contact fractions, and also ties body weight to ingestion rate by expression in terms of g/kg/day.	Household survey relies on head of household recall for week long food brought into home; whole food product do not include cooking losses, discarded amounts, etc.	All parameters evaluated as reasonable for general exposure to categories of fruit and vegetables; more refinement desired for specific assessments.
Below ground vegetable concentration	Used empirical RCF, root concentration factor, based on Kow, and VG_{bg}, below ground correction factor	Approach based on laboratory experiments; validation exercise on data for carrot peel concentrations grown in soils of known concentrations supports model capabilities.	VG_{bg} of 0.25 based on evidence of some translocation into carrots and potatoes; however, it remains most uncertain parameter; Kow is also uncertain, although validation exercise supports use of RCF	Further refinements to VG_{bg} may be warranted.
Above ground vegetable, fruit concentration	Air-to-leaf vapor phase transfer algorithm based on B_{vpa} (transfer factor) which was developed from field data; vapor phase impacts also include VG_{ag}; particle deposition algorithm for particle bound dioxins	Field experiments and modeling both show that vapor phase impacts dominate total plant concentrations; B_{vpa} calibrated from field data; particle deposition algorithm developed for radionuclide impacts to agriculture; VG_{ag} assignment of 0.01 considers both evidence of little within plant translocation for exposed bulky vegetations and reduction in plant concentrations due to peeling prior to consumption.	Model validation/comparison exercise showed the air-to-leaf model to work reasonably well in rural setting, but to underestimate grass concentrations when grass was grown in contaminated soils in an industrial setting; VG_{ag} still the most uncertain parameter.	Limited literature data and model validation exercise suggests that above ground vegetative impacts from contaminated soils may be underestimated; could be due to lack of consideration of rainsplash.
Overall: All ingestion parameters assumed are evaluated as reasonable for general exposure to broad categories of fruits and vegetables. However, great variability is expected if using these procedures on a specific site where home gardening practices can be more precisely ascertained. Validation exercises support both the soil to below ground vegetable and air-to-leaf algorithms. The most uncertain parameters for both algorithms are the "VG" parameters, VG_{ag} and VG_{bg}, which correct for evidence that there is little within plant translocation of dioxins in below as well as above ground bulky vegetations, and additionally considers peeling or washing of vegetations, which would further reduce whole plant concentrations.				

Table 8-8. Uncertainties associated with the terrestrial animal food pathways.

Assumption/ Method	Approach	Rationale	Uncertainty	Comments
Ingestion rates, contact fractions, food preparation consideration	Like for fruit/vegetables, ingestion rates and contact fractions developed from the household component of the National Food Consumption Survey (USDA, 1992; as interpreted in EPA, 1997). For meats, an additional pre- and post-cooking factor of about 0.50 further reduces consumption rates derived from this data to better relate food "brought into the house" to food "as eaten".			
Terrestrial animal bioconcentration models	Weighted average concentration in diet times BCF equals fat concentration; BCF for beef/milk developed from one experiment on one lactating cow.	Precedence and data support this approach. Two field studies collecting data to develop BCF for cow's milk arrive at very similar BCFs.	Uncertainty in applying milk-derived BCF to beef; chicken and egg BCFs separately derived in laboratory experiments; uncertainty in applying laboratory feeding experiments to field situations for chickens; dietary assumptions are variable and soil bioavailability correction factor, Bs, is uncertain and important for free range chicken scenario	Air-to-beef model validation exercise supports the use of milk-derived BCFs for beef, and approach in general. For predicting beef concentrations, site-specific consideration of fattening regime is important.
Related models	See previous sections for discussions on uncertainties in associated models including air dispersion and deposition modeling, soil-to-air and air-to-soil modeling, air-to-plant modeling, and soil concentration modeling.			
Overall: The demonstration scenarios showed that the terrestrial animal food pathways dominate human exposure. This was supported by similar findings in Volume II of this assessment, which estimated background exposures based on measured concentrations coupled with consumption rates. In site-specific applications, animal diet fractions in the various categories of animal feeds (leafy, partially protected, fully protected, soil) becomes important. The air-to-beef model validation exercise described earlier lends confidence to the use of the milk/beef bioconcentration algorithms.				

Table 8-9. Distributions for a Monte Carlo exercise which developed soil cleanup levels at residential and industrial sites.

Parameter	Range (Residential)	Range (Industrial)
Soil Contact μg/cm^2/d	200 - 1800	same
Dermal Bioavailability Fraction	0.01 - 0.025	same
Fraction soil from site	O-5 yr: 0.1 - 1.0 6-30 yr: 0.1 - 0.5	0.1 - 1.0
Fraction indoor dust contaminated	(not considered)	0.25 - 1.0
Indoor exposure duration	0-1.5 yr: 182-365 d/yr 1.5-30 yr: 200-365 d/yr	0 - 8 hr/d 220 - 260 d/yr
Outdoor exposure duration	0 - 1.5 yr 60-120 d/yr 1.5 - 30 yr 60-240 d/yr	0 - 8 hr/d 220 - 260 d/yr
Soil ingestion rate, μg/d	0 - 1.5 yr 100 - 10000 1.5 - 5 yr 9000 - 50000 6 - 12 yr 5000 - 50000 13 - 30 yr 100 - 50000	100 - 50000 (indoors) 100 - 10000 (outdoors)
Oral Bioavailability	0.38, 0.40, 0.47, 0.49	same
Air particulate concen., μg/m^3	25 - 45	same
Fraction outdoor dust contaminated	0.1 - 0.5	same
Inhalation rate m^3/hr	0-1.5 yr: 0.03 - 0.07 1.5-5 yr: 0.3 - 0.9 6-12 yr: 0.75 - 1.5 13-30 yr: 0.5 - 1.5	9 - 14.6 m^3/d
Lipid Content of Fish	0.01 - 0.05	
Fish Bioavailability Index	0.01 - 0.5	
Organic Carbon content of sediment	0.01 - 0.5	
Fish Consumption, g/d	0-1.5 yr: 0 1.5-5 yr: 0.38 - 0.62 6-12 yr: 0.63 - 1.0 13-30 yr: 1.1 - 1.8	
Fraction remaining after cooking	0.3 - 0.75	

Source: Paustenbach et. al. (1992a); uniform distributions assumed over ranges shown.

Table 8-10. Summary of Monte Carlo distributions used in a fish consumption assessment.

Exposure Parameter	Distribution Type	Mean	Standard Deviation	Min./Max.
Dioxin Conc. (ppt of TEQ)	truncated lognormal	3.3	8.7	0.0002 /16,000
Fraction caught in affected waters	triangular	0.09 (all US) 0.4 (near mill)	0.2 0.2	0/1.0 0/1.0
Consumption (g/d)	truncated lognormal	2.5 (all US) 19.1 (sport - fishermen)	7.3 27.9	0/240 0.2/403
Duration (yr)	truncated lognormal	13.3	12.3	0.1/70
Cooking Loss Fraction	uniform	0.1	0.3	0.25/0.75
Body Weight (kg)	normal	71	18.1	29.9/143.2

Source: Anderson et. al. (1992).

Table 8-11. Summary of Monte Carlo distributions used in food chain study.

Parameter	Geometric Mean	Geometric Standard Deviation	Distribution
Milk Ingestion 0-15 yr: kg/kg/d 15-70 yr:	0.014 0.0033	1.2 1.1	log normal
Meat Ingestion 0-15 yr: kg/kg/d 15-70 yr:	0.0044 0.0029	1.1 1.2	log normal
Fruit/Veg Ing. 0-15 yr: kg/kg/d 15-70 yr:	0.0081 0.0045	1.4 1.3	log normal
Grain Ing. 0-15 yr: kg/kg/d 15-70 yr:	0.0074 0.0030	1.2 1.2	log normal
Particle to Food Deposition Factor, m/d	300	3	log normal
Plant/Soil Part. Factor	0.013	4.0	log normal
Biotransfer Fac. Cattle Intake to Meat, d/kg	0.055	3.0	log normal
Biotransfer Fac. Cattle Intake to Milk, d/kg	0.01	3.0	log normal
	Lower Bound	Upper Bound	
Annual Inventory Food Crops, kg/m^2	1.0	10.0	log uniform
Annual Inventory Pasture Crops, kg/m^2	0.1	1.0	log uniform
Weathering Rate Constant, 1/d	0.01	0.1	log uniform
Cattle Inhalation Rate, m^3/d	63	177	uniform
Beef Cattle Ingestion of Pasture Grass, kg/d	4.0	20	uniform
Dairy Cattle Ingestion of Pasture Grass, kg/d	11	23	uniform
Cattle Soil Ingestion, kg/d	0.1	0.83	uniform

Source: McKone and Ryan, 1989.

Table 8-12. Summary of parameter distributions used for modeling terrestrial fruits and vegetables for human consumption in a Monte Carlo exercise.

Definition	Forms and Parameters	Distribution
I. Plant Concentration Modeling		
soil decay constant, 1/day	0.0001-0.0002	Uniform
soil mixing depth, m	0.15-0.25	Uniform
crop interception fraction	root, vine, tree: 0.05-0.25 Leafy: 0.16-0.40	Uniform
soil bulk density, g/m^3	median = 1.4; geo. stan. dev = 1.15	Lognormal
growing season duration, days	tree: 120-150 leafy: 40 - 60	Uniform
root uptake factor for translocation of TCDD from soil to crop, C_{plant}/ C_{soil}	root crop: 0.25-1.0 Vine, leafy: 0.05-0.15	Uniform
deposition velocity of particle or vapor class, m/day	median by diameter, variability = 0.8 log units	Loguniform
particle weather rate constant on plant, 1/day	0.01-0.1	Loguniform
crop yield, g/m^2	vine, tree: 5 - 15 leafy: 6 - 10	Uniform
II. Air Concentration Modeling		
dispersion factor calculated from air dispersion model, defined as air concentration in ith sector per unit mass emitted, $(mg/m^3)/(mg/s)$	median = -0.00017, geo. stan. dev = 1.4	Lognormal
2,3,7,8-TCDD mass emissions, mg/sec	$1.5*10^{-6}$ - $5*10^{-6}$	Loguniform

Source: Cullen (1995b)

1. DISPOSITION AND PHARMACOKINETICS

The disposition and pharmacokinetics of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds have been investigated in several species and under various exposure conditions. Several reviews on this subject focus on TCDD and related halogenated aromatic hydrocarbons (Neal et al., 1982; Gasiewicz et al., 1983a; Olson et al., 1983; Birnbaum, 1985; van den Berg et al., 1994). The relative biological and toxicological potency of TCDD and related compounds depends not only on the affinity of these compounds for the aryl hydrocarbon receptor (AhR), but on the species-, strain-, and congener-specific pharmacokinetics of these compounds (Neal et al., 1982; Gasiewicz et al., 1983a; Olson et al., 1983; Birnbaum, 1985; van den Berg et al., 1994, DeVito and Birnbaum, 1995).

2,3,7,8-TCDD and other similar compounds discussed here are rapidly absorbed into the body and slowly eliminated, making body burden (bioaccumulation) a reliable indicator of time-integrated exposure and absorbed dose. Because of the slow elimination kinetics, it will be shown in this section that lipid or blood concentrations, which are often measured, are in dynamic equilibrium with other tissue compartments in the body, making the overall body burden and tissue disposition relatively easy to estimate. Finally, it will be shown that body burdens can be correlated with adverse health effects (Hardell et al., 1995; Leonards et al., 1995), further leading to the choice of body burden as the optimal indicator of absorbed dose and potential effects.

1.1. ABSORPTION/BIOAVAILABILITY FOLLOWING EXPOSURE

Gastrointestinal, dermal, and transpulmonary absorptions represent potential routes for human exposure to this class of persistent environmental contaminants. Parenteral absorption is a route of exposure that has been used to generate disposition and pharmacokinetic data on these compounds.

1.1.1. Oral

1.1.1.1. *Gastrointestinal Absorption in Animals*

Much of human exposure to TCDD and related compounds is thought to be through the diet. Experimentally, these compounds are commonly administered in the diet or by gavage in an oil vehicle. Gastrointestinal absorption is usually estimated as the difference between the administered dose (100%) and the percent of the dose that was not absorbed. The unabsorbed fraction is estimated as the recovery of parent compound in feces within 24 to 48 hours of a single oral exposure by gavage. Table 1-1 summarizes gastrointestinal absorption data on TCDD and related compounds.

In Sprague-Dawley rats given a single oral dose of 1.0 μg [^{14}C]-2,3,7,8-TCDD/kg bw in acetone:corn oil (1:25, v/v), the fraction absorbed ranged from 66% to 93%, with a mean of ~84% (Rose et al., 1976). With repeated oral dosing of rats at 0.1 or 1.0 μg/kg/day (5 days/week for 7 weeks), gastrointestinal absorption of TCDD was observed to be approximately that observed for a single oral exposure (Rose et al., 1976). Oral exposure of Sprague-Dawley rats to a larger dose of TCDD in acetone:corn oil (50 μg/kg) resulted in an average absorption of 70% of the administered dose (Piper et al., 1973). More recently, Diliberto et al. (1996a) reported 88% absorption of TCDD in male Fischer 344 rats following oral exposure in Emulphor/95% ethanol/water (1:1:3). (Emulphor EL-620 is a polyoxyethylated vegetable oil preparation [GAF Corp., New York, NY]).

One study in the guinea pig reported that ~50% of a single oral dose of TCDD in acetone:corn oil was absorbed (Nolan et al., 1979). The gastrointestinal absorption of TCDD was also examined in the hamster, the species most resistant to the acute toxicity of this compound (Olson et al., 1980). Hamsters were given a single, sublethal, oral dose of [1,6-^{3}H]-2,3,7,8-TCDD in olive oil (650 μg/kg), and an average of 75% of the dose was absorbed. When TCDD was administered to rats in the diet at 7 or 20 ppb (0.5 or 1.4 μg/kg/day) for 42 days, 50% to 60% of the consumed dose was absorbed (Fries and Marrow, 1975). These findings indicate that oral exposure to TCDD in the diet or in an oil vehicle results in the absorption of >50% of the administered dose.

The intestinal absorption of [^{3}H]-2,3,7,8-TCDD has also been investigated in thoracic duct-cannulated rats (Lakshmanan et al., 1986). The investigators concluded that TCDD was absorbed into chylomicrons and transported through the lymphatic system before entering the systemic circulation.

The absorption of 2,3,7,8-TBDD in male Fischer 344 rats was studied after oral exposure by gavage at 5 μg/kg in Emulphor:ethanol:water (1:1:3) (Diliberto et al., 1990). The percent of the dose absorbed for this study was defined as 100% (% total oral dose in feces on days 1 and 2 minus % total intravenous dose in feces on days 1 and 2) using the intravenous pharmacokinetic data of Kedderis et al. (1991a).

The relative absorbed dose or bioavailability of 2,3,7,8-TBDD after oral exposure was estimated at 78%, 82%, 60%, and 47% at dose levels of 0.001, 0.01, 0.1, and 0.5 μmol/kg, respectively. These results suggest nonlinear absorption at the higher doses, with maximal oral absorption at an exposure of ≤0.01 μmol/kg (5 μg/kg).

The absorption of 2,3,7,8-TCDF has been investigated after oral exposure by gavage. Approximately 90% of the administered dose (0.1 and 1.0 μmol/kg) of 2,3,7,8-TCDF in Emulphor:ethanol (1:1) was absorbed in male Fischer 344 rats (Birnbaum et al., 1980). Similarly, >90% of the administered dose (0.2 μmol/kg, 6 μg/kg, and 1-15 μg/kg) of 2,3,7,8-

TCDF in Emulphor:ethanol:water (1:1:8) was absorbed in male Hartley guinea pigs (Decad et al., 1981a; Ioannou et al., 1983). Thus, 2,3,7,8-TCDF appears to be almost completely absorbed from the gastrointestinal tract. This absorption may be related to the greater relative solubility of 2,3,7,8-TCDF compared with that of 2,3,7,8-TCDD or 2,3,7,8-TBDD.

The oral bioavailability of 2,3,4,7,8-PeCDF and 3,3′,4,4′-TCB in corn oil was similar to that of 2,3,7,8-TCDD (Brewster and Birnbaum, 1987; Wehler et al., 1989; Clarke et al., 1984). Furthermore, 2,3,4,7,8-PeCDF absorption was independent of the dose (0.1, 0.5, or 1.0 μmol/kg). Incomplete and variable absorption of 1,2,3,7,8-PeCDD was reported in rats, with 19% to 71% of the dose absorbed within the first 2 days after oral exposure (Wacker et al., 1986).

Early studies on the pharmacokinetic behavior of OCDD by Williams et al. (1972) and Norback et al. (1975) demonstrated that OCDD was poorly absorbed after oral exposure. More recently, Birnbaum and Couture (1988) also found that the gastrointestinal absorption of OCDD in rats was very limited, ranging from 2% to 15% of the administered dose. Lower doses (50 μg/kg) in an o-dichlorobenzene:corn oil (1:1) vehicle were found to give the best oral bioavailability for this extremely insoluble compound.

Recently Mes et al. (1995) have reported PCBs in nondosed infants of dosed rhesus monkeys. Transfer to the infants was from both intrauterine and lactational exposure. Also, the infants showed a larger percentage of heptachorobiphenyls than did the dosed dams. Busbee and Zipring (1994) reported the direct absorption across the gastric mucosa of Aroclor 1232 (DCB) in an ovine. The absorption was rapid and the circulating DCB was not found to be associated with plasma lipid fractions. The researchers report no occurrence in the thoracic duct lymph prior to appearance in the circulating plasma. Also, the DCB did bind with plasma lipids in vitro. These data suggest that this DCB is transported similar to water soluble compounds.

1.1.1.2. *Gastrointestinal Absorption in Humans*

The above animal data indicate that gastrointestinal absorption of TCDD and related compounds is variable, incomplete, and congener- and vehicle-specific. More soluble congeners, such as 2,3,7,8-TCDF, are almost completely absorbed, whereas the extremely insoluble OCDD is poorly absorbed. In some cases, absorption has been found to be dose dependent, with increased absorption occurring at lower doses (2,3,7,8-TBDD, OCDD). The limited database in experimental animals also suggests that there are no major interspecies differences in the gastrointestinal absorption of these compounds.

Poiger and Schlatter (1986) investigated the absorption of TCDD in a 42-year-old man after ingestion of 105 ng [^{3}H]-2,3,7,8-TCDD (1.14 ng/kg bw) in 6 mL corn oil and found that >87% of the oral dose was absorbed from the gastrointestinal tract. Following absorption, the half-life for elimination was estimated to be 2,120 days.

Schlummer et al. (1998) used a mass balance approach to assess the gastrointestinal absorption of CDDs, CDFs, PCBs, and hexachlorobenzene (HCB) from food in seven individuals, 24 to 81 years of age, with different contaminant body burdens. The difference between the ingested (food concentration) and excreted (fecal concentration) amounts of each compound was defined as net absorption. Three types of net absorption were observed in this study: (1) nearly complete net absorption (e.g. 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF); (2) incomplete net absorption (e.g., TCDD and 1,2,3,7,8-PeCDD in the younger subjects); and (3) net excretion (excretion to a greater extent than ingestion, e.g., 1,2,3,6,7,8-HxCDD and OCDD). In terms of TEQs, the maximum net absorption of CDDs and CDFs was 63% in one individual, while a net excretion of TEQs was found for the three oldest subjects, which also have the highest serum concentration of these congeners. When PCB 126 (3,3'4,4',5), with a TEF of 0.1, is included in the TEF calculation, the TEQ balance was dominated by this congener, resulting in a maximum net TEQ absorption of 80% and a net TEQ absorption in all but the oldest subject. Table 1-1 illustrates that compounds showing nearly complete net absorption had very low or nondetectable levels in the serum lipids, and for other congeners, there was a trend for decreasing net absorption/increasing net excretion with increasing congener concentration in serum lipids. Together, the data support the passive diffusion model for gastrointestinal absorption, where the concentration of the contaminant in the blood is the major factor determining absorption. However, the relatively high absorption levels of many congeners could not be explained on the basis of diffusive gradients estimated from the difference between the lipid-based food and serum concentrations, as the lipid-based food levels were always lower, favoring net excretion. The authors propose a fat-flush theory, which hypothesizes that the fat compartment of the absorbing tissue (gut wall) expands because of the uptake of dietary fat, resulting in a decrease in the lipid-based concentration of the gut wall below that of the food, thus facilitating absorption. Therefore, as food passes through the duodenum and the jejunum, CDDs, CDFs and PCBs experience a diffusion gradient and net absorption as a result of the fat-flush. As the gut contents reach the colon, dietary fat has been absorbed, causing a reduction in the concentration gradient favoring absorption of CDDs, CDFs, and PCBs. Thus, the fat-flush theory supports the hypothesis that absorption and excretion of CDDs, CDFs, and PCBs are distinct processes occurring at different locations in the digestive tract.

Duarte-Davidson and Jones (1994) report an average intake of a sum of several PCB congeners in the contemporary United Kingdom population of 0.53 micrograms/person/day. They estimate 97% of exposure can be accounted for by food consumption. This indicates that PCBs can likewise be absorbed through the gastrointestinal system.

Because CDDs, CDFs, and PCBs are present in human milk, McLachlan (1993) investigated the net absorption of these compounds in a nursing infant. The contaminant input,

through the ingestion of mother's milk, and the contaminant output in the feces were measured to estimate the digestive tract absorption of these compounds. For almost all congeners, more than 90% of the ingested compound was absorbed, indicating that the common assumption of 100% absorption of CDDs, CFFs, and PCBs in nursing infants is reasonable. Dahl et al. (1995) provide further evidence of this, as they report > 95% absorption in postpartum infants (1, 2, 3 months) in Sweden. Abraham et al. (1996) assessed the oral intake and fecal excretion of CDDs and CDFs in one formula-fed and two breast-fed infants at 1 and 5 months of age. The breast-fed infants had significantly more exposure to CDDs and CDFs, with >90% of the 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD, and 1,2,3,6,7,8-HxCDD (>93% of TEQs) being absorbed from mother's milk. Less complete bioavailability of higher CDDs was observed, with 62% to 88% of 1,2,3,4,6,7,8-HepCDD and 16% to 75% of OCDD absorbed from mother's milk (Abraham et al., 1996). Furst et al. (1994), Hong et al. (1994), Schecter et al. (1994a,b), Georgii et al. (1994), and others provide further evidence of the presence of dioxins, PCPs, and PCBs in human milk. This important route for excretion and exposure is discussed later in the chapter.

1.1.1.3. *Bioavailability Following Oral Exposure*

Oral exposure of humans to TCDD and related compounds usually occurs as a complex mixture of these contaminants in food, soil, dust, water, or other mixtures that would be expected to alter absorption.

The influence of dose and vehicle or adsorbent on gastrointestinal absorption has been investigated in rats by Poiger and Schlatter (1980), using hepatic concentrations 24 hours after dosing as an indicator of the amount absorbed (Table 1-2). Administration of TCDD in an aqueous suspension of soil resulted in a decrease in the hepatic levels of TCDD as compared with hepatic levels resulting from administration of TCDD in 50% ethanol. Likewise, Diliberto et al. (1996a) report 24.4% (+ 1.4) in the liver after dosing male Fischer 344 rats with TCDD in a solution of 1:1:3 ratio of Emulphor/95% ethanol/distilled water. The extent of the decrease was directly proportional to the length of time the TCDD had been in contact with the soil. When TCDD was mixed in an aqueous suspension of activated carbon, absorption was almost totally eliminated (<0.07% of the dose in hepatic tissues).

Philippi et al. (1981) and Huetter and Philippi (1982) have shown that radiolabeled TCDD becomes progressively more resistant with time to extraction from soil. Similarly, the feeding of fly ash, which contains CDDs, to rats in the diet for 19 days resulted in considerably lower hepatic levels of CDDs than did the feeding of an extract of the fly ash at comparable dietary concentrations of CDDs (van den Berg et al., 1987a). The CDDs were tentatively identified as 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD, and the difference in hepatic levels noted between fly ash-treated and extract-treated rats was greater

for the more highly chlorinated isomers than for 2,3,7,8-TCDD. These results indicate the importance of the formulation or vehicle containing the toxin(s) on the relative bioavailability of 2,3,7,8-TCDD, PeCDD, and HxCDDs after oral exposure.

Because TCDD in the environment is likely to be absorbed to soil, McConnell et al. (1984) and Lucier et al. (1986) compared the oral bioavailability of TCDD from environmentally contaminated soil with that from TCDD administered in corn oil in guinea pigs and rats, respectively. As indicated by biological effects and the amount of TCDD in the liver, the intestinal absorption from soil from Times Beach and Minker Stout, Missouri, was ~50% less than that from corn oil. Shu et al. (1988a) reported an oral bioavailability of ~43% in rats dosed with three environmentally contaminated soil samples from Times Beach, Missouri. This figure did not change significantly over a 500-fold dose range of 2-1,450 ng 2,3,7,8-TCDD/kg bw for soil contaminated with ~2, 30, or 600 ppb of TCDD TCDD. In studies of other soil types, Umbreit et al. (1986a,b) estimated an oral bioavailability in the rat of 0.5% for soil at a New Jersey manufacturing site and 21% for a Newark salvage yard. These results indicate that bioavailability of TCDD from soil varies between sites and that TCDD content alone may not be indicative of potential human hazard from contaminated environmental materials. Although these data indicate that substantial absorption may occur from contaminated soil, soil type and duration of contact, as suggested from the data that demonstrated decreased extraction efficiency with increasing contact time between soil and TCDD (Philippi et al., 1981; Huetter and Philippi, 1982), may substantially affect the absorption of TCDD from soils obtained from different contaminated sites.

1.1.2. Dermal Absorption

Brewster et al. (1989) examined the dermal absorption of TCDD and three CDFs in male Fischer 344 rats (10 weeks old; 200-250 g). The fur was clipped from the intrascapular region of the back of each animal. A single compound in 60 μL of acetone was then applied over a 1.8 cm^2 area of skin, which then was covered with a perforated stainless steel cap. Table 1-3 summarizes data on the absorption of each compound at 3 days after a single dermal exposure. At an exposure of 0.1 μmol/kg, the absorption of 2,3,7,8-TCDF (49% of administered dose) was greater than that of 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDF, and 2,3,7,8-TCDD. For each compound, the relative absorption (percentage of administered dose) decreased with increasing dose, while the absolute absorption (μg/kg) increased nonlinearly with dose. Results also suggest that the majority of the compound remaining at the skin exposure site was associated with the stratum corneum and did not penetrate through to the dermis. In a subsequent study, Banks and Birnbaum (1991a) examined the rate of absorption of TCDD over 120 hours after the dermal application of 200 pmol (1 nmol/kg) to male Fischer 344 rats. The absorption kinetics appeared

to be first order, with an absorption rate constant of 0.005 $hour^{-1}$. With a similar exposure protocol, the dermal absorption of 2,3,7,8-TCDF was found to follow a first-order process, with a rate constant of 0.009 $hour^{-1}$ (Banks and Birnbaum, 1991b). Together, these results on dermal absorption indicate that at lower doses (≤0.1 μmol/kg), a greater percentage of this administered dose of TCDD and three CDFs was absorbed. Nonetheless, the rate of absorption of TCDD is still very slow (rate constant of 0.005 $hour^{-1}$), even following a low-dose dermal application of 200 pmol (1 nmol/kg). Results from Table 1-3 also suggest that the dermal absorption of 2,3,7,8-TCDF, 2,3,4,7,8-PeCDF, and 1,2,3,7,8-PeCDF occurs at a very slow rate. Using a similar exposure protocol, the dermal absorption of 2,3,7,8-TBDD was only 30% to 40% of that observed for TCDD (Diliberto et al., 1993a; 1996a).

The dermal absorption of several polyhalogenated aromatic hydrocarbons in male F344 rats was also compared with estimates of their respective octanol-water partition coefficients (Jackson et al., 1993). Inverse correlations were found between octanol-water partition coefficient estimates and the single-dose (~1.0 nmol/kg and ~0.1 μmol/kg) dermal absorption for most of the compounds studied. The differential dermal absorption of TCDD and 2,3,7,8-TBDD may result, in part, from the diminished ability of the more lipophilic 2,3,7,8-TBDD to partition out of the stratum corneum and into the underlying epidermal and dermal layers.

Rahman et al. (1992) and Gallo et al. (1992) compared the in vitro permeation of TCDD through hairless mouse and human skin. In both species, the amount of TCDD permeated increased with the dose, but the percentage of the dose permeated decreased with increasing dose. The permeability coefficient of TCDD in human skin was about one order of magnitude lower than that in mouse skin. The hairless mouse skin does not appear to be a suitable model for the permeation of TCDD through human skin because the viable tissues were major barriers to TCDD permeation in hairless mouse skin, while the stratum corneum layer provided the greater resistance in human skin. A significant increase in TCDD permeation through human skin was observed when the skin was damaged by tape-stripping. Gallo et al. (1992) suggested that washing and tape-stripping of the exposed area might remove most of the TCDD and reduce the potential for systemic exposure and toxicity because most of the TCDD remained within the horny layer of human skin even at 24 hours following exposure.

Weber et al. (1991) also investigated the penetration of TCDD into human cadaver skin at concentrations of 65-6.5 ng/cm^2. This study found that the stratum corneum acted as a protective barrier, as its removal increased the amount of TCDD absorbed into layers of the skin. With intact skin and acetone as the vehicle, the rate of penetration of TCDD into the dermis ranged from 6 to 170 $pg/hour/cm^2$, while penetration into the dermis and epidermis ranged from 100 to 800 $pg/hour/cm^2$. With mineral oil as the vehicle, there was about a five-to-tenfold reduction in the rate of penetration of TCDD into the intact skin.

Wester et al. (1993a) studied the dermal permeation potential of two PCBs, Aroclor 1242 and Aroclor 1254, from soil. Soil is the most common medium of contact for humans; hence any permeation potential is of great interest for risk assessment purposes. This study consisted of experiments conducted in rhesus monkeys (in vivo), in vitro human skin, and powdered human corneum. The monkeys were exposed topically for a 5-week period. Percutaneous absorption was determined by urinary and fecal [^{14}C]-PCB excretion. The percutaneous absorption in the monkey was 13.8% (±2.7%) for Aroclor 1242 and 14.1% (±1.0%) for Aroclor 1254. The authors report that these absorption rates for soil are similar to those from vehicles such mineral oil, trichlorobenzene, and acetone. These rates are somewhat higher than those for other compounds such as the pesticide butachlor, which was about 5.0% when applied to human skin (Ademola et al., 1993). On the other hand, Wester et al. (1993b) report a much higher absorption for pentachlorophenol (PCP) (24.4% from soil and 29.2% from acetone) in the rhesus monkey. The authors report that PCP is one of the more extensively absorbed compounds they have studied. Thus, at least for these two PCBs (Aroclor 1242 and Aroclor 1254), the absorption in the rhesus monkey appears to be intermediate between that of other compounds tested. In summary, these studies indicate that these two PCBs show significant partitioning into the stratum corneum from soil, a common environmental matrix.

1.1.2.1. *Bioavailability Following Dermal Exposure*

Dermal exposure of humans to TCDD and related compounds usually occurs as a complex mixture of these contaminants in soil, oils, or other mixtures, which would be expected to alter absorption. Poiger and Schlatter (1980) presented evidence that the presence of soil or lipophilic agents dramatically reduces dermal absorption of TCDD compared with absorption of pure compound dissolved in solvents. In a control experiment, 26 ng of TCDD in 50 μL methanol was administered to the skin of rats; 24 hours later the liver contained 14.8±2.6% of the dose. By comparing this value to the hepatic levels obtained after oral administration in 50% ethanol (in the same study), the amount absorbed from a dermal application can be estimated at ~40% of the amount absorbed from an equivalent oral dose. This comparison assumes that hepatic levels are valid estimates of the amount absorbed from both oral and dermal routes and that absorption from methanol is equivalent to absorption from 50% ethanol. The dose-dependent distribution of TCDD in the liver is another factor that may limit quantitative conclusions regarding bioavailability that are based solely on hepatic levels following exposure to 2,3,7,8-TCDD. As compared with dermal application in methanol, dermal application to rats of TCDD in vaseline or polyethylene glycol reduced the percentage of the dose in hepatic tissue to 1.4% and 9.3%, respectively, but had no observable effect on the dose of TCDD required to induce skin lesions (~1 μg/ear) in the rabbit ear assay. Application of TCDD in a soil/water

paste decreased hepatic TCDD to ~2% of the administered dose and increased the amount required to produce skin lesions to 2-3 μg in rats and rabbits, respectively. Application in an activated carbon/water paste essentially eliminated absorption, as measured by percent of dose in the liver, and increased the amount of TCDD required to produce skin lesions to ~160 μg. These results suggest that dermal absorption of TCDD depends on the formulation (vehicle or adsorbent) containing the toxin.

Shu et al. (1988b) investigated the dermal absorption of soil-bound TCDD in rats. Relative dermal bioavailability was estimated by comparing the level of TCDD in the liver of rats given soil-bound TCDD dermally to that of rats given oral doses of TCDD dissolved in corn oil. The level of TCDD in livers of rats dosed orally with TCDD in corn oil, following correction for unabsorbed TCDD TCDD, is assumed to represent 100% bioavailability. The dermal penetration of TCDD after 4 hours of contact with skin was ~60% of that after 24 hours of contact. After 24 hours of contact with the skin, the degree of dermal uptake from contaminated soil was ~1% of the administered dose. The authors observed that the degree of uptake does not appear to be influenced significantly by the concentration of TCDD in soil, by the presence of crankcase oil as a co-contaminant, or by environmentally versus laboratory-contaminated soil.

A major limitation of these studies is the uncertainty regarding the extrapolation of dermal absorption data on these compounds from the rat to the human. The in vitro dermal uptake of TCDD has been investigated in hairless mouse and human skin (Gallo et al., 1992; Rahman et al., 1992). In vitro dermal uptake of TCDD from laboratory-contaminated soil indicated that aging of soils (up to 4 weeks) and the presence of additives (2,4,5-trichlorophenol and motor oil) in the soil did not have any significant effect on dermal uptake (Gallo et al., 1992). Because most of the TCDD remained in the stratum corneum layer of human skin, the permeation of TCDD was significantly lower in human than in hairless mouse skin. There are no published quantitative in vivo data on the dermal absorption of TCDD and related compounds in the human, and data on the rhesus monkey are very limited. Brewster et al. (1988) found that 1,2,3,7,8-PeCDF was poorly absorbed in the monkey after dermal application, with <1% of the administered dose being absorbed in 6 hours. This provides further evidence for the very slow rate of dermal absorption of TCDD and related compounds.

1.1.3. Transpulmonary Absorption

The use of incineration as a means of solid and hazardous waste management results in the emission of contaminated particles that may contain TCDD and related compounds into the environment. Thus, significant exposure to TCDD and related compounds may result from inhalation of contaminated fly ash, dust, and soil. In an attempt to address the bioavailability and

potential health implications of inhaling contaminated particles, Nessel et al. (1990) examined the potential for transpulmonary absorption of TCDD in female Sprague-Dawley rats after intratracheal instillation of the compound in a corn oil vehicle or as a laboratory-prepared contaminant of gallium oxide particles. Several biomarkers of systemic absorption were measured, including the dose-dependent effects of TCDD on hepatic microsomal cytochrome P-450 content, AHH activity, and liver histopathology. Significant dose-related effects were observed at an exposure of $\geq$0.55 μg TCDD/kg. The authors found that induction was slightly higher when animals received TCDD in corn oil than when animals received TCDD-contaminated particles, and was comparable to induction after oral exposure. The results from Nessel et al. (1990) indicate that systemic effects occur after pulmonary exposure to TCDD, suggesting that transpulmonary absorption of TCDD does occur.

The pulmonary bioavailability of TCDD was also examined in female Sprague-Dawley rats following intratracheal instillation of PCDD-contaminated soil from a former 2,4,5-trichlorophenoxy-acetic acid manufacturing site (Nessel et al., 1992). A size-dependent enrichment of PCDDs and PCDFs was observed, with the smaller particles being more highly contaminated. TCDD was enriched up to 33-fold in small respirable particles as compared with unfractionated soil. Pulmonary bioavailability of TCDD was assessed by hepatic enzyme induction (AHH activity) and TCDD concentration. The data indicate that the relative pulmonary bioavailability of TCDD on respirable soil particles is 100% as compared with laboratory-recontaminated gallium oxide.

The transpulmonary absorption of TCDD was assessed in male Fischer 344 rats following intratracheal instillation of a 1 nmol/kg dose in Emulphor:ethanol:water (1:1:3) (Diliberto et al., 1996a). Transpulmonary absorption was 95%, suggesting that there was almost complete absorption of TCDD by inhalation under these conditions. Similar results also were observed for the transpulmonary absorption of 2,3,7,8-TBDD under similar exposure conditions (Diliberto et al., 1993a,b). Recent studies (Diliberto et al., 1996a) further show the importance of transpulmonary absorption for 2,3,7,8-TCDD. Tissue distributions were measured 3 days after administration via different routes. Comparisons show that the percentage of dose distributed to the liver after intratracheal (itr) injection is similar to that after intravenous administration (iv) (33% for itr, 37% for iv). Also, both the iv and itr routes show a preference for greater sequestration in the liver over fat when compared to the oral (po) route. These results suggest that the transpulmonary absorption of 2,3,7,8-TCDD and 2,3,7,8-TBDD was similar to that observed following oral exposure.

1.1.4. Parenteral Absorption

In an effort to obtain more reproducible and complete absorption of TCDD and related compounds for pharmacokinetic studies, Abraham et al. (1989a, b) used various vehicles to investigate the absorption of TCDD after parenteral application in rats. These investigators observed optimal results with the subcutaneous injection of TCDD with a mixture of toluene:DMSO (1:2) as the vehicle. At 3 and 5 days after treatment, the percentages of administered dose remaining at the injection site under the skin of the back were ~10% and 2%, respectively. The vehicle did not cause adverse effects at an applied volume of 0.2 mL/kg bw. The absorption of a defined mixture of CDDs and CDFs in the rat was also examined after subcutaneous injection with toluene:DMSO (1:2) as a vehicle. Of the 97 congeners analyzed, 70 were ≥95% absorbed 7 days after exposure; 21 were 90%-95% absorbed; and 1,2,3,9-TCDD, 1,2,3,6,7,9-/1,2,3,6,8,9-HxCDD, 1,2,3,4,6,7,9-HpCDD, OCDD, 1,2,4,6,8,9-HxCDF and 1,2,3,7,8,9-HxCDF were 84%-89% absorbed. Greater than 90% absorption of CDDs and CDFs also was observed under these conditions in the marmoset monkey, with the exception of 1,2,3,4,7,8,9-HpCDF, OCDF, and OCDD, which had ~50%-80% of the administered dose absorbed (Neubert et al., 1990; Abraham et al., 1989a). Although the absorption of CDDs and CDFs after subcutaneous administration in toluene:DMSO (1:2) is somewhat slow in rats and monkeys, absorption of most congeners was >90% within 7 days. Even for highly chlorinated insoluble congeners, such as OCDD and OCDF, subcutaneous absorption was >84% in the rat and >50% in the monkey.

Less complete and slower absorption of CDDs and CDFs was observed after subcutaneous injection of these compounds using an oil-containing vehicle (Brunner et al., 1989; Abraham et al., 1989a). Using a corn oil:acetone vehicle (24:1, v/v), Lakshmanan et al. (1986) observed that only 7% of the administered dose of TCDD was absorbed 24 hours after subcutaneous injection and that only 35% was absorbed after intraperitoneal injection. Brunner et al. (1989) also reported that intraperitoneal administration of CDDs and CDFs revealed a delayed absorption from the abdominal cavity that varied for the different congeners. Therefore, concentrations measured in abdominal adipose tissue after intraperitoneal administration may not represent average values of adipose tissue in the whole body, particularly at early time points following exposure. This may also be true following oral exposure because of different perfusion rates of different fat depots (McKinley et al., 1993).

1.2. DISTRIBUTION

1.2.1. Distribution in Blood and Lymph

Once a compound is absorbed, its distribution is regulated initially by its binding to components in blood and its ability to diffuse through blood vessels and tissue membranes.

Lakshmanan et al. (1986) investigated the absorption and distribution of TCDD in thoracic duct-cannulated rats. The results suggest that after gastrointestinal absorption, TCDD is absorbed primarily by the lymphatic route and is transported predominantly by chylomicrons. Ninety percent of the TCDD in lymph was associated with the chylomicron fraction. The plasma disappearance of TCDD-labeled chylomicrons followed first-order decay kinetics, with 67% of the compound leaving the blood compartment very rapidly ($t_{½}$=0.81 minutes), whereas the remainder of the TCDD had a $t_{½}$ of 30 minutes. TCDD was then found to distribute primarily to the adipose tissue and the liver.

In vitro studies have investigated the distribution of TCDD in human whole blood. Henderson and Patterson (1988) found ~80% of the compound associated with the lipoprotein fraction, 15% associated with protein (primarily human serum albumin), and 5% associated with cellular components. A subsequent in vivo investigation reported a similar distribution of TCDD in the various fractions of human whole blood (Patterson et al., 1989). Theoretical and limited experimental data also suggest that TCDD and related compounds may be associated with plasma prealbumin (McKinney et al., 1985; Pedersen et al., 1986). The distribution of [^{3}H]-2,3,7,8-TCDD among lipoprotein fractions from three fasting, normolipemic donors indicated a greater percentage associated with LDL (55.3% ± 9.03% SD) than with VLDL (17.4% ± 9.07% SD) or HDL (27.3% ± 10.08% SD). The distribution of TCDD among the lipoprotein fractions was similar to that reported earlier by Marinovich et al. (1983). When the binding of TCDD was calculated per mole of lipoprotein, it was suggested that the maximal binding capacity was exerted by VLDL, followed by LDL and HDL (Marinovich et al., 1983). The results also suggest that variations in the amounts of each lipoprotein class may alter the distribution of TCDD among lipoproteins in a given subject. Significant species differences also exist; in the case of the rat, which has markedly lower plasma lipids compared to humans, TCDD was distributed almost equally among the lipoprotein fractions (Marinovich et al., 1983).

Congener-specific differences have been observed for the in vivo binding of the 2,3,7,8-substituted PCDDs and PCDFs to different serum fractions in human blood (Patterson et al., 1989). Binding to the lipoproteins gradually decreased with increasing chlorine content, with about 75% of TCDD bound to lipoproteins while approximately 45% of OCDD was bound to this fraction. In contrast, binding to other serum proteins increased with chlorine content, from approximately 20% for TCDD to 50% for OCDD. The results indicate that the higher chlorinated PCDDs and PCDFs do not partition according to the lipid content of these blood fractions. However, Busbee and Zipring (1994) report that at least one lower chlorinated PCB, dichlorobiphenyl, absorbs and distributes with the nonlipid plasma fractions, rather than the lipid fractions as might be expected.

In addition, there is indirect evidence that suggests that the binding of TCDD to lipoproteins may alter the pharmacokinetics and toxic potency of the compound. Marinovich et al. (1983) found that experimentally induced hyperlipidemia in rats delayed the development of overt toxicity (lethality). However, the disposition of TCDD was not investigated under these conditions. These investigators suggest that the release of lipoprotein-bound TCDD is related to the metabolic turnover of lipoproteins. In hyperlipidemic rats, the turnover of VLDL and LDL is delayed significantly compared to that in normolipidemic animals, and this may contribute to the plasma lipoprotein binding modifying the toxicity of TCDD in hyperlipidemic rats.

The time- and temperature-dependent cellular uptake of lipoprotein-associated TCDD by cultured human fibroblasts was greatest from LDL, intermediate from HDL, and least from serum (Shireman and Wei, 1986). Decreased cellular uptake of LDL and TCDD was observed in mutant fibroblasts, which lack the normal cell membrane receptor for LDL. This provides some evidence that specific binding of LDL and the LDL receptor pathway may account for some of the rapid early uptake of TCDD with LDL entry. The results suggest that the entry of TCDD into cells may not be solely by simple diffusion. However, nonspecific binding of the LDL and transfer of TCDD from LDL to the cell membranes are probably also important, as significant time- and temperature-dependent uptake of TCDD and LDL occurred in the mutant fibroblasts.

Thus, upon absorption, TCDD and probably related compounds are bound to chylomicrons, lipoproteins, and other serum proteins that assist in distributing these uncharged, lipophilic compounds throughout the vascular system. These compounds then partition from blood components into cellular membranes and tissues, probably largely by passive diffusion. In addition, cellular uptake may be facilitated partly through the cell membrane LDL receptor, the hepatic receptor for albumin (Weisiger et al., 1981), and other systems.

1.2.2. Tissue Distribution

Once absorbed into blood, TCDD and related compounds readily distribute to all organs. Tissue distribution within the first hour after exposure parallels blood levels and reflects physiological parameters such as blood flow to a given tissue and relative tissue size. For example, high initial concentrations of TCDD, 1,2,3,7,8-PeCDF, and 3,3′,4,4′-TCB were observed in highly perfused tissue such as the adrenal glands during the 24-hour period after a single exposure (Birnbaum et al., 1980; Olson et al., 1980; Pohjanvirta et al., 1990; Brewster and Birnbaum, 1988; Durham and Brouwer, 1990). A high percentage of the dose of 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF was also found in muscle within the first hour after intravenous exposure because of the large volume of this tissue (Birnbaum et al., 1980; Birnbaum, 1985; Brewster and Birnbaum, 1988). Nevertheless, within several hours the liver, adipose tissue, and skin become the primary sites of disposition, when expressed as percent of administered dose per gram tissue

and as percent of dose per organ. Liver, adipose tissue, skin, and thyroid were the only tissues to show an increase in the concentration of TCDD during the initial 4 days after a single intra peritoneal exposure of rats (Pohjanvirta et al., 1990). In this study, a similar general pattern of disposition was observed in Han/Wistar and Long-Evans rats, which are, respectively, most resistant and susceptible to the acute toxicity of TCDD (Pohjanvirta et al., 1990).

Table 1-4 illustrates the tissue distribution of TCDD in female Wistar rats 7 days after a single subcutaneous exposure (Abraham et al., 1988). This general pattern of distribution is similar to that observed in mice, rats, rhesus monkeys, hamsters, and guinea pigs, where liver and adipose tissue consistently have the highest concentrations of TCDD (Piper et al., 1973; Fries and Marrow, 1975; Rose et al., 1976; Allen et al., 1975; van Miller et al., 1976; Kociba et al., 1978a,b; Gasiewicz et al., 1983b; Manara et al., 1982; Olson et al., 1980; Gasiewicz and Neal, 1979; Birnbaum, 1986; Pohjanvirta et al., 1990; Abraham et al., 1988). A similar pattern of disposition also was observed for 2,3,7,8-TCDF in the guinea pig, rat, C57BL/6J and DBA/2J mouse, and rhesus monkey, with 2,3,7,8-TCDF concentrations highest in liver and adipose tissue (Decad et al., 1981b; Birnbaum et al., 1980, 1981). In summary, there do not appear to be major species or strain differences in the tissue distribution of TCDD and 2,3,7,8-TCDF, with the liver and adipose tissue being the primary disposition sites. For the PCBs, Ness et al. (1994) provide evidence of accumulation of PCB congeners in rat brain. Dams were dosed with Aroclor 1242 and pups from litters were euthanized at weaning. No differences in PCB concentrations between sexes or among brain regions were found, but the different congeners differed from each other in degree of bioaccumulation.

The tissue distribution of the coplanar PCBs and PBBs also appears to be similar to that of TCDD and 2,3,7,8-TCDF. Limited studies in rats and mice found that 3,3′,4,4′-TCB, 3,3′,4,4′-TBB, and 3,3′,4,4′,5,5′-HxBB distributed preferentially to adipose tissue and liver (Clarke et al., 1983, 1984; Millis et al., 1985; Wehler et al., 1989; Clevenger et al., 1989). Lindenau et al. (1994) studied the distribution of PCBs in the reproductive tissues of female rabbits after long-term low-dose exposures. Chlorinated hydrocarbons were found to accumulate especially in oviductal and uterine tissues and in follicular and uterine fluids.

Although the liver and adipose tissue contain the highest concentrations of TCDD and 2,3,7,8-TCDF, there are some congener-specific differences in the relative tissue distribution of related compounds. 2,3,7,8-TBDD and 1,2,3,7,8-PeCDD disposition in the rat was very similar to that of TCDD (Kedderis et al., 1991a; Wacker et al., 1986). The hepatic concentration of OCDD and 2,3,4,7,8-PeCDF in the rat, however, was approximately 10- to 20-fold greater than that in adipose tissue, which generally contains the second highest levels of these compounds (Birnbaum and Couture, 1988; Norback et al., 1975; Williams et al., 1972; Brewster and Birnbaum, 1987). The tissue distribution of a defined mixture of CDDs and CDFs (28.8 μg

CDDs+CDFs/kg bw containing 120 ng TCDD/kg bw) was measured in marmoset monkeys 7 days after a single subcutaneous exposure (Abraham et al., 1990). For most of the 2,3,7,8-substituted congeners, the highest concentrations were detected in hepatic and adipose tissue, with correspondingly lower values detected in kidney, brain, lung, heart, thymus, or testes. The hepatic and adipose tissue concentrations were similar for TCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDF, and 1,2,3,7,8-/1,2,3,4,8-PeCDF. Nonetheless, the hepatic concentrations were approximately tenfold or more greater than those of adipose tissue for 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, and OCDF. The lungs and thymus contained higher concentrations of all of these congeners than were detected in kidney, brain, heart, and testes. Unexpectedly, the concentrations of these HxCDDs, HpCDDs, OCDD, and HxCDFs were similar in the adipose tissue, lungs, and thymus. In the case of HpCDFs and OCDF, the concentrations were greater in the lungs than in the adipose tissue. The enhanced disposition of highly chlorinated congeners to the lungs and thymus is of interest and deserves further investigation. For example, it is possible that the high concentration in the lungs could be related to the insolubility of these compounds. Further, Diliberto et al. (1995) report that in mice, the ratio of liver to adipose tissue concentration of TCDD changes with dose. As the dose increases, the adipose (and other nonhepatic tissues) tissue dose/g decreases while it increases in the liver. Section 1.2.5 of this document discusses induction of hepatic cytochrome P-450 1A2 (CYP1A2) as the primary factor responsible for the hepatic sequestration of TCDD and related compounds.

It is also to be expected that exposure to a mixture of these compounds can cause effects in the uptake and distribution. Darnerud et al. (1993) report on the effects of pretreatment of various PCBs on the hepatic uptake of 2,3,7,8-TCDF in mice. After a 4-hour pretreatment, several mono- and di-ortho PCB congeners and Aroclor 1254 increased the hepatic uptake of TCDF. Non-ortho congeners decreased the uptake of TCDF. At longer pretreatment times (48 hours), both non-ortho and mono-ortho PCBs increased the hepatic uptake of TCDF. These studies illustrate the complexity of the pharmacokinetics of mixtures.

Whole-body autoradiography of mice and rats after intravenous administration of [^{14}C]-2,3,7,8-TCDD showed a selective localization of radioactivity in the liver and nasal olfactory mucosa (Appelgren et al., 1983; Gillner et al., 1987). The selective localization of TCDD in the nasal olfactory mucosa was apparently overlooked by other distribution studies that only examined selected organs. Gillner et al. (1987) found no TCDD-derived radioactivity in the olfactory mucosa after solvent extraction of sections, suggesting that TCDD was not covalently bound in this tissue. In addition, Gillner et al. (1987) reported induction of mRNA coding for P-4501A2 (CYP1A2) in the absence of P-4501A1(CYP1A1) induction in olfactory mucosa of rats.

The selective distribution of 2,3,7,8-TCDD in the liver and olfactory mucosa correlates with the tissue-specific localization of CYP1A2, which represents a potential sequestration (binding) protein (see Section 1.2.5). Increases in the incidence of squamous cell carcinoma of nasal turbinates and carcinoma of the liver were observed in rats after a 2-year exposure to TCDD in rat chow (Kociba et al., 1978a); however, this effect was not observed in nasal tissues of mice or rats intubated with TCDD.

Evidence has also been reported that suggests that TCDD uptake and retention by the liver is dependent on the cell type within the liver. Hakansson et al. (1989) found that at 4 days after exposure of rats to TCDD, 60% of the dose distributed to hepatocytes and 12% was retained by stellate cells. Half-lives for TCDD in hepatocytes and stellate cells were calculated to be 13 and 50 days, respectively, suggesting that TCDD is more persistent in nonparenchymal cells. The induction of CYP1A2 in hepatocytes is the primary factor responsible for the hepatic sequestration of TCDD and related compounds (see Section 1.2.5 of this document).

1.2.2.1. *Tissue Distribution in Humans*

Fachetti et al. (1980) reported tissue concentrations of TCDD at levels of 1-2 ng/g in adipose tissue and pancreas, 0.1-0.2 ng/g in the liver, and ≤0.1 ng/g in thyroid, brain, lung, kidney, and blood in a woman who died 7 months after potential exposure to TCDD from the Seveso accident. This pattern of TCDD distribution, however, may not be representative for humans because the woman at the time of death had an adenocarcinoma (which was not considered related to the accident) involving the pancreas, liver, and lung.

Ryan et al. (1985a) examined the distribution of TCDD in two humans at autopsy. They determined on a weight basis that TCDD distributed in descending order to fat (~6 ppt) and liver (~2 ppt), with levels in muscle and kidney below detection; however, TCDD levels compared on a per lipid basis were similar between tissues. These data should be interpreted with caution because only two subjects were examined and one of the subjects was suffering from fatty liver syndrome; therefore, the data cannot be generalized to the entire population.

Poiger and Schlatter (1986) estimated that ~90% of the body burden of TCDD was sequestered in the fat after a volunteer ingested [^{3}H]-2,3,7,8-TCDD in corn oil at a dose of 1.14 ng/kg. During this 135-day study, elevated radioactivity was detected in the blood only during the first 2 days after treatment. The data would be consistent with the high lipid bioconcentration potential of TCDD in humans, as calculated by Geyer et al. (1986) from daily intake assumptions, levels in human adipose tissue, and pharmacokinetic models. Geyer et al. (1986) estimated a BCF of between 104 and 206 for TCDD in human adipose tissue.

In human adipose tissue, levels of TCDD averaging 5-10 ppt have been reported for background populations in St. Louis, Missouri, by Graham et al. (1986), in Atlanta and Utah by

Patterson et al. (1986), and in Canada by Ryan et al. (1985b). Sielken (1987) evaluated these data and concluded that the levels of TCDD in human adipose are log-normally distributed and positively correlated with age. Among the observed U.S. background levels of TCDD in human adipose tissue, more than 10% were >12 ppt.

Patterson et al. (1987) developed a high-resolution gas chromatographic/high-resolution mass spectrometric analysis for TCDD in human serum. The arithmetic mean of the individual human serum samples was 47.9 ppt on a whole-weight basis and 7.6 ppt on a lipid-weight basis. Paired human serum and adipose tissue levels of TCDD have been compared by Patterson et al. (1988), Kahn et al. (1988), and Schecter et al. (1990a). All three laboratories reported a high correlation between adipose tissue and serum TCDD levels when the samples were adjusted for total lipid content. This correlation indicates that serum TCDD is a valid estimate of the TCDD concentration in adipose tissue.

Congener-specific partitioning of 2,3,7,8-substituted PCDDs and PCDFs between adipose tissue and plasma lipids has also been reported in a study of 20 Massachusetts Vietnam veterans (Schecter et al., 1990b). The distribution ratio between plasma lipid and adipose tissue increased with chlorine substitution on the PCDDs and PCDFs. Whereas 2,3,7,8-substituted TCDD, TCDF, PeCDD, PeCDF, HxCDD, and HxCDF had a plasma lipid-to-adipose tissue ratio of about 1.0, OCDD had a ratio of 2.0. On the other hand, whole blood PCDDs and PCDFs seem to be found at the same concentrations as in adipose tissue on a lipid basis (Schecter, 1991).

The disposition of 2,3,7,8-substituted PCDDs and PCDFs in human liver and adipose tissue was assessed in a study of 28 people from the Munich area (Thoma et al., 1989; 1990). Table 1-5 summarizes these results, which are expressed both on a lipid and wet-weight basis. The concentrations of PCDDs and PCDFs in adipose tissue and liver are not the same when calculated on a lipid basis. This is in contrast to the high correlation that was reported between adipose tissue and serum TCDD levels when expressed on a lipid-weight basis (Patterson et al., 1988; Kahn et al., 1988; Schecter et al., 1990a). Furthermore, the liver/adipose tissue ratio increased with the higher chlorinated PCDDs and PCDFs. The congener-specific hepatic disposition is also similar to that observed in rats and marmoset monkeys exposed to a complex mixture of PCDDs and PCDFs (Abraham et al., 1989b; Neighbored et al., 1990). Therefore, it is important to consider congener- and tissue-specific differences in disposition of PCDDs and PCDFs when blood levels are used to estimate tissue levels or body burdens.

Schecter et al. (1998a) assessed the disposition of PCDDS, CDFS, and coplanar PBS in the blood, milk, adipose tissue, placenta, and cord blood from five American women. When expressed on a pg/g lipid basis, the mean total TEQs were 11.6, 12.1, 10.5, 5.8, 10.0, and 10.2 in adipose tissue, predelivery blood, placenta, cord blood, postpartum blood, and breast milk, respectively. The results suggest that CDDs, CDFs, and PCBs, when expressed as total TEQs on

a lipid basis, partition to a similar extent between these tissues. Even though 2,3,4,7,8-PeCDF and PCB 126 were lower in cord blood than other tissues, the levels of TCDD were similar in these tissues.

In a study of potentially heavily exposed Vietnam veterans, MMWR (1988) reviewed an Air Force study of Ranch Hand veterans who were either herbicide loaders or herbicide specialists in Vietnam. The mean serum TCDD levels of 147 Ranch Hand personnel was 49 ppt in 1987, based on total lipid weight, while the mean serum level of the 49 controls was 5 ppt. In addition, 79% of the Ranch Hand personnel and 2% of the controls had TCDD levels $\geq$10 ppt. The distribution of TCDD levels in this phase of the Air Force health study indicates that only a small number of Ranch Hand personnel had unusually heavy TCDD exposure. Similar results were obtained by Kahn et al. (1988), who compared TCDD levels in blood and adipose tissue of Agent Orange-exposed Vietnam veterans and matched controls (Kahn et al., 1988). This study also examined moderately exposed Vietnam veterans who handled herbicides regularly while in Vietnam. Although this study can distinguish moderately exposed men from others, the data do not address the question of identifying persons whose exposures were relatively low and who constitute the bulk of the population, both military and civilian, that may have been exposed to greater than background levels of TCDD.

1.2.3. Time-Dependent Tissue Distribution

2,3,7,8-TCDD and related compounds exhibit congener-specific disposition, which depends on tissue, species, and time after a given exposure. In general, these compounds are cleared rapidly from the blood and distributed to liver, muscle, skin, adipose tissue, and other tissues within the first hour(s) after exposure. This is followed by redistribution to the liver and adipose tissue, which exhibit increasing tissue concentrations over several days after exposure. Elimination from tissues then occurs at rates that are congener-, tissue-, and species-specific. Thus, the ratio of the concentration of TCDD and related compounds in different tissues (i.e., liver/adipose) may not remain constant over an extended period after a single exposure. Abraham et al. (1988) examined the concentrations of TCDD in liver and adipose tissue of female Wistar rats over a 91-day period after a single subcutaneous exposure at a dose of 300 ng/kg bw (Figure 1-1). The maximum concentration of TCDD in the liver and adipose tissue was reached at 3 and 7 days after exposure, respectively. The liver/adipose tissue concentration ratio does not remain constant over time because the concentration of TCDD decreases more rapidly in the liver than in the adipose tissue. For example, the liver/adipose tissue concentration ratio (for TCDD) was 10.3 at 1 day after exposure and 0.5 at 91 days after exposure (Figure 1-1). Results from other disposition studies also indicate that the ratio of the concentration of TCDD and related compounds in liver, adipose tissue, and other tissues does not remain constant over

an extended period after a single exposure (Pohjanvirta et al., 1990; Birnbaum, 1986; Birnbaum et al., 1980; Decad et al., 1981a; Birnbaum and Couture, 1988; Olson et al., 1980; Kedderis et al., 1993a; Brewster and Birnbaum, 1987, 1988; Neubert et al., 1990). This relationship is important in attempting to correlate dose-response data with tissue concentrations of TCDD and related compounds.

In an attempt to maintain constant TCDD levels in tissues to study long-term effects, Krowke et al. (1989) investigated several loading-dose/maintenance-dose exposure regimens. They found that similar liver/adipose tissue concentrations ranging from 5 to 8 could be maintained in rats over a 22-week period with a loading dose of 25 μg/kg followed by weekly maintenance doses of 5 μg/kg.

A large body of data on the tissue concentrations of TCDD and related compounds over time after exposure can be evaluated by estimating congener-specific half-life values for a given tissue and species. Table 1-6 summarizes pharmacokinetic elimination parameters for TCDD and related compounds from major tissue depots. Data from Abraham et al. (1988) (see Figure 1-1) were used to estimate the half-life for TCDD in the liver and adipose tissue of rats (Table 1-6). The decrease in the TCDD concentration in adipose tissue is a linear function in the semilogarithmic plot in Figure 1-1 (log concentration versus time), which indicates apparent first-order elimination kinetics with a half-life of 24.5 days (Table 1-6). Liver tissue exhibits a biphasic (two-component) exponential decay pattern, with a half-life of 11.5 days for the first component (days 10-49) and a half-life of 16.9 days for the second component (days 49-91) (see Figure 1-1 and Table 1-6). Santostefano et al. (1997) reported a similar half-life of approximately 10 days in female Sprague-Dawley rats administered a 10 μg/kg oral dose of TCDD/kg. Results of Abraham et al. (1988) and Lakshmanan et al. (1986) indicate that in the rat, TCDD is more persistent in the adipose tissue than in the liver. This is in contrast to the mouse, where liver and adipose tissue have similar half-lives (Birnbaum, 1986). TCDD is exceptionally persistent in the adipose tissue of the rhesus monkey, with a half-life approximately ten- to fortyfold greater than that observed in the rat and mouse (Bowman et al., 1989). Thus, the relative persistence of TCDD is tissue-specific and exhibits marked interspecies variability.

Most of the pharmacokinetic data on the relative persistence of other congeners in Table 1-6 have been reported in rat studies, which limits interspecies comparisons. Results in the rat suggest that the distribution and elimination of 2,3,7,8-TBDD from tissue are similar to those of 2,3,7,8-TCDD. The most persistent congeners are OCDD, 2,3,4,7,8-PeCDF, and 1,2,3,6,7,8-HxCDF, which distribute almost entirely to the liver. OCDD and 2,3,4,7,8-PeCDF also exhibit similar elimination kinetics, with a relative half-life in the liver more than twofold greater than that in adipose tissue. The least persistent congeners are 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, and 3,3′,4,4′-TCB. These congeners exhibit similar elimination kinetics in the rat, with half-lives in

the adipose tissue greater than those in liver. The relative tissue distribution of these congeners varies, however, with 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF distributing primarily to the liver while 3,3′,4,4′-TCB distributes predominantly to the adipose tissue.

Viluksela et al. (1997) conducted a subchronic/chronic toxicity study with 1,2,3,4,6,7,8-HpCDD (13 weeks of dosing, 13 week off-dosing) in Sprague-Dawley rats. Liver concentrations during the study provided a hepatic half-life estimate for 1,2,3,4,6,7,8-HpCDD of 237 days in male rats and 314 days in female rats. Under similar exposure conditions, TCDD had half-lives of 12.4 and 15.8 days in male and female rats, respectively. Liver concentrations of CDDs were also assessed in a subchronic/chronic toxicity study in rats administered a mixture of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, and 1,2,3,4,6,7,8-HpCDD orally in corn oil (13 weeks of dosing, 13 weeks of off-dosing) (Viluksela et al., 1998). Average liver half-lives were 14.5, 29.3, 45.6, and 100 days, respectively, in males and 17.8, 38.2, 63.3, and 195.8 days, respectively, in females. When administered individually, 1,2,3,4,7,8-HxCDD had liver half-lives of 36.2 days in males and 55.5 days in females and 1,2,3,7,8-PeCDD had a liver half-life of 36.1 days in male rats. Together, these results indicate that CDDs are more persistent in female rats and that the hepatic half-life of these compounds is similar following exposure to individual CDDs and mixtures of CDDs.

The experimental tissue distribution and elimination data in Table 1-6 were obtained after exposure to a single congener, but real-world exposure to TCDD and related compounds occurs as a complex mixture of congeners. Neubert et al. (1990) examined the persistence of various CDDs and CDFs in hepatic and adipose tissue of male and female marmoset monkeys. Animals received a single subcutaneous exposure to a defined CDD/CDF mixture (total dose of 27.8 μg/kg bw), which contained 0.12 μg 2,3,7,8-TCDD/kg bw. Using the international toxicity equivalency (I-TE) factors (NATO, 1988; U.S. EPA, 1989), the total administered dose corresponded to 0.464 μg I-TE/kg bw. The concentrations of specific congeners in liver and adipose tissue were measured at 1, 6, 16, or 28 weeks after exposure, and elimination constants and half-lives were estimated assuming first-order kinetics (Table 1-7). Data in Table 1-7 were determined from pregnant and nonpregnant female and male marmosets (total of 12 animals), because no obvious differences in tissue concentrations were observed among these groups. All 2,3,7,8-substituted CDDs and CDFs were consistently more persistent in the adipose tissue than in the liver of marmoset monkeys. In general, the persistence in adipose tissue was from ~1.3- to 2.0-fold greater than that in liver, with the exception of 1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF, HpCDFs, and OCDF, which were even more persistent in adipose tissue. For the latter congeners and OCDD, there was marked variance in half-life values, which may be due to delayed and incomplete absorption of the exceptionally persistent congeners and the relatively short (28 weeks) period of investigation. A significant species difference exists for OCDD and

2,3,4,7,8-PeCDF, which, in contrast to the results in the marmoset monkey, was found to be more persistent in the liver of the rat, with half-lives more than twofold greater than that in adipose tissue (Birnbaum and Couture, 1988; Brewster and Birnbaum, 1987) (see Table 1-6). Further comparison of tissue elimination data in the rat (Table 1-6) and monkey (Table 1-7) indicates that 2,3,7,8-TCDD, OCDD, 2,3,7,8-TCDF, 1,2,3,6,7,8-HxCDF, and 2,3,4,7,8-PeCDF (adipose tissue only) are more persistent in the marmoset monkey than in the rat. The exception to this relationship is 2,3,4,7,8-PeCDF, which is more persistent in rat liver compared to the monkey.

The exposure of marmoset monkeys to a complex mixture of CDDs and CDFs included exposure to both 2,3,7,8- and non-2,3,7,8-substituted congeners (Neubert et al., 1990). One week after exposure to this complex mixture, the non-2,3,7,8-substituted CDDs and CDFs were present in liver and adipose tissue in relatively minor quantities when compared with 2,3,7,8-substituted congeners; however, non-2,3,7,8-substituted compounds represented a considerable percent of the exposure mixture. In this study, none of the non-2,3,7,8-substituted TCDDs, PeCDDs, TCDFs, or PeCDFs could be detected in the liver. Some of the hexa- and hepta-congeners were detected in adipose tissue and liver, but after 1 week, the total amount in the liver was >5% of the administered dose only in the case of 1,2,4,6,8,9-HxCDF. Similar results were obtained in rats after exposure to a defined, complex mixture of CDDs and CDFs (Abraham et al., 1989c). Additional short-term studies in rats provide evidence that the low tissue concentrations of non-2,3,7,8-substituted congeners, measured 1 week after exposure, were the result of rapid elimination, as these congeners were detected at higher levels in the liver 13 to 14 hours after exposure (Abraham et al., 1989d). These results in monkeys and rats are compatible with data from analysis of human tissue samples and milk, in which the non-2,3,7,8-substituted congeners have also not been shown to be present in significant concentrations when compared with the 2,3,7,8-substituted congeners (Schecter et al., 1985, 1986; Ryan, 1986; Rappe et al., 1986; Beck et al., 1987, 1989; Thoma et al., 1989).

Several human studies also show the importance of time dependence and age on tissue distribution within the body. Duarte-Davidson and Jones (1994) reported that in a population in the United Kingdom adipose tissue concentrations of PCBs increased at a slower rate as age increased. The researchers attributed this to the dilution effect caused by the increase in body fat with age. Wolfe et al. (1994) reported similar findings with TCDD. They found significant increases in half-life with increases in percent body fat and with age. As will be discussed in a later section, body burden levels could also be decreasing with time because of reduced exposure levels (Furst et al., 1994).

Other recent studies also show that age is an important factor affecting distribution of these compounds within the body. Pegram et al. (1995) show that the hepatic concentration of

TCDD was about 25% greater in young mice than in old mice. No age-related differences in nuclear TCDD concentration was found in the liver fat tissue concentration ratios, adipose tissue, or blood concentrations. In old mice kidney, skin, and muscle concentrations were about twofold higher than in younger mice at a dose of 15 μg/kg. The authors suggest that these age-related differences represent differences in Ah receptor-mediated enzyme induction.

A potential problem of tissue distribution and elimination studies after exposure to a complex mixture of CDDs and CDFs is the possible interaction of the mixture during the uptake and elimination of specific congeners from tissues. A similar hepatic distribution (~25% of dose) and liver/adipose tissue concentrations ratio (~2) for TCDD were observed in rats 7 days after exposure to TCDD (100 ng/kg bw) when the compound was administered alone or in combination with a large amount of other CDDs/CDFs (total 23,222 ng/kg bw) (Abraham et al., 1988, 1989d). This suggests that under these experimental conditions, the tissue distribution of TCDD was not altered when the exposure included a complex mixture of CDDs/CDFs. van den Berg et al. (1989) studied the hepatic disposition and elimination of CDFs administered individually (see Table 1-6) and as mixtures. Co-administration of 1,2,3,7,8- and 2,3,4,7,8-PeCDF resulted in 46% of the dose of 1,2,3,7,8-PeCDF distributing to the liver, while 70% was distributed to the liver after administration of the single-compound (see Table 1-6). Nevertheless, this combined exposure did not alter the rate of elimination of 1,2,3,7,8-PeCDF from the liver. Co-administration of 2,3,4,7,8-PeCDF and 1,2,3,6,7,8-HxCDF did not alter the hepatic uptake of either congener or the hepatic elimination of 2,3,4,7,8-PeCDF but increased the hepatic half-life of 1,2,3,6,7,8-HxCDF to 156 days from the single-compound exposure half-life of 73 days (see Table 1-6). However, these values must be considered rough estimates because the experimental period of 42 days was too short to calculate half-lives accurately. Although there are few investigations of potential interactions of mixtures of CDDs and CDFs on the uptake and elimination of individual congeners, the limited available data suggest that exposure to complex mixtures (see Table 1-7) may alter the tissue disposition of individual congeners.

Several studies have investigated potential pharmacokinetic interactions following exposure to two or more PCDDs, PCDFs, or PCBs (DeJongh et al., 1992, 1993a, 1993b, van Birgelen et al., 1996a). Interactive effects on the hepatic disposition of these compounds may in some cases explain, in part, the potentiation and antagonistic effects on CYP1A1/1A2 activities observed with combined exposure to some of these compounds. In the case of 1,2,3,7,8-PeCDD and 2,4,5,2′,4′,5′-HxCB, no pharmacokinetic bases were found to explain the antagonistic effects of the combined exposure on CYP1A1/1A2 activities in mice (DeJongh et al., 1992). In a subsequent study the hepatic disposition of 1,2,3,7,8-PeCDD in mice was increased with combined exposures to 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PeCDF, and/or 2,4,5,2′,4′,5′ HxCB (De Jongh et al., 1993b).

De Jongh et al. (1995) report that TCDD co-administration with 2.2',4,4'5,5'-hexachlorobiphenyl (HxCB) in mice results in an increased disposition of TCDD in the liver. At the same time, the results do not show any effect of the TCDD on the HxCB disposition. The distribution of TCDD (0, 0.1, 1.0, or 10 μg/kg) and/or 2.2',4,4',5,5'-hexachlorobiphenyl (PCB 153; 0, 3.58, 35.8, or 358 mg/kg) were investigated alone and in all possible combinations of these doses following oral administration in corn oil to female B6C3F1 mice (van Birgelen et al., 1996b). Coadministration of the low doses of TCDD and PCB 153 had little or no effect on the distribution of either compound. Interactive effects on the pharmacokinetic behavior occurred only at high doses. For example, the hepatic disposition of TCDD increased when it was administered in combination with the highest dose of PCB 153. Although there is evidence that PCDDs, PCDFs, and PCBs may influence each other's pharmacokinetics when administered in mixtures, this area needs investigation.

1.2.4. Dose-Dependent Tissue Distribution

Recent evidence suggests that the tissue distribution of TCDD and related compounds is dose-dependent. Abraham et al. (1988) investigated the distribution of TCDD in liver and adipose tissue of rats 7 days after a single subcutaneous exposure to TCDD at doses of 1-3,000 ng/kg bw. More than 97% of the administered TCDD was absorbed at all doses, with the exception of the 3,000 ng/kg group, where 84% of the dose was absorbed. Figure 1-2 illustrates the dose-dependent disposition of TCDD in liver and adipose tissue (% dose/g) 7 days after exposure. A sharp increase in TCDD concentration in liver was observed at exposure levels >10 ng/kg bw. Disposition in the liver increased from ~11% of the administered dose at an exposure level of 1-10 ng/kg bw to ~37% of the dose at an exposure level of 300 ng/kg bw. The increase in distribution to the liver was accompanied by a dose-related decrease in the concentration of TCDD in the adipose tissue. As a result, the liver/adipose tissue concentration ratio for TCDD at 7 days after exposure increased with increasing doses, starting at an exposure level of 30 ng/kg bw (Table 1-8). Thus, the tissue-specific disposition of TCDD is regulated by a complex relationship, which includes species, time after a given exposure, and dose (see Figures 1-1 and 1-2; Tables 1-6 and 1-7).

Other studies on the tissue disposition of TCDD and related compounds report similar dose-dependent behavior with disproportionately greater concentrations in the liver at high doses compared with low doses. Poiger et al. (1989) observed a dose-related increase in distribution to the liver (% of dose/liver) and an increase in the liver/adipose tissue concentration ratio for 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDF, and 1,2,3,6,7,8-HxCDF in the rat. Kedderis et al. (1991a) also observed a dose-related increase in hepatic disposition (1.27% versus 10.05% of dose/liver) and an increase in the liver/adipose tissue concentration ratio (0.16 versus 2.59) for

2,3,7,8-TBDD at 56 days after exposure at doses of 0.001 and 0.1 μmol/kg bw, respectively. In a related study, pretreatment of mice with TCDD (5 or 15 μg/kg) produced a dose-related, enhanced hepatic accumulation of a subsequent oral dose of TCDD (Curtis et al., 1990). Diliberto et al. (1993b) also observed a dose-dependent tissue distribution of TCDD in female B6C3F1 mice. In all tissues except the liver, the relative percent of the total dose of TCDD decreased while it increased in the liver with higher doses. Similarly, a dose-related increase in hepatic uptake of [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-p-dioxin was observed after pretreatment of mice with TCDD (Poland et al., 1989a; Leung et al., 1990a). Shen and Olson (1987) also observed an increase in the uptake of TCDD by isolated hepatocytes from TCDD-pretreated mice.

Chronic studies also support dose-dependent alterations in the tissue distribution of these compounds. Kociba et al. (1978a,b) found that female rats maintained on a daily dietary TCDD intake of 100 ng for 2 years had an average TCDD content of 8,100 ppt in fat and 24,000 ppt in the liver. Rats given 10 ng/kg/day had an average of 1,700 ppt TCDD in the fat and 5,100 ppt in the liver. For both of these exposures the liver/adipose tissue concentration ratio of TCDD was ~3. At the lowest dose level of 1 ng/kg/day, both fat and liver contained an average of 540 ppt TCDD. Kociba et al. (1976) presented evidence that steady state had been reached by <13 weeks of feeding of TCDD.

Other studies do not support the dose-dependent tissue distribution of TCDD and related compounds described above. Rose et al. (1976) reported a lack of a dose-dependent accumulation of [^{14}C]-TCDD in male and female rat liver and adipose tissue following 7, 21, and 49 days of exposure at 0.01, 0.1, or 1.0 μg/kg/day, Monday through Friday. The rates of accumulation of TCDD-derived radioactivity were similar in fat, liver and whole body; however, the concentration in the liver was about fivefold greater than in fat. Brewster and Birnbaum (1987) also observed similar concentrations (% dose/g) of 2,3,4,7,8-PeCDF in liver, adipose tissue, and other tissues 3 days after oral exposure at doses of 0.1, 0.5, or 1.0 μmol/kg bw. These results conflict with the above studies, which support the dose-dependent tissue distribution of these compounds. An explanation for the lack of a dose-dependent accumulation is that all of the doses administered in the studies of Rose et al. (1976) and Brewster and Birnbaum (1987) were inducing hepatic CYP1A2, which is now known to be primarily responsible for the hepatic sequestration of these compounds (see Section 1.2.5).

The dose-dependent tissue distribution of TCDD and related compounds is a critical factor that must be considered in estimating the concentration of these compounds in human tissues after chronic low-level exposure. This is particularly important because the general human population is exposed to much smaller daily doses (possibly 0.3 pg TCDD/kg/day) than those used in experimental disposition studies. Owing at least partly to the long half-life of

TCDD in humans, however, this exposure results in concentrations of 3-18 pg/g in human adipose tissue (Leung et al., 1990b). Similar levels of TCDD in adipose tissue (14 pg/g) were observed in rats 7 days after subcutaneous exposure to 3 ng/kg bw (see Table 1-8) (Abraham et al., 1988). Under these experimental conditions, the liver/adipose tissue TCDD concentration was 0.74. Nonetheless, steady state was definitely not reached under these conditions, and with increasing time after exposure, this ratio may decrease, based on the observation that TCDD was more persistent in adipose tissue than in liver in rats exposed to 300 ng/kg bw (see Figure 1-1 and Table 1-6) (Abraham et al., 1988). Human data on the liver/adipose tissue concentration ratio of TCDD and related compounds are limited, but suggest that the ratio may vary by at least an order of magnitude between individuals. Leung et al. (1990b) observed a geometric mean adipose tissue TCDD concentration of 7.78 ppt in 26 individuals and a concentration in liver at about one-tenth of that in adipose tissue on a whole-weight basis. When measured on a total lipid basis, the concentrations of TCDD in both tissues were approximately the same. Thoma et al. (1990) reported a liver/adipose tissue TCDD concentration on a wet weight basis of 0.14, whereas on a lipid basis the ratio was 2.05 (Table 1-5). Considerable variability in CDD and CDF concentrations in liver and adipose tissues was also observed between individual marmoset monkeys (Neubert et al., 1990), suggesting that individual variability may also contribute to the difficulty in assigning a constant liver/adipose tissue ratio for CDDs and CDFs in humans and nonhuman primates.

1.2.5. Potential Mechanisms for Dose-Dependent Tissue Distribution

The observation that exposure to higher doses of TCDD and related compounds results in a disproportionately greater hepatic concentration of these compounds may be explained by a hepatic binding species that is induced by TCDD and other agonists for the Ah receptor. The studies of Voorman and Aust (1987, 1989) and Poland et al. (1989a, b) provide evidence that this binding species is CYP1A2.

Poland et al. (1989a, b) reported that TCDD and other Ah agonists (2,3,7,8-TCDF, β-naphthoflavone, 3,3′,4,4′,5,5′-hexabromobiphenyl) act through the Ah receptor to increase a liver binding species that increases the hepatic uptake of [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin (a radiolabeled isosteric analogue of TCDD) in vivo and binding of this radioligand to liver homogenate in vitro. Twenty-four hours after the administration of a non-AHH-inducing dose (1×10^{-10} mol/kg) of [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin to C576BL/6J mice, the hepatic concentration of radioactivity was 1%-2% of the administered dose, whereas in mice pretreated 48 hours earlier with an AHH-inducing dose of TCDD (1×10^{-7} mol/kg), the hepatic accumulation of radiolabel was 25%-30% of that administered. A similar, though less dramatic, effect was observed in vitro, with liver homogenate from TCDD-treated mice binding about four

times more [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin than homogenate from control mice. The administration of TCDD to C57BL/6J mice produced a dose-related stimulation of in vivo hepatic uptake of [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin, increased binding of radioligand to liver homogenate, and induction of hepatic activity, with an ED_{50} ranging from 1.5 to 4.0 × 10^{-9} mol/kg. In congenic C57BL/6J (Ah^d/Ah^d) mice, which express the lower affinity Ah receptor, the ED_{50} values for all three responses were shifted to doses that were about tenfold higher. The observed effects on hepatic disposition were tissue-specific, with no remarkable dispositional changes being observed in kidney, lung, spleen, small intestine, or muscle. This is significant in that TCDD and other agonists for the Ah receptor induce CYP1A1 in liver and other tissues, whereas CYP1A2 is apparently inducible only in liver (Tuteja et al., 1985; Gillner et al. 1987). Furthermore, the changes in hepatic disposition were not species-specific; similar responses were observed in guinea pigs, rats, mice, and hamsters (Poland et al., 1989a).

The following evidence reported by Poland et al. (1989b) supports the hypothesis that the TCDD-inducible hepatic binding protein is CYP1A2: the TCDD-induced hepatic binding species was found predominantly in the microsomal fraction and was inactivated by heating at 60°C, trypsin, and mercurials; the TCDD-induced hepatic binding species was specific for the liver, with a large pool size (B_{max} of 22 ± 5 nmol/g liver); the major microsomal binding species covalently labeled with the photoaffinity ligand [^{125}I]-2-iodo-3-azido-7,8-dibromodibenzo-*p*-dioxin migrates with that immunochemically stained with polyclonal antiserum, which binds to CYP1A2.

One observation of Poland et al. (1989a,b) does not support the hypothesis that the TCDD-inducible hepatic protein is CYP1A2. These investigators found that dietary administration of isosafrole did not stimulate hepatic uptake of [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin or the in vitro binding of this ligand to liver homogenate. Isosafrole is not an agonist for the Ah receptor, but it selectively induces CYP1A2 (Ryan et al., 1980). Poland et al. (1989a,b) suggest that this may be attributable to the high affinity binding of an isosafrole metabolite to the protein, which might inhibit the binding of [^{125}I]-iodo-3,7,8-trichlorodibenzo-*p*-dioxin to CYP1A2 at or near the active site of the enzyme. This does not explain why TCDD, which also has high affinity for CYP1A2, cannot displace some of the isosafrole metabolite from the protein, which should produce enhanced hepatic disposition of TCDD.

A more recent study used pretreatment with isosafrole to investigate the role of CYP1A2 in the hepatic disposition of TCDD (Kedderis et al., 1993a). Although isosafrole is an inducer of CYP1A2, it also has high affinity for the protein and thus is a selective inhibitor of CYP1A2. A greater than threefold decrease in the hepatic disposition of TCDD in isosafrole-pretreated rats supports the conclusion that TCDD is bound to CYP1A2 in the liver.

Olson et al. (1994) have reported the results of in-vitro studies with isolated hepatocytes and liver slices of rats pretreated with TCDD. Pretreatment increased the uptake of TCDD but not TCDF. There was an increase in both CYP1A1 and CYP1A2. The authors interpret these results as consistent with CYP1A2 being a hepatic binding protein for TCDD but not TCDF.

Voorman and Aust (1987, 1989) support further the hypothesis that CYP1A2 is the TCDD-inducible hepatic binding species. These investigators found that 3,3′,4,4′,5,5′-HxBB, an agonist for the Ah receptor, was associated only with CYP1A2 through the immunoprecipitation of CYP1A1 and 1A2, which were induced in 3,3′,4,4′,5,5′-HxBB-treated rats. In addition, they found that 3,3′,4,4′,5,5′-HxBB inhibited estradiol 2-hydroxylase activity of purified CYP1A2. A similar association of PAHs with immunoprecipitated CYP1A2 was observed for other agonists for the Ah receptor, including TCDD, 3,3′,4,4′-TCB, 3,3′,4,4′,5-PeCB, and 3,3′,4,4′,5,5′-HxCB. The association of TCDD with CYP1A2 occurred within 2 minutes, with maximum inhibition of estradiol 2-hydroxylase occurring at a concentration comparable to the concentration of the enzyme (50 nm). CYP1A2 was inhibited (complexed) by TCDD with nearly 1:1 stoichiometry, and the K_i for TCDD was calculated to be 8 nM. Therefore, TCDD can be considered a higher binding inhibitor of CYP1A2.

Santostefano et al. (1996) assessed the subcellular and tissue-specific disposition of TCDD in rats and mice. TCDD was equally distributed between the hepatic P9 (mitochondrial, lysosomal, and nuclear) and S9 (cytosol and microsomal) fractions, with the microsomal fraction retaining the TCDD present in the S9 fraction. In contrast, TCDD was retained in the P9 fractions of lung and liver at all doses tested. The lack of pulmonary or renal sequestration coupled with the lack of localization of TCDD to pulmonary and renal microsomes supports the role of CYP1A2 as a hepatic microsomal binding protein involved in the hepatic sequestration of TCDD. Recently, Santostefano et al. (1999) assessed the intralobular hepatic distribution of TCDD in rats and observed that centrilobular hepatocytes had a 2.7- to 4.5-fold higher concentration of TCDD than did periportal hepatocytes. The enhanced centrilobular distribution of TCDD was associated with elevated CYP1A2-mediated MROD activity and CYP1A2 mRNA in centrilobular hepatocytes.

The TCDD-induced binding species was found to have an apparent equilibrium dissociation constant, K_D, for [^{125}I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin of 56 ± 16 nM, and a pool size, B_{max}, of 22±5 nmol/g of liver in C57BL/6J mice (Poland et al., 1989b). The induced microsomal binding species has an affinity about 10^4 times less than the Ah receptor but a pool size that is ~2×10^3 greater. Thus, agonists for the Ah receptor may significantly affect their disposition through a dose-related enhancement of hepatic uptake, which should correlate with induction of CYP1A2.

More recently, Diliberto et al. (1997) used transgenic mice lacking the CYP1A2 gene to study the influence of CYP1A2 in the hepatic sequestration and distribution of TCDD, 2,3,4,7,8-PeCDF, and PCB 153 (2,2',4,4',5,5'-HexCB), a non-dioxin-like PCB. The liver/fat concentration ratios of these compounds in the parental lineage (C57BL6N and 129/Sv) were approximately 3.6, 18, and 0.07, respectively, indicating a high degree of hepatic sequestration for TCDD and 2,3,4,7,8-PeCDF. Under identical exposure conditions, the 1A2 knockout mice had liver/fat concentration ratios of 0.17, 0.34, and 0.10, respectively. Thus, in the absence of the CYP1A2 gene, mice exhibited no hepatic sequestration of these compounds. This study and a related study in CYP1A2 knockout mice by Diliberto et al. (1999) provide direct confirmation of the hypothesis that CYP1A2 is the dioxin-inducible hepatic binding protein responsible for the hepatic sequestration of TCDD and related compounds, such as 2,3,4,7,8-PeCDF.

The disposition and pharmacokinetics of 2,2′,4,4′,5,5′-HxCB and -HxBB have been investigated in several species (Tuey and Matthews, 1980; Lutz et al., 1984). These lipophilic compounds are similar to TCDD in that they are slowly metabolized and that metabolism is required for urinary and biliary elimination; however, they do not exhibit dioxin-like activity. 2,2′,4,4′,5,5′-HxCB and -HxBB distribute primarily to adipose tissue, with partition coefficients (tissue/blood ratio) ranging from 300 to 500 in the mouse, rat, monkey, dog, and human. The liver is not a major site for the disposition of 2,2′,4,4′,5,5′-HxCB and -HxBB, in contrast to TCDD and related compounds. Partition coefficients in the liver range from 10 to 30 in these species. 2,2′,4,4′,5,5′-HxCB and -HxBB do not induce hepatic CYP1A1 or 1A2 and do not exhibit dioxin-like activity. The lack of induction of hepatic CYP1A2 may explain the lack of a dose-dependent hepatic disposition of these compounds.

Kedderis et al. (1991b) assessed the dose-response relationship for the induction of hepatic CYP1A1 and 1A2 in male Fischer 344 rats exposed to 2,3,7,8-TBDD at doses as low as 0.1 nmol/kg. They reported that induction of P-4501A2 by 2,3,7,8-TBDD appeared to be a more sensitive response than P-4501A1 induction over the dose range studied. In addition, comparison of hepatic P-4501A2 levels and liver:adipose tissue concentration ratios suggested that induction of P-4501A2 alone would not directly account for the preferential hepatic accumulation of 2,3,7,8-TBDD and that additional factors must be involved. One explanation may be that at low 2,3,7,8-TBDD concentrations, endogenous substrates bind to CYP1A2, not allowing 2,3,7,8-TBDD to be sequestered by the protein (Kedderis et al., 1993b). At higher 2,3,7,8-TBDD concentrations, new protein is formed and 2,3,7,8-TBDD can compete for binding to CYP1A2, resulting in the increased hepatic disposition observed at higher exposures of 2,3,7,8-TBDD (Kedderis et al., 1991b).

The structure-activity relationship for the disposition and hepatic sequestration of CDDs, CDFs, and PCBs was investigated by DeVito et al. (1998). Female B6C3F1 mice were treated

for 13 weeks with different oral doses of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TBDD, 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, OCDF, PCB126 (3,3',4,4',5-PeCB), PCB169 (3,3'4,4',5,5'HxCB), PCB105 (2,3,3',4,4' PeCB), PCB118 (2,3',4,4',5-PeCB), and PCB156 (2,3,3',4,4',5-HxCB). All of these compounds exhibited dose-dependent increases in the liver/fat concentration except PCBs 105, 118, and 156. 4-PeCDF, PeCDD, OCDF, TCDF, and PCB126 were sequestered in hepatic tissue to a greater extent than was TCDD. Together, the results support the presence of an inducible protein (CYP1A2) and the congener-specific binding of some dioxin-like compounds to this hepatic sequestration protein.

Other factors may also regulate the intracellular distribution of TCDD and related compounds. The possible role of hepatic lipoproteins as intracellular carriers in the transport of TCDD has been assessed by in vitro and in vivo studies (Souès et al., 1989a,b). TCDD and 2,3,7,8-TCDF were bound to lipoproteins in mouse and rat liver, which subsequently underwent rapid and pronounced degradative processing, possibly catalyzed by lipoprotein lipase, to heavier entities. The in vitro incubation of TCDD-lipoprotein complex with separated Ah receptor demonstrated that a passive transfer occurred. The authors suggest a carrier role for lipoproteins in the intracellular transport of TCDD and related compounds.

1.3. METABOLISM AND EXCRETION

Although early in vivo and in vitro investigations were unable to detect the metabolism of TCDD (Vinopal and Casida, 1973; van Miller et al., 1976), there is evidence that a wide range of mammalian and aquatic species are capable of biotransforming TCDD to polar metabolites (Ramsey et al., 1979, 1982; Poiger and Schlatter, 1979; Olson et al., 1980; Olson, 1986; Gasiewicz et al., 1983a; Poiger et al., 1982; Sijm et al., 1990; Kleeman et al., 1986a,b, 1988). Although metabolites of TCDD have not been directly identified in humans, recent data regarding feces samples from humans in a self-dosing experiment suggest that humans can metabolize TCDD (Wendling et al., 1990).

Table 1-9 summarizes data on the metabolism and excretion of TCDD and related compounds after exposure to a single radiolabeled congener. Investigations of TCDD in rats, mice, guinea pigs, and hamsters found that >90% of the radiolabeled material excreted in urine and bile represented polar metabolites. Similar results were also observed for other congeners (see Table 1-9), with the exception of OCDD; however, studies were often limited to the rat. OCDD is apparently not metabolized by the rat, or metabolized to a very minimal extent (Birnbaum and Couture, 1988). For all of the congeners in Table 1-9, essentially all of the CDD, BDD, CDF, or PCB-derived radioactivity in liver, adipose tissue, and other tissues represented parent compound, suggesting that metabolites of these compounds were readily excreted. Thus, with the exception of OCDD, the metabolism of TCDD and related compounds is required for

urinary and biliary elimination and therefore plays a major role in regulating the rate of excretion of these compounds. In addition, direct intestinal excretion of parent compound is another route for excretion of TCDD and related compounds that is not regulated by metabolism.

1.3.1. Structure of Metabolites

Several metabolites of TCDD have recently been identified. Sawahata et al. (1982) investigated the in vitro metabolism of TCDD in isolated rat hepatocytes. The major product was deconjugated with β-glucuronidase, derivatized with diazomethane, and separated into two compounds by high-performance liquid chromatography. These metabolites were subsequently identified as 1-hydroxy-2,3,7,8-TCDD and 8-hydroxy-2,3,7-trichlorodibenzo--*p*-dioxin. Poiger et al. (1982) identified six metabolites in the bile of dogs that were given a lethal dose of [^{3}H]-2,3,7,8-TCDD. The major metabolite was 1,3,7,8-tetrachloro-2-hydroxydibenzo-*p*-dioxin; however, 3,7,8-trichloro-3-hydroxydibenzo-p-dioxin and 1,2-dichloro-4,5-hydroxybenzene were identified as minor metabolites. The structures of the three remaining metabolites were not determined; however, two appeared to be trichlorohydroxydibenzo-*p*-dioxins and the third was apparently a chlorinated 2-hydroxydiphenyl ether. Poiger and Buser (1984) reported differences in the relative amounts of various TCDD metabolites in dog and rat bile. Trichlorodihydroxy-dibenzo-*p*-dioxin and tetrachlorodihydroxydiphenyl ether appear to be major metabolites in rat bile. Furthermore, conjugates, presumably glucuronides, were formed in the rat but not in the dog. The investigators also observed a generally higher metabolism rate of TCDD in the dog. This finding is in good agreement with the unique ability of the dog to readily metabolize persistent PCBs such as 2,4,5,2′,4′,5′-HxCB (Sipes et al., 1982).

Biliary metabolites of 2,3,7,8-TCDF have been investigated by Poiger et al. (1984); however, unequivocal structure assignment of the metabolites could not be made using gas chromatography/mass spectroscopy. With the use of synthetic standards and GC/MS, Burka et al. (1990) identified 4-hydroxy-2,3,7,8-TCDF and 3-hydroxy-2,7,8-TCDF as major biliary metabolites of 2,3,7,8-TCDF in rats. Small amounts of 3-hydroxy-2,4,7,8-TCDF and 2,2′-dihydroxy-4,4′,5,5′-TCB were also detected. 4-Hydroxy-2,3,7,8-TCDF was also the major TCDF metabolite formed by hepatic microsomes from TCDD-pretreated rats (Tai et al., 1993). This suggests that the preferred site of metabolism of 2,3,7,8-TCDF is near the furan oxygen, with oxygenation at C4 predominating over C3. The authors speculate that epoxidation of the C4-C4a bond or the C3-C4 bond could lead to formation of the above metabolites. The results of Burka et al. (1990) and Sawahata et al. (1982) suggest that oxygenation of the unsubstituted carbon nearest the bridging oxygen in both 2,3,7,8-TCDF and TCDD is the major route of metabolism of these compounds in the rat. Furthermore, data on the rate of elimination of these compounds summarized in Tables 1-6 and 1-8 indicate that this reaction occurs at a faster rate for

the furan, since the rate of urinary and biliary elimination and resulting persistence of these compounds depend on metabolism.

Data summarized in Tables 1-6 and 1-9 indicate that 1,2,3,7,8-PeCDF is metabolized and eliminated at a greater rate than 2,3,4,7,8-PeCDF. The preference for oxygenation at C4 in 2,3,7,8-TCDF offers an explanation for the observation that 2,3,4,7,8-PeCDF is metabolized at a much slower rate than 1,2,3,7,8-PeCDF because one of the preferred sites for metabolism is blocked in the 2,3,4,7,8-substituted compound. The rate of metabolism of these compounds and their resulting relative persistence in rodents correlate with analysis of human tissues from the Yusho cohort, where the relative concentrations were 2,3,4,7,8-PeCDF > 1,2,3,7,8-PeCDF > 2,3,7,8-TCDF (Masuda et al., 1985).

Pluess et al. (1987) investigated the structure of 1,2,3,7,8-PeCDF metabolites in rat bile. A dihydroxy-tetra-CDF was identified as the major metabolite. The authors propose that this compound could be formed either via further oxidation of the hydroxy-tetra-CDF or possibly via hydrolytic dechlorination of a hydroxy-penta-CDF. Minor metabolites include dihydroxy-tri-CDF, hydroxy-tetra-CDF, and hydroxy-penta-CPF.

Pluess et al. (1987) also investigated the metabolites of 2,3,4,7,8-PeCDF in rat bile. A total of 10 metabolites were detected, with dihydroxy-penta-CB and hydroxy-penta-CDF representing the major metabolites. The biphenyl metabolite indicates that cleavage of the ether bridge of the furan is an important pathway for metabolism of this congener. Other less abundant metabolites of 2,3,4,7,8-PeCDF include hydroxy-tetra-CDF, dihydroxy-tri-CDF, dihydroxy-tetra-CDF, and thio-tetra-CDF. Sulfur-containing metabolites were also identified as minor metabolites of 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF in rats (Kuroki et al., 1990). These sulfur-containing metabolites probably arise from CDF-glutathione conjugates.

In another study, a dihydroxy-PeCDF was identified as the only detectable biliary metabolite of 1,2,3,6,7,8-HxCDF, while no metabolites of 1,2,3,4,6,7,8-HpCDF were detected in the bile of rats treated with this congener (Poiger et al., 1989).

Several in vivo and in vitro studies have investigated the metabolism of 3,3′,4,4′-TCB. Rat feces were found to contain 5-hydroxy-3,3′,4,4′-TCB and 4-hydroxy-3,3′,4′,5-TCB as major metabolites (Yoshimura et al., 1987) and 2,5-dihydroxy-3,3′,4,4′-TCB, 4,4′-dihydroxy-3,3′,5,5′-TCB, 5,6-dihydroxy-3,3′,4,4′-TCB, 4-hydroxy-3,3′,4-TCB, and 4-hydroxy-4′,5′-epoxy-3,3′,4′,5-TCB as minor metabolites (Koga et al., 1989).

Mouse feces were found to contain 5-hydroxy- and 6-hydroxy-3,3′,4,4′-TCB and 4-hydroxy-3,3′,4′,5-TCB, whereas urine contained 2-hydroxy-3,3′,4,4′-TCB in addition to these metabolites (Wehler et al., 1989). 3,3′,4,4′-TCB was the major compound present in mouse liver and a minor portion was due to 4-hydroxy-3,3′,4,4′-TCB (Wehler et al., 1989). Darnerud et al. (1986) found 2-hydroxy-3,3′,4,4′-TCB and methylsulphonyl-TCB as major metabolites in the

mouse fetus. Sulfur-containing metabolites of non-co-planar, nondioxin-like PCBs have also been reported to accumulate in the bronchial mucosa and uterine luminal fluid of mice (Bergman et al., 1979; Brandt et al., 1982) and in human lung, liver, and adipose tissue (Haraguchi et al., 1986, 1989). PCB methyl sulfones are stable lipophilic metabolites formed by the mercapturic acid pathway. The toxicological significance of these metabolites of nondioxin-like PCBs remains generally unknown.

1.3.2. Toxicity of Metabolites

The discussion above indicates that metabolism of TCDD and related compounds is required for urinary and biliary elimination and thus plays a major role in regulating the rate of excretion of these compounds. At present, metabolism is also generally considered a detoxification process.

Data on the metabolism of TCDD suggest that reactive epoxide intermediates may be formed. Poland and Glover (1970) investigated the in vivo binding of [1,6-^{3}H]-2,3,7,8-TCDD-derived radioactivity to rat hepatic macromolecules and found maximum levels equivalent to 60 pmol of TCDD/mol of nucleotide in RNA and 6 pmol of TCDD/mol of nucleotide in DNA. This corresponds to one TCDD-DNA adduct per 35 cells. These investigators suggest that it is unlikely that TCDD-induced oncogenesis is through a mechanism of covalent binding to DNA and somatic mutation. Further studies of TCDD and related compounds are needed to confirm these results and assess the relationship between covalent binding and the short- and long-term toxicity of these compounds.

Weber et al. (1982a) investigated the toxicity of TCDD metabolites by administering extracts of bile from TCDD-treated dogs to male guinea pigs in single oral doses equivalent to 0.6, 6.0, and 60 μg/kg of parent compound. Other groups of guinea pigs were given bile extract from untreated dogs or TCDD itself. A comparison of the mortality data at 5 weeks after dosing indicated that the acute toxicity of TCDD to guinea pigs was at least 100 times higher than the acute toxicity of its metabolites.

Mason and Safe (1986) synthesized 2-hydroxy-3,7,8-TCDD and 2-hydroxy-1,3,7,8-TCDD, which are metabolites of TCDD, and assessed the toxicity of these compounds in male Wistar rats. The compounds produced no significant effect on body weight gain and thymus, liver, or spleen weights after exposure to a dose of ≤5,000 μg/kg bw. 2-Hydroxy-3,7,8-TCDD induced hepatic microsomal AHH, EROD, and 4-chlorobiphenylhydroxylase activity at exposures of 1,000 and 5,000 μg/kg bw, whereas 2-hydroxy-1,3,7,8-TCDD was inactive as an inducer. Thus, while 2-hydroxy-3,7,8-TCDD has dioxin-like activity as an inducer of the hepatic monooxygenase system, the potency of the metabolite is more than three orders of magnitude

less than that of TCDD. Furthermore, results are consistent with the expected rapid conjugation and excretion of these TCDD metabolites (Weber et al., 1982b).

Metabolism of co-planar PCBs and PBBs also appears to be a detoxification process. 5-Hydroxy-3,3′,4,4′-TCB and 4-hydroxy-3,3′,4′,5-TCB did not produce liver hypertrophy, induction of hepatic AHH or DT-diaphorase activities, or thymus atrophy (Yoshimura et al., 1987). Thus, monohydroxy metabolites of 3,3′,4,4′-TCB are much less toxic than the parent compound. Further evidence for metabolism as a detoxification process comes from comparison of the metabolism and toxicity of two co-planar PBBs. Millis et al. (1985) found that 3,3′,4,4′,5,5′-HxBB exhibited greater toxic potency in rats than 3,3′,4,4′-TBB, even though 3,3′,4,4′-TBB had about a 10-fold greater affinity for the Ah receptor. Although receptor binding affinities imply that 3,3′4,4′-TBB should be more toxic than 3,3′,4,4′5,5′-HxBB, it was less toxic than the HxBB because 3,3′,4,4′-TBB was metabolized at a much greater rate than 3,3′,4,4′,5,5′-HxBB. In addition to supporting metabolism as a detoxification process, the results of Millis et al. (1985) also suggest that receptor binding and in vitro AHH induction do not accurately reflect toxicity for PAHs, which are more readily metabolized, presumably because continued occupation of the receptor is required for toxicity.

Structure-activity studies of TCDD and related compounds support the widely accepted principle that this parent compound is the active species. The relative lack of activity of readily excreted monohydroxylated metabolites of TCDD and 3,3′4,4′-TCB suggests that metabolism is a detoxification process necessary for the biliary and urinary excretion of these compounds. This concept has also been generally applied to TCDD-related compounds, although data are lacking on the structure and toxicity of metabolites of other CDDs, BDDs, CDFs, BDFs, PCBs, and PBBs.

It is possible that low levels of unextractable and unidentified metabolites may contribute to one or more of the toxic responses of TCDD and related compounds. Further studies on the nature of the biotransformation products of these compounds will help address this uncertainty.

1.3.3. Autoinduction of Metabolism

Accurate rate constants for metabolism are important in developing pharmacokinetic models that describe the disposition of TCDD and related compounds. Metabolism plays a major role in regulating the excretion and relative persistence of these compounds because metabolism is required for urinary and biliary excretion. Although the relative rate of metabolism of TCDD and related compounds can be estimated from tissue and excretion half-life data (see Tables 1-6 and 1-9), other factors such as relative body composition, hepatic and extrahepatic binding proteins, and direct intestinal elimination of the parent compound can also regulate the excretion of TCDD and related compounds. Therefore, in vivo disposition data (see

Tables 1-6 and 1-9) provide only a limited approximation of the relative rate of metabolism of a specific congener in a given species. In vivo disposition data were also obtained at exposures that were associated with induction of CYP1A1 and 1A2 and other potentially adverse responses that could alter metabolism and disposition. Therefore, it may not be appropriate to directly extrapolate these data to predict the pharmacokinetics at low levels of exposure. Low-dose extrapolations can be assisted by assessments of the potential for autoinduction of metabolism that may occur at exposures associated with enzyme induction. Characterization of the dose-dependent disposition of TCDD and related compounds is particularly important in the extrapolation of high-exposure animal data to low-exposure human data.

The excretion of metabolites of TCDD and related compounds into bile represents a direct means for estimating the rate of metabolism because biliary elimination depends on metabolism and is the major route for excretion of these compounds. The rate of metabolism of CDFs was estimated from the relative abundance of metabolites in rat bile (Poiger et al., 1989). The rates of biotransformation of 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, and 1,2,3,6,7,8-HxCDF were characterized as fairly high, moderate, low, and very low, respectively. Kedderis et al. (1991b, 1993a) observed 10% of the dose of [^{3}H]-2,3,7,8-TBDD excreted in bile 5 hours after intravenous administration of 1 nmol/kg to male Fischer 344 rats. All biliary radioactivity was attributable to metabolites. This rate of elimination is similar to the fecal excretion (~8% of the dose) 24 hours after intravenous administration of 1 nmol/kg [^{3}H]-2,3,7,8-TBDD (Kedderis et al., 1991a) and reflects the effect of intravenous bolus versus oral administration on distribution and elimination. The large percent dose excreted within the first few days may also be due to a rapidly excreted impurity in the radiolabeled 2,3,7,8-TBDD (Kedderis et al., 1993a). To assess the ability of TCDD and 2,3,7,8-TBDD to induce their own metabolism (biliary elimination), rats were pretreated with 100 nmol/kg, per of, of each compound 3 days prior to intravenous injection of 1 nmol/kg of the respective [^{3}H]-congeners. Biliary excretion of the radiolabeled dose was quantitatively and qualitatively unaffected by pretreatment, despite a twofold increase in hepatic levels of [^{3}H] in the pretreated animals and significant induction of CYP1A1 and 1A2 (Kedderis et al., 1991b). Therefore, under these conditions, autoinduction of TCDD and 2,3,7,8-TBDD metabolism did not occur in the rat in vivo at doses that elicited enhanced hepatic uptake. Similarly, Curtis et al. (1990) observed no change, or even an apparent decrease, in gastrointestinal contents and fecal elimination of TCDD equivalents in pretreated versus naive mice 24 hours after oral administration of [^{14}C]-2,3,7,8-TCDD, despite significantly enhanced levels of TCDD in the livers of pretreated mice.

Although the above studies suggest that autoinduction of TCDD metabolism does not occur, other results indicate that metabolism may be induced under certain conditions. Poiger and Buser (1984) observed a small yet significant increase in biliary excretion over a 72-hour

period, with pretreated rats (10 μg/kg, intraperitoneal) excreting 9.7±1.9% of the radiolabeled dose of TCDD (200-300 μg/kg, per of) compared with 7.0±0.9% excreted by naive animals. In addition to being small changes, these results were obtained using a dose of TCDD in excess of the LD_{50} in the rat. Poiger and Schlatter (1985) examined the influence of pretreatment with phenobarbital and TCDD on the biliary excretion of [^{3}H]-2,3,7,8-TCDD metabolites in a dog given a single oral dose of the [^{3}H]-congener (31 or 33.8 ng/kg). Without pretreatment, 24.5% of the absorbed dose was excreted in the bile within 110 hours. Phenobarbital did not alter this rate, whereas pretreatment with TCDD (10 μg/kg) 9 days earlier resulted in a doubling of the amount of metabolites excreted in bile (47.4%). Although this observation is limited to one dog and requires further investigation, the results suggest that significant autoinduction of TCDD metabolism and biliary excretion may occur in the dog. Nonetheless, the small increase in metabolism and biliary excretion of TCDD in the rat observed by Poiger and Buser (1984) and the negative results of Kedderis et al. (1991b; 1993a) and Curtis et al. (1990) suggest that autoinduction of TCDD metabolism and biliary excretion in the rat may not occur or occurs to an extent that is not biologically relevant.

More recently, Jackson et al. (1998) investigated the effects of age, sex, and pretreatments with phenobarbital, dexamethasone, and 1-aminobezotriazole (a CYP450 inhibitor) to modulate the rate of metabolism-dependent biliary elimination of TCDD in F344 rats. Biliary excretion of TCDD-derived radioactivity was measured over a 6-hour period following iv administration. Male adult and juvenile rats and female juvenile rats excreted from 0.63% to 0.68% of the administered dose, while adult females, male senescent, and male adults pretreated with the above drugs excreted from 0.28% to 0.45% of the dose of TCDD in bile. The results suggest some variability in the metabolism-dependent biliary excretion of TCDD-derived radioactivity; however, the differences between groups were not great.

Limited data suggest that autoinduction of metabolism and biliary excretion does occur for CDFs. Pretreatment of rats with 2,3,7,8-TCDF (1.0 μmol/kg, 3 days earlier) significantly increased the biliary excretion of a subsequent dose of [^{14}C]-2,3,7,8-TCDF (McKinley et al., 1993). The naive rats excreted 5.69±2.35% of the dose over the initial 8 hours, while the pretreated rats excreted 13.18±3.15% of the [^{14}C]-2,3,7,8-TCDF. Similarly, pretreatment of rats with 2,3,4,7,8-PeCDF (500 μg/kg, per of, 3 days earlier) resulted in a twofold increase in the biliary elimination of a subsequent dose of [^{14}C]-2,3,4,7,8-PeCDF (Brewster and Birnbaum, 1987). These results suggest that pretreatment with 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF induces the metabolism of these congeners.

3,3′,4,4′-TCB and 3,3′,4,4′-TBB appear to be metabolized by a 3-methylcholanthrene-inducible form of hepatic CYP(1A1 or 1A2), which is also induced by 3,3′,4,4′-TCB (Shimada

and Sawabe, 1983; Mills et al., 1985; McKinley et al., 1993). This suggests that these compounds can induce their own rate of metabolism and subsequent excretion.

Isolated hepatocytes in suspension culture have been demonstrated to provide a useful in vitro system for studying the hepatic metabolism of TCDD under the same conditions in species that have a wide range of sensitivity to the compound (Olson et al., 1981). The in vitro rate of metabolism of TCDD in guinea pig, rat, C57BL/6J mouse, DBA/2J mouse, and hamster hepatocytes was estimated to be 0.2, 1.2, 1.1, 0.9, and 1.2 pmol/mg protein/hour, respectively (Wroblewski and Olson, 1985, 1988; Shen and Olson, 1987). These results indicate that TCDD is metabolized by the guinea pig liver at a rate about fivefold less than that observed for the rat, mouse, and hamster. The limited ability of the guinea pig to metabolize TCDD can explain the limited excretion of TCDD metabolites in feces, which represents the major route for TCDD excretion (Olson, 1986). In addition, the limited metabolism in the guinea pig may partly explain the relatively long excretion half-life for TCDD in the guinea pig and may contribute to the remarkable sensitivity of the guinea pig to the acute toxicity of this agent (Olson, 1986).

Isolated hepatocytes in suspension culture have been used as an in vitro system for studying the autoinduction of metabolism of TCDD and related compounds. Wroblewski and Olson (1988) investigated the metabolism of [^{14}C]-2,3,7,8-TCDD (2.2 μM) in hepatocytes isolated from untreated TCDD-, 3-MC-, isosafrole-, and phenobarbital-pretreated rats and hamsters. In both species, TCDD and 3-MC pretreatments elevated the rate of TCDD metabolism by five- to sixfold, while phenobarbital pretreatment had no effect. Isosafrole produced a 1.8- to 2.5-fold increase in metabolism. These in vitro results at a high substrate concentration (2.2 μM) indicate that TCDD can induce its own rate of metabolism in the rat and hamster. In contrast, TCDD was not able to induce its own rate of metabolism in guinea pig and mouse hepatocytes (Wroblewski and Olson, 1985; Shen and Olson, 1987). Together, these results indicate that TCDD is metabolized in the liver by a TCDD-inducible enzyme, which is expressed in the rat and hamster but not in the guinea pig and mouse. More recently, the kinetics of TCDD metabolism were investigated in isolated rat hepatocytes incubated with [^{3}H]-2,3,7,8-TCDD at concentrations of 0.01, 0.1, and 1.0 μM (Olson et al., 1994). Lower TCDD concentrations in the media result in concentrations in hepatocytes that are more similar to the levels in the liver after in vivo exposure. For example, the concentration of TCDD in hepatocytes incubated at 0.01 μM is similar to hepatic levels after in vivo exposure of rats at a dose of ~10 μg/kg. At 0.01 and 0.1 μM, the rate of metabolism of [^{3}H]-2,3,7,8-TCDD was

similar in hepatocytes isolated from control and TCDD-pretreated rats, whereas at 1.0 μM, [^{3}H]-2,3,7,8-TCDD metabolism was greater in hepatocytes isolated from TCDD-pretreated rats. The results indicate that TCDD can induce its own rate of metabolism in the rat, but only at high hepatic concentrations, which are generally not attained after in vivo exposure. Therefore, in vitro studies of the hepatic metabolism of TCDD (at 0.01 and 0.1 μM) are consistent with the lack of autoinduction of TCDD metabolism and biliary excretion observed in vivo in the rat (Kedderis et al., 1991b; Curtis et al., 1990).

The metabolism of [^{3}H]-2,3,7,8-TCDF was also investigated in isolated rat hepatocytes incubated at concentrations of 0.01, 0.1, and 1.0 μM (Olson et al., 1994). At all concentrations, hepatocytes from TCDD-pretreated rats metabolized 2,3,7,8-TCDF at a rate from 4- to 25-fold greater than that observed in hepatocytes from control rats. The results indicate that 2,3,7,8-TCDF is metabolized in rat liver by a TCDD-inducible enzyme, possibly CYP1A1 or 1A2. These in vitro results support the in vivo autoinduction of 2,3,7,8-TCDF metabolism and biliary elimination observed in the rat (McKinley et al., 1993).

2,3,7,8-TCDF metabolism was also investigated in rat liver, kidney, and lung microsomes in the presence and absence of selective chemical inhibitors and antibodies to CYP1A1 and CYP1A2 (Tai et al., 1993). Together, the results of this investigation indicate that CYP1A1 is the primary enzyme responsible for the metabolism of 2,3,7,8-TCDF. 2,3,7,8-TCDF was also metabolized by recombinant yeast microsomes expressing human CYP1A1 and reductase. However, based on EROD activity, a marker of CYP1A1, the relative rate of 2,3,7,8-TCDF metabolism was about 100-fold greater in TCDD-induced rat liver microsomes than in yeast microsomes expressing human CYP1A1 and reductase (Tai et al., 1993). Although 2,3,7,8-TCDF was metabolized by rat and human CYP1A1, the results indicated that there are marked quantitative differences in metabolism that suggest that 2,3,7,8-TCDF will be more persistent in humans.

In summary, there are in vivo and in vitro data suggesting that autoinduction of TCDD and 2,3,7,8-TBDD metabolism does not occur in the rat after exposure to sublethal doses of these agents. This is in contrast to 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF, where in vivo and in vitro results support the autoinduction of metabolism and biliary elimination of these compounds in the rat.

1.3.4. Excretion in Animals

Data regarding the excretion of 2,3,4,7-TCDD and related compounds after exposure to a single radiolabeled congener (see Table 1-9) support the assumption of a first-order elimination process consisting of one or more components. These studies show that TCDD was excreted slowly from all species tested, with half-lives ranging from 11 days in the hamster to 2,120 days

in humans. TCDD is exceptionally persistent in humans relative to other animal models. Elimination data in tissues (see Tables 1-6 and 1-7) also indicate that TCDD and related compounds are exceptionally persistent in nonhuman primates (Bowman et al., 1989; Neubert et al., 1990). These differences may also be in part related to the dose dependency of the excretion of these compounds. In general, the congener- and species-specific rates of elimination of TCDD and related compounds from major tissue depots (see Table 1-6) are similar to the excretion data summarized in Table 1-9.

In the Syrian Golden hamster, the mammalian species least sensitive to the acute toxicity of TCDD, excretion occurred readily through both the urine (35% of administered dose, 41% of total excreted radioactivity) and feces (50% of the administered dose, 59% of total excreted radioactivity) (Olson et al., 1980). A similar excretion pattern, with significant urinary elimination, was observed in mice, although there was significant strain variability (Gasiewicz et al., 1983b; Birnbaum, 1986). In all the other species, excretion occurred mainly through the feces, with relatively minor amounts of TCDD metabolites found in the urine (Piper et al., 1973; Allen et al., 1975; Olson, 1986; Rose et al., 1976; Gasiewicz and Neal, 1979; Pohjanvirta et al., 1990). Results in Table 1-9 also indicate that fecal elimination was the primary route for the excretion of 1,2,3,7,8-PeCDD, OCDD, 2,3,7,8-TBDD, 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, and 3,3′,4,4′-TCB. Only Piper et al. (1973) reported the excretion of metabolites in the expired air. During 21 days following administration of a single oral dose of [^{14}C]-2,3,7,8-TCDD to rats, 3.2% of the administered radioactivity (4.6% of the excreted radioactivity) was recovered in the expired air.

Studies in the rat, guinea pig, hamster, and mouse have found that essentially all of the TCDD-derived radioactivity excreted in the urine and bile corresponds to metabolites of TCDD (see Table 1-9). The apparent absence of TCDD metabolites in liver and fat suggests that, once formed, the metabolites of TCDD are excreted readily. Thus, urinary and biliary elimination of TCDD depends on metabolism of the toxin. The more limited data for other compounds also suggest that this relationship may be true for 1,2,3,7,8-PeCDD, 2,3,7,8-TBDD, 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, and 3,3′,4,4′-TCB (see Table 1-9).

Although urine and bile appear to be free of unmetabolized TCDD, data indicate that TCDD and its metabolites are excreted in the feces of guinea pigs, rats, mice, and hamsters treated with [^{3}H]- or [^{14}C]-2,3,7,8-TCDD (see Table 1-9). Whereas 15% to 35% of the TCDD-derived radioactivity in rat, mouse, and hamster feces represents unchanged TCDD, 81% of the radioactivity in guinea pig feces represents unmetabolized TCDD (Olson, 1986; Neal et al., 1982; Gasiewicz et al., 1983b; Olson et al., 1980). The daily presence of unchanged TCDD in feces and its absence in bile suggest that direct intestinal elimination may be the source for the fecal excretion of TCDD. Data also suggest that direct intestinal elimination of parent compound

contributes to the fecal excretion for 2,3,7,8-TBDD (Kedderis et al., 1991a). Direct intestinal elimination of the parent compound may occur for other congeners (see Table 1-9), but this conclusion cannot be made at this time because of the lack of experimental data. Nonetheless, the species-specific fecal excretion of 2,3,7,8-TCDF is very similar to that observed for TCDD, with >90% of the 2,3,7,8-TCDF-derived radioactivity excreted in guinea pig feces representing parent compound (Decad et al., 1981a). In addition, the excretion of unchanged CDDs and CDFs was detected in rat feces after subcutaneous exposure to a defined mixture of congeners (Abraham et al., 1989d). Studies in lactating rats have also found that unchanged TCDD may be excreted in the milk of lactating animals (Moore et al., 1976; Lucier et al., 1975; Nau et al., 1986). Lactation, direct intestinal elimination, and perhaps sebum may serve as routes for excretion of TCDD that do not depend on metabolism of the toxin. These data suggest that the in vivo half-life for elimination of TCDD and related compounds provides only an approximation of the rate of metabolism of these compounds in a given animal. The results in Table 1-9 suggest that 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, and 3,3′,4,4′-TCB are metabolized and excreted more rapidly than 2,3,7,8-TCDD, 2,3,7,8-TBDD, 1,2,3,7,8-PeCDD, 2,3,4,7,8-PeCDF, and OCDD.

The rate of excretion of TCDD and related compounds is species- and congener- specific (see Table 1-9). TCDD is most persistent in human and nonhuman primates. In the hamster, the least sensitive species to the acute toxicity of TCDD, the mean $t_{½}$ was 10.8 days (Olson et al., 1980), and in the guinea pig, the most sensitive species to the acute toxicity of TCDD, the mean $t_{½}$ was 94 days (Olson, 1986). 2,3,7,8-TCDF was also most persistent in the guinea pig, with a $t_{½}$ of 20 to 40 days (Decad et al., 1981a; Ioannou et al., 1983). Furthermore, results indicate that the relatively limited ability of the guinea pig to metabolize TCDD and -TCDF may contribute to the greater persistence and greater acute toxicity of these congeners in the guinea pig.

The tissue distribution, metabolism, and excretion of TCDD were also investigated in Han/Wistar and Long-Evans rats, which were, respectively, more resistant (LD_{50}>3,000 μg/kg) versus more susceptible (LD_{50} ~10 μg/kg) to the acute toxicity of TCDD (Pohjanvirta et al., 1990). The results suggest that the metabolism and disposition of TCDD do not have a major role in explaining the strain differences in toxicity.

The intraspecies differences in the $t_{½}$ of TCDD in three mouse strains may be due to the finding that the DBA/2J strain possesses about twofold greater adipose tissue stores than the C57BL/6J and B6D2F_1/J strains (Gasiewicz et al., 1983b). The sequestering of the lipophilic toxin in adipose tissue stores of the DBA/2J mouse may contribute to the greater persistence of TCDD in this strain. Birnbaum (1986) examined the effect of genetic background on the distribution and excretion of TCDD in two sets of congenic mouse strains in which the congenic pairs differed only at the Ah locus. The Ah locus had no effect on the tissue distribution or excretion of TCDD. Thus, the distribution and excretion of TCDD were primarily governed by

the total genetic background rather than the allele present at the Ah locus. These findings are consistent with the in vitro results of Shen and Olson (1987), who found that the hepatic uptake and metabolism of TCDD did not correlate with genetic differences at the murine Ah locus. However, it is important to note that all of these are relatively high-dose studies, which may not allow for detection of Ah receptor-mediated effects on disposition.

Although the dose-related tissue distribution of TCDD and related compounds has been described recently, very limited data are available on the dose-related excretion of these compounds. Rose et al. (1976) investigated the elimination of [^{14}C]-2,3,7,8-TCDD in rats given repeated oral doses of 0.01, 0.1, or 1.0 μg/kg/day Monday through Friday for 7 weeks or a single dose of 1.0 μg/kg. In the single-dose study, no ^{14}C was excreted in the urine or expired air; in the repeated-dose study, however, 3% to 18% of the cumulative dose was excreted in the urine by 7 weeks. This study indicated that steady-state concentrations will be reached in the bodies of rats in ~13 weeks. The rate constant defining the approach to steady-state concentrations was independent of the dose of TCDD over the range studied. Relatively small changes in the excretion of 2,3,7,8-TBDD were also observed after exposures at 1 and 100 nmol/kg (Kedderis et al., 1991a). These results are consistent with the in vivo and in vitro evidence suggesting that autoinduction of TCDD and 2,3,7,8-TBDD metabolism does not occur in the rat after exposure to sublethal doses of these compounds (Kedderis et al., 1991b; Curtis et al., 1990; Olson et al., 1994). In contrast to these compounds, 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF can induce their own rate of metabolism and biliary excretion (Brewster and Birnbaum, 1987; McKinley et al., 1993; Olson et al., 1994). Autoinduction of metabolism suggests that these compounds may exhibit dose-related excretion, with longer half-lives for elimination at lower doses, which are not associated with enzyme induction. Further data are needed to test this hypothesis.

1.3.5. Excretion in Humans

Poiger and Schlatter (1986) investigated the excretion of TCDD in a 42-year-old man (92 kg) after ingestion of 105 ng (1.14 ng/kg) [^{3}H]-2,3,7,8-TCDD in 6 mL corn oil (see Tables 1-9 and 1-10). The half-life for elimination was estimated to be 2,120 days based on fecal excretion over a 125-day period following the single exposure. The concentration of ^{3}H-TCDD-derived radioactivity was also measured in adipose tissue in the same individual over a 6-year period following exposure. A more accurate estimate of TCDD half-life of 9.7 years was calculated based on adipose tissue concentrations over a 6-year period (Schlatter, 1991). Table 1-10 summarizes additional half-life estimates for TCDD and related compounds in humans, on the basis of serum and adipose tissue concentrations at two or more time points.

The Air Force is conducting a 20-year prospective study of veterans of Operation Ranch Hand, the unit responsible for the aerial spraying of herbicides, contaminated with TCDD, in

Vietnam from 1962 to 1971. A subset of the Ranch Hand cohort has had a series of up to four serum TCDD analyses conducted to investigate the elimination of TCDD in humans. Initially, the half-life of TCDD in humans was estimated to be ~7 years on the basis of TCDD levels in serum samples taken in 1982 and 1987 from 36 of the Ranch Hand personnel who had TCDD levels >10 ppt in 1987 (Pirkle et al., 1989). Subsequently, Wolfe et al. (1994) investigated the half-life of TCDD in an expanded cohort of 337 Air Force veterans of Operation Ranch Hand that also included the 36 subjects of the earlier half-life study by Pirkle et al. (1989). Based on paired TCDD measurements from serum collected in 1982 and in 1987, the authors reported a mean predicted half-life of 11.6 years and a median observed half-life of 11.3 years with a nonparametric 95% confidence interval of 10.0 to 14.1 years. The authors also investigated how the TCDD half-life varied with percent body fat (PBF), relative changes in PBF from 1982 to 1987, and age. They found that the TCDD half-life increased significantly with a high PBF, suggesting that persons with more body fat tend to eliminate TCDD more slowly. In contrast, increasing age was associated with a shorter half-life. The redistribution of fat stores from subcutaneous to abdominal areas with aging, resulting in greater mobilization of TCDD, could in part explain the shorter half-life observed in older veterans. An increase in PBF from 1982 to 1987 was also associated with a decrease in half-life, which can be explained by a dilution of the existing body burden of TCDD into the increasing adipose tissue mass.

More recently, Michalek et al. (1996) estimated the half-life of TCDD in 213 veterans of Operation Ranch Hand on the basis of TCDD serum analyses conducted in 1982, 1987, and 1992. Of the 278 subjects with complete data in all 3 years, 213 were included for analysis of half-life 3 on the basis of TCDD levels greater than 22.3 ppt in 1982, >14.9 ppt in 1987, and >10 ppt in 1992. All TCDD levels were background-corrected by subtracting 4 ppt, and the logarithm of the background-corrected levels were modeled as a linear function of time to estimate decay rates using first-order kinetics. Using the Toeplitz assumption, the unadjusted estimated decay rate is 0.0797 per year (95% CI of 0.0727 to 0.0868), giving an unadjusted half-life estimate of 8.7 years (95% CI of 8.0 to 9.5 years). The adjusted half-life was found to increase significantly with an increase in PBF in 1982, but the half-life did not vary with age or relative changes in PBF. Most recently, Michalek and Tripathi (1999) estimated the half-life of TCDD in 97 veterans of Operation Ranch Hand on the basis of TCDD serum analyses conducted in 1982, 1987, 1992, and 1997. Of the 244 subjects with complete data at all four time points, only 97 were included for analysis of half-life based on the criteria of TCDD levels greater than 39.5 ppt in 1982, >25.0 ppt in 1987, >15.8 ppt in 1992, and >10 ppt in 1997. With increasing time since the initial exposure to TCDD, a greater proportion of the population was excluded from the analysis, as more subjects approached background body burdens of TCDD. Using the methods of the previous report (Michalek et al., 1996), the unadjusted estimated elimination rate

was 0.0915 per year (95% CI of 0.0844 to 0.0986), giving an unadjusted half-life estimate of 7.6 years (95% CI of 7.0 to 8.2 years). Because of the smaller sample size, the current elimination rate estimate, based on four measurements per subject, has less precision than the earlier estimate of Michalek et al. (1996), which was based on three measurements per subject. Once again, the elimination rate decreased slightly but significantly as PBF increased, supporting the hypothesis that individuals with more body fat tend to eliminate TCDD more slowly than those with less body fat. Michalek and Tripathi (1999) also reported no significant change in the elimination rate with age or with relative changes in PBF.

The half-life of TCDD has also been investigated in two additional populations. Flesch-Janys et al. (1996) studied a group of 43 German herbicide plant workers that had initial TCDD serum levels from 15.6 to 300 ppt. A median half-life estimate of 7.2 years was reported for this occupational cohort, which received an initial exposure to TCDD similar to that of the Ranch Hand veterans. A similar half-life estimate of 8.2 years was reported in 27 victims of the accident in Seveso, Italy (Needham et al., 1994). This cohort had a greater initial exposure, resulting in serum levels of 130 to 3,830 ppt TCDD. This study also included the early and later portions of the TCDD decay curve, as the initial blood sampling began immediately following exposure and continued for 15.9 years. Thus, based on results from the Ranch Hand, the German, and the Seveso studies, the estimated half-life of TCDD in humans is from 7.2 to 8.7 years (Table 1-10).

Half-life estimates for other CDDs and CDFs have been estimated to range from 0.8 to 19.6 years (Table 1-10). Some of the half-life values in Table 1-10 are rough estimates based on a small number of individuals and analysis at as few as two time points. Phillips (1989) discusses this issue. Estimates also assume a simple, single-compartment, first-order elimination process.

In the largest and most comprehensive study, Flesch-Janys et al. (1996) investigated the elimination of 2,3,7,8-chlorine substituted CDDs and CDFs in a cohort of workers from a herbicide-producing plant in Germany (summarized in Table 1-10). The study group consisted of 45 males and 3 females with a mean duration of employment of 13.1 years. Mean time between end of employment and first blood sample was 5.4 years (median 2 years) and mean time between first and last blood sample was 5.6 yr (median 6.3 years). A total of 43 subjects with two serum samples and 5 subjects with three serum samples were included in the study. For each congener, only those subjects whose congener serum levels exceeded 95% of German background concentration were included in the analysis. The mean background concentration was also subtracted from every original measurement before analysis. For 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF and OCDF, no half-life was estimated because no person in the study passed the above inclusion criteria. 2,3,7,8-TCDF and 1,2,3,7,8-PeCDF are excreted in animals much

more rapidly than other congeners (van den Berg et al., 1994), suggesting that these congeners may also be excreted more rapidly in humans. Conversely, 2,3,4,7,8-PeCDF is far more persistent in animal models than is TCDD, which supports the estimated 19.6-year half-life of 2,3,4,7,8-PeCDF and 7.2-year half-life of TCDD in humans. However, this estimate was based on only five subjects who met the criteria for inclusion in the study. With the exception of 1,2,3,7,8-PeCDD and 1,2,3,6,7,8-HxCDD, the median half-lives of the CDDs are generally similar. The estimates for these two congeners may be somewhat unstable because of variable individual rate constants for elimination and the fact that about 25% of the population showed no decrease in serum levels over the sampling period. Furthermore, the investigation found that increasing age and PBF were associated with increasing half-life for most congeners. Finally, it is important to note that the half-life data reflect only the elimination of CDDs and CDFs from blood lipid and may not reflect elimination from different storage sites for all congeners. In the case of TCDD, it can be assumed that the half-life estimate reflects elimination from the main storage site, because about 90% of the body burden is sequestered in fat and the blood fat/adipose tissue concentration is about 1 (Patterson et al., 1987; Kahn et al., 1988; Schecter et al., 1990a; van den Berg et al., 1994). Data are more limited on the relative amount of other congeners stored in adipose tissue in humans, and limited and somewhat conflicting data suggest that the blood fat/adipose tissue concentration ratio may increase up to a factor of 2 for OCDD (Schecter et al., 1990a; Gurn et al., 1995). Thus, some uncertainties remain regarding the extent that the observed decrease in serum levels of higher CDDs and CDFs reflects the elimination of these compounds from the body.

Ryan and Masuda (1991) reported on their continuing investigation into the elimination of CDFs in humans from the Yusho and Yu-Cheng rice oil poisonings. Yu-Cheng individuals had CDF blood levels on a lipid basis of 1-50 μg/kg, whereas Yusho patients had levels of 0.1-5 μg/kg. In the Yu-Cheng individuals, half-lives for three CDFs were 2 to 3 years, whereas elimination from Yusho individuals was more variable and slower, with half-lives >5 years (see Table 1-10) and, in several cases, no measurable elimination during the 7 years in which samples were available. The limited results suggest that clearance of these CDFs in the human is biphasic, with faster elimination at higher exposure. Schecter et al. (1990b) and Ryan and Masuda (1989) also reported longer half-life values for CDFs in humans at later time points after exposure, when concentrations are closer to the background levels of individuals with no unusual exposure.

While results from animal studies (summarized in Table 1-9) suggest that direct fecal excretion of unmetabolized CDDs and CDFs represents a significant mechanism for the elimination of these lipophilic compounds, human data have been limited until recently. The mass balance study of Schlummer et al. (1998) provided the experimental human data in support

of the two-step model of CDD and CDF transfer in the gastrointestinal tract, where absorption and excretion are distinct processes occurring at the small and large intestine, respectively (see Section 1.1.1.2). Rohde et al. (1999) conducted a digestive tract mass balance study of six German men (age 41 to 73 years) with occupational exposure to CDDs and CDFs. Blood lipid levels of the subjects in 1996 ranged from 84 to 505 pg/g lipid for TCDD and 270 to 640 pg/g lipid for TEQs, compared with background levels in unexposed individuals of 5.2 and 32 pg/g lipid, respectively. The daily quantity of nonmetabolized 2,3,7,8-chlorine-substituted CDDs and CDFs excreted in the feces exceeded the daily uptake from food, indicating significant clearance across the gastrointestinal tract. The concentration of these compounds in feces was also found to be highly correlated with that in blood, demonstrating that the fecal CDD and CDF content was directly related to the body burden of these compounds. No significant clearance (excretion via feces at least fourfold greater than uptake by food) was observed for congeners, including 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 1,2,3,4,7,8,9-HepCDF, or OCDF, which were not markedly elevated in the serum lipids. Together, these results support the relationship that fecal excretion is regulated by the lipid-based blood concentration of these compounds. Because of fecal clearance of nonmetabolized congeners, the half-lives in these subjects were estimated from the excretion rate and current body burden and ranged from 10 years for OCDD to 22 years for TCDD to 33 years for 2,3,4,7,8-PeCDF. Congener-specific half-lives, similar to those reported by Flesch-Janys et al. (1996), were also calculated based on the decrease in serum lipid level of congeners between 1990/92 and 1996. The fecal clearance of nonmetabolized CDDs and CDFs contributed on average between 37% (2,3,7,8-TCDD) and 90% (OCDD) to the total elimination. Thus, fecal clearance plays an important role in the overall elimination of most congeners, with the daily fecal excretion estimated to be equivalent to the amount of TEQ present in about 1.7 g of blood lipids (Rohde et al., 1999).

Because direct fecal excretion is a significant route for the excretion of nonmetabolized CDDs and CDFs (Schlummer et al., 1998; Rohde et al., 1999), two recent studies investigated whether Olestra, a nonabsorbable sucrose-polyester synthetic fat substitute, may enhance the elimination of these compounds in humans. Moser and McLachlan (1999) compared the fecal excretion of CDDs, CDFs, PCBs, and HCB with background exposures in three subjects who ate an Olestra-free diet and who ate a diet supplemented with 25 g/day of Olestra. The fecal excretion while on the Olestra diet was 1.5 to 11-fold higher, depending on the congener. If fecal excretion is estimated to contribute 40% of the overall elimination of TCDD, and the Olestra diet enhanced fecal excretion 5.7-fold, the overall rate of elimination of TCDD would be more than doubled on the Olestra diet. Geusau et al. (1999) investigated the effect of an Olestra-supplemented diet on the excretion of TCDD in two patients with chloracne and very high serum TCDD levels of 144,000 and 26,000 pg/g lipid. A diet supplemented with fat-free potato chips

(33 to 66 g Olestra/day) enhanced the fecal excretion of TCDD by up to eight- to ten-fold. Results suggest that the increase in fecal excretion of TCDD was due mainly to an increase in the amount of fat (dietary fat plus Olestra) excreted via the feces. The resulting elimination half-lives of TCDD due to fecal excretion were estimated to be 1.4 years in the more highly exposed patient and 1.9 years in the other individual. However, half-lives of 200 days and 230 days, respectively, were determined through analysis of serum and adipose tissue TCDD levels over the 8-month observation period. The observed half-lives were far shorter than could be explained by an enhanced fecal or other elimination mechanism. In addition to the enhanced fecal excretion with Olestra, the authors speculate that the high levels of TCDD may have also induced the metabolism of TCDD in these subjects, resulting in the shorter observed half-lives.

In related studies, Morita et al. (1993, 1995, 1997, 1999) investigated the role of dietary fiber or Chlorella in the fecal excretion of CDDs and CDFs in rats. Chlorella is a unicellular green algae, sold as a health food or health supplement. Chlorella in the diet of rats also enhanced the fecal excretion of CDDs from 0.8- to 5.6-fold and CDFs from 0.9- to 11.1-fold above that of rats on a control diet (Morita et al., 1999). Rice bran fibers enhanced the fecal excretion of CDDs from 0.6- to 2.3-fold and CDFs from 0.5- to 10.4-fold above that of rats on a control diet (Morita et al., 1997). Dietary fiber, chlorophyll, and/or lipid in the Chlorella may be factors responsible for the enhanced fecal excretion of CDDs and CDFs observed in this study. Thus, fiber and/or Chlorella may be other dietary factors capable of increasing the fecal excretion of CDDs and CDFs.

Because of the lipophilic nature of milk, lactation can provide a relatively efficient mechanism for decreasing the body burden of TCDD and related compounds in females. As discussed by Graham et al. (1986), this elimination of TCDD through mother's milk can result in high exposure levels in the infant. The relatively high bioavailability of CDDs and CDFs from mother's milk in nursing infants was discussed earlier in Section 1.1.1.2. Further discussion of lactation as a route for excretion of CDDs and CDFs in women and exposure in infants is given in Section 1.4.5.

1.4. PHARMACOKINETICS AND EXPOSURE

1.4.1. Introduction

Pharmacokinetic models, often simple models that represent the human body or a specific tissue in the human body as a storage compartment for a chemical, can be used to relate doses to internal tissue concentrations or to some other metric of toxic action. These models are represented by a differential equation that accounts for the mass balance about the compartment. In the simplest case, the change in mass of a chemical within the storage compartment is equal to

the difference between the mass entering the compartment and the mass leaving the compartment over a specified time period.

Physiologically based pharmacokinetic (PBPK) models are special extensions of the simple pharmacokinetic model. These models utilize multiple compartments to represent the different tissues or physiological regions of the body. They incorporate known or estimated anatomical, physiological, and physicochemical parameters to describe quantitatively the disposition of a chemical between different tissues. PBPK models are useful to extrapolate between high- to low-dose kinetics within a species, to estimate equivalent doses by different routes of administration, and to extrapolate doses across species (Scheuplein et al., 1990). Given some knowledge of possible exposure patterns and scenarios, PBPK models can be used in an inverse fashion to estimate exposures on the basis of internal body doses. Some examples of how to use simple PK and PBPK models to estimate exposure to TCDD and related compounds will be given here. In addition, this section will utilize model estimations to examine some special cases of exposure, in particular, exposure to lactating infants and the elderly.

1.4.2. Estimating Daily Intake of TCDD

Because TCDD is highly lipophilic, it has been shown that a majority of the TCDD in any body tissue is stored in the fat (van der Molen et al., 1996). As a first approximation, a one-compartment pharmacokinetic model with first-order elimination may be used to compute the daily intake of TCDD based on steady-state concentrations in the fat. The mass balance model is:

$$V_F \frac{dC_F}{dt} = D - k_e A_F \qquad (1\text{-}1)$$

where:

V_F = volume of fat
CF = concentration of TCDD in fat
D = daily dose (mass/time)
A_F = mass of TCDD in fat
k_e = first order elimination constant ($time^{-1}$)

Concentration, C_F, is given by:

$$C_F = \frac{A_F}{V_F} \qquad (1\text{-}2)$$

Then, at steady state ($dC_F/dt = 0$), daily dose exactly balances elimination.

$$D = k_e A_F = k_e V_F C_F \qquad (1\text{-}3)$$

Note that k_e can be expressed in terms of half-life:

$$k_e = \frac{ln2}{t_{1/2}} \qquad (1\text{-}4)$$

Substituting Equation 1-4 into Equation 1-3, one obtains the following expression for daily dose in terms of fat concentration:

$$D = \frac{ln2}{t_{1/2}} V_F C_F \qquad (1\text{-}5)$$

It is important to recall the two assumptions implicit in the derivation of the above formula for daily uptake. First, steady-state conditions are assumed. Given that the half-life of some of these compounds is long (e.g., for TCDD the half-life is 7 years), steady-state levels would only be approached if the level of exposure were constant for 15-30 years. Pinsky and Lorber (1998) compiled data from several studies that indicate that environmental concentrations of TCDD and related compounds have been decreasing over the past 20-30 years. They use a single-compartment model similar to the one presented above, but with a time-varying exposure profile rather than the constant input. The profile was determined statistically on the basis of previously recorded environmental trends. Using the prior exposure knowledge, Pinsky and Lorber found that the pharmacokinetic model was better able to predict body burdens that have been recorded over time than was the steady-state model. By manipulating the non-steady-state model and comparing results to the steady-state approximation, it can be shown for a given body burden measurement, the steady-state approximation would result in an overestimate of daily intake. Using some estimates of the decreasing exposure function presented by Pinsky and Lorber (1998), it appears that the overestimate of daily intake could be 20% or more with the steady-state model.

Another assumption of the simple model presented in this section is that the elimination kinetics are assumed to be constant over the entire life of the individual. Because TCDD and related compounds are stored primarily in fat, sudden weight loss and lactation would result in alterations of the TCDD elimination rate. Again, it would be assumed that for calculation of daily intake due to background exposure, the body burden data from such individuals would be identified and calculations handled accordingly.

Figure 1-3 shows a sample calculation for TCDD using Equation 1-5. A fat volume of 14 L was chosen, representing 20% of the body weight. Also, for the purposes of this example, 1 mL of tissue was assumed to be equivalent to 1 g. Table 1-11 shows the estimated daily intake of TCDD at several conditions. The range of daily intakes calculated is in agreement with those reported elsewhere (Fürst et al., 1991).

Thomaseth and Salvan (1998) developed a minimal PBPK model for TCDD in humans and utilized this model to estimate occupational exposures to TCDD. The model was reduced to one compartment for ease of solution and was based on the following assumptions: (1) dynamic equilibrium of TCDD concentration between different body lipid distribution volumes, (2) first-order elimination proportional to TCDD liver content, and (3) daily intake proportional to body weight. The best parameter estimates based on Ranch Hand data were obtained with log-transformed data under a mixed-effects model, with liver elimination $k_f = 0.022$ days^{-1} (95% CI of 0.02-0.024), and background input = 0.125 pg/kg/day (95% CI of 0.071-0.179). The model accounts for changes in body mass index (BMI) over time, with higher BMI being related to a longer half-life for TCDD. The model was then used to estimate occupational exposure of 253 U.S. chemical plant workers for whom one measure of serum TCDD was available. The estimated exposure of the NIOSH cohort was 233 pg/kg/day (95% CI of 192-273). This model is much more rigorous than the simple steady-state approximation, and if a PK model is to be used to attempt to estimate intake, this model would be preferable. However, solving this model for daily intake is more complex and requires some assumption of the pattern of exposure over time. Alternatively, one could estimate daily intake by direct exposure calculations, that is, by examining the interaction of humans with environmental media containing the highest concentrations of dioxins. More information on this is provided in the chapter on exposure (Part II, Chapter 4).

1.4.3. Daily Intake of Congeners

Steady-state average dose calculations may be performed for other congeners in a manner similar to that presented for TCDD. Three pieces of information are necessary. First, concentrations in the adipose tissues must be known. Second, the half-lives of the compounds within the body must be known. Third, some understanding of the kinetics and exposure

conditions is required to ensure that steady-state conditions were achieved at the time of monitoring.

Concentrations of various congeners in adipose tissues can be found in several sources (Stanley et al., 1986; Schecter, 1991). Values range from around 2 ppt for 2,3,7,8-TCDF to several hundred ppt for 1,2,3,4,6,7,8,9-OCDD.

Half-lives could be determined from elimination data, if available. Methods have been suggested to determine the half-life of such compounds from uptake data relative to TCDD. Schlatter (1991) has proposed one such method. The following has been adapted from that proposed method. Manipulation of Equation 1-5 results in:

$$C_{TCDD} = \frac{D_{TCDD} \quad t_{1/2,TCDD}}{V \ln 2} \tag{1-6}$$

For some other congener x:

$$C_x = \frac{D_x \quad t_{1/2,x}}{V \ln 2} \tag{1-7}$$

Thus, the ratio of concentrations of TCDD to x can be described by:

$$\frac{C_{TCDD}}{C_x} = \left(\frac{D_{TCDD} \quad t_{1/2,TCDD}}{V \ln 2} \right) \quad \left(\frac{V \ln 2}{D_x \quad t_{1/2,x}} \right) \tag{1-8}$$

Which, with algebraic manipulation and simplification, becomes:

$$t_{1/2,x} = \left(\frac{D_{TCDD} \quad t_{1/2,TCDD}}{C_{TCDD}} \right) \quad \left(\frac{C_x}{D_x} \right) \tag{1-9}$$

Assuming intake D to be mostly from food, especially animal-fat products, it can be related to absorption from these foods according to:

$$D_{TCDD} = (k_{a,TCDD}) (A_{TCDD}) \tag{1-10}$$

where:

$k_{a,TCDD}$ = absorption rate constant for TCDD

A_{TCDD} = concentration of TCDD in animal fat (diet)

and

$$D_x = (k_{a,x})\ (A_x) \tag{1-11}$$

where:

$k_{a,x}$ = absorption rate constant for x

A_x = concentration of x in animal fat (diet)

As a result, the half-life for compound x can be described by:

$$t_{1/2,x} = t_{1/2,TCDD}\left(\frac{A_{TCDD}}{C_{TCDD}}\right)\left(\frac{C_x}{A_x}\right)\left(\frac{k_{a,TCDD}}{k_{a,x}}\right) \tag{1-12}$$

When the absorption rate constants for each are equal or when the difference between them is small compared to differences in other parameters (concentration, half lives), Equation 1-12 can be further simplified to:

$$t_{1/2,x} = t_{1/2,TCDD}\left(\frac{A_{TCDD}}{C_{TCDD}}\right)\left(\frac{C_x}{A_x}\right) \tag{1-13}$$

It should be noted that for some of these substances exposure is expected from other than food sources. For such cases Equation 1-12 would be modified to include these other sources as follows.

$$t_{1/2,x} = t_{1/2,TCDD}\left(\Sigma\frac{k_{a,i,TCDD}\ \ A_{i,TCDD}}{C_{TCDD}}\right)\left(\Sigma\frac{C_x}{k_{a,i,x}}\ \ A_{i,x}\right) \tag{1-14}$$

where:

$k_{a,i,TCDD}$ = absorption rate constants for TCDD from each of the i media

$A_{i,TCDD}$ = concentration of TCDD in each of the i media

$k_{a,i,x}$ = absorption rate constants for x from each of the i media

$A_{i,x}$ = concentration of x in each of the i media

Other symbols: as previously defined

Again, if the differences between the absorption rate constants for TCDD and x are judged to be small, then the following variation of Equation 1-14 can be used:

$$t_{1/2,x} = t_{1/2,TCDD}\left(\Sigma\left(\left(\frac{A_{i,TCDD}}{C_{TCDD}}\right)\left(\frac{C_x}{A_{i,x}}\right)\right)\right) \quad (1\text{-}15)$$

Table 1-12 shows the results of some half lives calculated in this manner.

The half lives calculated using Equation 1-15 for the first three compounds in Table 1-12 agree with those calculated by Schlatter (1991). The large difference in the two calculations for OCDD is due to significant differences in absorption rates between TCDD and OCDD. Schlatter notes in his paper that for some compounds, including OCDD, corrections were made of differences in absorption. No explanation was offered on how this was done. However, Flesch-Janys et al. (1996) report a half-life of 6.7 years for OCDD. In addition, Flesch-Janys et al. (1996) report longer half-lives for 1,2,3,7,8-PeCDD (15.7 years) and 2,3,4,7,8-PeCDF (19.6 years). These differences could be due to a variety of factors including the dietary concentrations, absorption rates, other background sources, etc. Table 1-13 summarizes the results reported by Flesch-Janys.

When using this method to estimate daily intake of TCDD and congeners, it should be noted that studies (Kim and Dubin, 1996; Shirai and Kissel, 1996) have indicated that there is considerable uncertainty associated with half-life measurements published in the literature.

1.4.4. Induction of Liver Binding Proteins and Resultant Distribution

Andersen et al. (1997a) developed a multicompartment geometric model of the liver in relation to regional induction of cytochrome P-450s. The model was based on five morphological and functional zones of the liver acinus: a concentric periportal zone, a fenestrated periportal region that interconnects among multiple functional units, and three concentric centrilobular areas. At low doses, TCDD exhibits centrilobular expression of CYP1A1, and with increasing dose, adjacent areas radiating out from the centrilobular region also begin to express CYP1A1. To create realistic total induction curves that are relatively smooth, the differences in K_d (dissociation constant) values between adjacent subcompartments must be less than fivefold. Because of the high n (Hill constant) values, the low-dose induction characteristics predicted with the multicompartment liver model differ significantly from those predicted with a model that considers the liver as a single homogeneous compartment. A physiologically based pharmacokinetic (PBPK) model for TCDD was then combined with a five-compartment geometric model of hepatic zonation to predict both total and regional induction of CYPs within the liver (Andersen et al., 1997b). The model predicts an 81-fold difference in the affinity of the

AhR-TCDD complex binding to DNA response elements for CYP1A1 between the centrilobular and the periportal regions. The PBPK analysis based on the multicompartment liver model suggests that the low-dose behavior for hepatic CYP1A1/1A2 induction by TCDD is highly nonlinear.

1.4.5. Pregnancy and Lactation (Exposure of Offspring)

The distribution and excretion of [^{14}C]-2,3,7,8-TCDD (30 μg/kg) and [^{14}C]-2,3,7,8-TCDF (800 μg/kg) were studied in pregnant C57BL/6N mice after oral exposure on gestation day 11 (Weber and Birnbaum, 1985). The distribution and excretion of TCDD and 2,3,7,8-TCDF in pregnant mice were similar to those of males of the same strain (Gasiewicz et al., 1983b; Decad et al., 1981b) (see Tables 1-6 and 1-9), although elimination rates were higher in the pregnant mice for both congeners. For TCDD, liver, urinary, and fecal elimination was 3.0, 3.4, and 14.4 times faster than that reported for males. For 2,3,7,8-TCDF, liver, urinary, and fecal elimination was 1.3, 1.8, and 1.8 times faster than that observed for males. Elimination data from pregnant mice were based on only three time points (gestation days 12, 13, and 14) and thus represent only rough estimates. In addition, the greater fecal excretion could have been due to incomplete absorption of TCDD after oral exposure. Although these results need further substantiation, it is conceivable that the sex of the animal, pregnancy, and the route of exposure could have a significant impact on the pharmacokinetics of these compounds.

In a related study, Krowke (1986) compared the TCDD concentrations in the livers of pregnant and nonpregnant NMRI mice exposed subcutaneously to 12.5 or 25 nmol/kg/day on gestation days 9-11. At 7 days after exposure to the lower dose, the hepatic TCDD concentrations were 7 and 32 ng/g in pregnant and nonpregnant mice, respectively. At the higher exposure, 5.5 times lower concentrations of TCDD were found in the livers of pregnant animals on gestation day 18. A similar effect on hepatic TCDD levels was observed in combined exposure, which contained 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, or 2,3,7,8-TCDF. The decreased hepatic levels of TCDD in pregnant mice are consistent with the Weber and Birnbaum (1985) observation of more rapid elimination of TCDD in pregnant mice. Further investigations are necessary to better characterize the apparently significant effects of pregnancy on the disposition of TCDD and related compounds.

Weber and Birnbaum (1985) also investigated the distribution of [^{14}C]-2,3,7,8-TCDD (30 μg/kg) and [^{14}C]-2,3,7,8-TCDF (800 μg/kg) to the embryos of pregnant C57BL/6N mice after oral exposure on gestation day 11. On gestation days 12, 13, and 14, the percent of the maternal dose in the embryo remained constant at 0.032%-0.037%/embryo, while the concentrations in the embryo were 0.34%, 0.17%, and 0.15% of the dose/g embryo, respectively. Embryos had approximately 11-fold higher concentrations of TCDD than 2,3,7,8-TCDF when exposed on a

percent of total dose/g tissue basis. This may be due to the more rapid metabolism and excretion of 2,3,7,8-TCDF compared with TCDD. Assuming that all radioactive material found in embryos was parent compound, at most 2.6 ng (8 pmol) of TCDD and 6.4 ng (21 pmol) of 2,3,7,8-TCDF/g tissue were detected under these conditions.

The transfer of [^{14}C]-2,3,7,8-TCDD to the embryo during early gestation was assessed in NMRI mice given a dose of 25 μg/kg by intraperitoneal injection on days 7, 8, 9, 10, 11, or 13 of gestation (Nau and Bass, 1981). The mice were sacrificed after 48 hours, and TCDD concentrations were determined by liquid scintillation counting of solubilized tissue and by GC-ECD and GC/MS. Similar results were given by these methods, suggesting that TCDD-derived [^{14}C] in maternal and embryonic tissue was the parent compound. The maternal liver contained from 4% to 8% of the dose/g, or 40-80 ng/g. TCDD in embryonic tissue from gestation days 11-15 ranged from 0.04% to 0.1% of the dose/g, or 0.4-1.0 ng/g. In contrast, higher levels were found earlier in gestation, with 10 ng/g embryo on gestation day 9 and 2 ng/g on day 10. The higher levels may be related to placentation, which occurs at approximately gestation days 10-11 in this mouse strain. The affinity of fetal liver for TCDD was relatively low, as compared to maternal liver; however, TCDD levels in fetal livers were two to four times higher than levels in other fetal organs. Nau and Bass (1981) also attempted to correlate TCDD levels in the fetuses with the observed incidence of cleft palate. Three groups of mice were given either a single intraperitoneal exposure to 25 μg/kg TCDD on gestation day 7 or 10 or 5 μg/kg/day, intraperitoneally, on gestation days 7-11. On gestation day 13, TCDD concentrations in maternal tissues were very similar in the three exposure groups. At day 13, however, the embryo contained 0.038±0.011% (0.36 ng/g), 0.096±0.027% (0.92 ng/g), and 0.12±0.05% (1.1 ng/g) of the dose (mean±SD) in the 7-, 10-, and 7- to 11-day exposure groups, respectively. Cleft palate incidence on gestation day 18 was 16%, 84%, and 65% for the 7-, 10-, and 7- to 11-day exposure groups, respectively. Although further studies are needed, these results suggest that cleft palate incidence is generally related to the TCDD concentration in the embryo. In a related study, Couture et al. (1990) found that gestation day 12 was the peak period of sensitivity for TCDD-induced cleft palate in C57BL/6N mice; however, tissue levels were not investigated.

In the same laboratory, Abbott et al. (1989) investigated the distribution of TCDD in the C57BL/6N mouse fetus following maternal exposure on gestation day 11 to 30 μg/kg. 2,3,7,7-TCDD was detected in the gestation day-11 embryo at 3 hours postexposure and was equally distributed between the embryonic head and body. At 72 hours postexposure, 0.035% of the total dose was in fetal tissues and 1% of the TCDD in the fetus (1.4-3.5 pg) was found in the palatal shelf. More recently, Abbott et al. (1996) found that TCDD was detected in maternal blood, liver, and fat and in the placenta, embryonic liver, and palate within 30 min after oral exposure of mice on gestation day 12. The levels peaked in blood and placenta at 3 hours and in

the other tissues at 8 hours. At 24 hours following a single oral dose of 24 μg TCDD /kg, the above respective tissues contained 0.25, 98.8, 72.9, 1.22, 1.03, and 0.44 ng TCDD/g.

Krowke (1986) also measured the concentration of TCDD in the placenta, amniotic fluid, and fetus of NMRI mice exposed to 2.5 nmol/kg by subcutaneous injection on days 9-11 of gestation. Similar concentrations of TCDD were observed in the placenta, amniotic fluid, and fetus (~0.5 ng/g) on day 16 of gestation. Fetal liver TCDD concentrations were at least five times greater than in other fetal tissue. Krowke (1986) reported slightly lower TCDD levels in the fetal head relative to other extrahepatic fetal tissue, while Weber and Birnbaum (1985) found a slightly higher TCDD concentration in the head relative to other extrahepatic fetal tissue.

Nau et al. (1986) investigated the transfer of TCDD via the placenta and milk in NMRI mice exposed to 25 μg/kg on day 16 of gestation. The authors confirmed the relatively low fetal tissue levels with prenatal exposure to TCDD (Nau and Bass, 1981) and found that postnatally TCDD was transferred efficiently to mouse neonates and offspring by lactating mothers. During the first 2 postnatal weeks, the pups were given doses of TCDD via the milk that were, on a body-weight basis, similar to those that had been administered prenatally to their mothers. TCDD levels in the tissue of lactating mothers decreased within the first 3 postnatal weeks by two to three orders of magnitude to reach levels that were only ~2% of the corresponding levels in the pups that these mothers had nursed. Thus in mice, excretion into milk represents a major pathway for maternal elimination of TCDD and for the subsequent exposure of pups.

The disposition of TCDD in rat pups was assessed after the prenatal (via placental transfer) and postnatal (via milk) exposure from pregnant Wistar rats given a single dose of 3, 30, or 300 ng/kg, subcutaneously, on day 19 of gestation (Korte et al., 1990). Lactation resulted in the rapid elimination of TCDD from maternal tissues, with the half-life of TCDD in the liver of lactating rats estimated to be ~7 days. This compares to a half-life of 13.6 days in the liver of nonlactating rats (Abraham et al., 1988). At postnatal day 7, exposure via the milk resulted in pup liver TCDD concentrations that were greater than the corresponding levels in maternal liver. In cross-fostering experiments, the concentrations of TCDD in the liver of offspring at postnatal day 7 were 0.47, 2.59, and 4.16 ng/g in the 300 ng/kg groups exposed through the placenta only, via the milk only, and through the placenta and via the milk, respectively. These results support the earlier observations that the placental transfer of TCDD in rats and mice is relatively limited compared with the efficient transfer via maternal milk.

Van den Berg et al. (1987b) investigated the transfer of CDDs and CDFs to fetal and neonatal rats. Prenatal exposure of the fetus was assessed in pregnant Wistar rats fed a diet containing a fly ash extract from a municipal incinerator on days 10-17 of gestation. Postnatal exposure of 10-day-old pups was assessed through feeding lactating mothers the same contaminated diet for the first 10 days after delivery. Although the fly ash extract contained

almost all of the 136 tetra– to octa-CDDs and -CDFs, only 17 CDD and CDF congeners were detected as major compounds in the tissue of fetuses, pups, and dams. All of the congeners were 2,3,7,8-substituted with the exception of 2,3,4,6,7-PeCDF. TCDD had the highest retention (0.0092% of the dose/g) in the fetus, while 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, and hepta- and octa-CDDs and -CDFs were not detected in the fetus. In the liver of offspring, the highest retention was found for TCDD, 1,2,3,7,8-PeCDD, and the three 2,3,7,8-substituted HxCDDs (0.74%-1.13% dose/g). The 2,3,7,8-substituted penta- and hexachlorinated congeners showed the highest retention in the livers of dams (2.05%-5.17% of dose/g liver), while 2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, and 2,3,4,6,7-PeCDF had the lowest retention. A linear relationship was found between the retention of CDDs and CDFs in the livers of pregnant and lactating rats. Furthermore, a linear relationship was found between the retention of CDDs and CDFs in the livers of the lactating rats and livers of the offspring.

In a related study, Hagenmaier et al. (1990) investigated the transfer of CDDs and CDFs through the placenta and via milk in a marmoset monkey. A defined mixture of CDDs and CDFs was given as a single subcutaneous injection to a pregnant marmoset monkey at the end of the organogenesis period (week 10 of gestation, 11 weeks prior to delivery). Transfer of CDDs and CDFs through the placenta was investigated in a newborn 1 day after birth, and transfer through the placenta and via milk was assessed in an infant of the same litter after a lactation period of 33 days. Tissue concentrations of the offspring were compared with those of the mother at the end of the lactation period and with data from other adult marmosets obtained at this time of maximum absorption (1 week after injection) and 6 weeks after injection. Deposition of CDDs and CDFs into the newborn liver was very low, suggesting very little transplacental transport and hepatic accumulation of these compounds. TCDD and 1,2,3,7,8-PeCDD were found at the highest concentration in the liver of the newborn (~0.15% of dose/g). For all other congeners, the concentrations in the liver of the newborn were <10% of the corresponding concentrations in adults. In contrast to liver, concentrations of 2,3,7,8-substituted congeners in the adipose tissue of the newborn were at least 33% of the levels in adults, and in the case of OCDD and OCDF, levels were threefold higher in the newborn than in the adult. The adipose tissue/liver concentration ratios for 2,3,7,8-substituted congeners in the newborn ranged from 2.2 for 1,2,3,4,6,7,8-HpCDF to 10.9 for 2,3,7,8-TCDF. Furthermore, the concentration of these congeners in the newborn was highest in the adipose tissue, followed by the skin and liver. This is in contrast to the relative distribution in the adult, where the liver generally contains the highest levels of these congeners. The results indicate that hepatic concentrations in the fetus may not be representative of the rate of placental transfer of CDDs and CDFs. In the marmoset monkey, substantial placental transfer into fetal adipose tissue can be observed for most of the 2,3,7,8-substituted congeners during the fetal period. As expected from rodent studies, the

transfer of CDDs and CDFs via mothers' milk was considerable, resulting in hepatic concentrations of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, and 1,2,3,6,7,8-HxCDD in the suckled infant (postnatal day 33) higher than those in the dam. The hepatic concentration of TCDD in the 33-day-old infant was ~0.9% of the dose/g tissue. Transfer of hepta- and octa-CDDs and CDFs to the suckled infant was rather low, only ~10% of the levels in the dam. When total exposure of the mother and offspring at the end of the 33-day nursing period was assessed in terms of I–TE factors (U.S. EPA, 1989), the liver of the mother contained 2,494 pg I–TE/g, whereas the offspring liver contained 2,022 pg I-TE/g. This approach is necessary to assess total exposure due to the congener-specific transfer via lactation.

The pre– and postnatal transfer of TCDD to the offspring of rhesus monkeys was investigated by Bowman et al. (1989). Animals were fed a diet containing TCDD at concentrations of 5 or 25 ppt for ~4 years and were on a TCDD-free diet for ~18 months prior to parturition. Maternal TCDD levels (mean±SE) in adipose tissue were 49±11 (n=7) and 173±81 (n=3) ppt in the 5 and 25 ppt groups, respectively. Corresponding levels in the adipose tissue of offspring at weaning (4 months) were 187±58 and 847±298 ppt in the 5 and 25 ppt groups, respectively. From these data, a TCDD BCF of 4.29 was estimated from mother to nursing infant. This value is similar to that observed for TCDD in the marmoset monkey (Hagenmaier et al., 1990). The milk of the rhesus monkeys in the 25 ppt group contained from 4 to 14 ppt of TCDD, which corresponds to 150-500 ppt on a lipid basis. The authors calculated that the three mothers in the 25 ppt group excreted from 17% to 44% of their TCDD body burden by lactation. They also concluded that the results are generally consistent with overall triglyceride movement as mediating the excretion of TCDD in milk.

In a subsequent study, Bowman et al. (1990) reported the relative persistence of TCDD in the offspring of rhesus monkeys that were exposed earlier to 5 or 25 ppt of TCDD in the diet. The concentration of TCDD in adipose tissue was measured in offspring at ~4-5, 12, and 24 months of age. The decrease of TCDD levels in adipose tissue of seven young monkeys departed somewhat from first-order, single-compartment kinetics, but with the limited data and an assumption of first-order kinetics, a half-life of 121 days was estimated. When the data were adjusted within each animal for body weight gain and for average fat content at each age, the adjusted data apparently followed first-order, single-compartment kinetics, with a half-life of ~181 days. Thus, young monkeys apparently eliminate TCDD from adipose tissue at a faster rate than adult rhesus monkeys, which had individual half-lives ranging from 180 to 550 days (Bowman et al., 1989).

Several studies provide data in support of the transplacental transport of CDDs and CDFs to the human fetus. Kreuzer et al. (1997) measured the concentration of CDDs and CDFs in the lipids of adipose tissue and livers of 3 stillborn infants and detected 16 of a possible 17

congeners, with the exception of 1,2,3,7,8,9-HxCDF. TEQ levels ranged from 6.2 to 10.8 pg/g lipid, and TCDD levels ranged from 0.8 to 2.1 pg/g lipid for human infants that died at birth. These levels are similar to those reported in the lipid fractions of maternal tissues, suggesting that prenatal exposure to CDDs and CDFs reflects the levels present in maternal tissues. Similar findings were reported earlier by Schecter et al. (1990c), who detected TCDD (1.3 to 4.3 pg/g lipid) in the livers of three stillborn infants. Thus, significant prenatal exposure to CDDs and CDFs occurs, with the concentration of these compounds in the lipids of the newborn infants generally reflecting that in maternal lipids.

A significant source of postnatal exposure of human infants to CDDs and CDFs is through the ingestion of human milk. Several investigators have quantified the levels of TCDD in human milk samples. Many of the milk samples were pooled (Jensen, 1987). Rappe (1984) reported levels of 1-3 ppt TCDD in milk fat (lipid adjusted) from five volunteers in West Germany, and in a later report, Rappe et al. (1985) reported an average level of 0.6 ppt TCDD in milk fat from four volunteers in northern Sweden. Furst et al. (1986) reported an average level of 9.7 ppt TCDD in milk fat from three individuals in the Netherlands and <1.0 ppt TCDD in milk fat from two individuals in Yugoslavia. Nygren et al. (1986) reported average levels of TCDD in human milk samples from four subjects in Sweden to be 0.6 ppt in milk fat, in five subjects from West Germany to be 1.9 ppt in milk fat, and in four subjects from Vietnam to be <0.5 ppt in milk fat.

High levels of TCDD have been detected in the milk of mothers exposed to high levels of TCDD in the environment. Reggiani (1980) reported levels between 2.3 and 28.0 ppt TCDD in whole milk from mothers in Seveso. Baughman (1975) reported levels between 40.0 and 50.0 ppt TCDD in whole milk from mothers in South Vietnam. Schecter et al. (1987) also found high ppt levels of TCDD in human milk samples from South Vietnam. These authors found that levels from samples taken in 1985 from South Vietnamese mothers were comparable to the level of TCDD currently found in North American human milk samples (5 ppt).

Furst et al. (1989) examined the levels of CDDs and CDFs in human milk and the dependence of these levels on the period of lactation. The mean concentrations of CDDs in human milk (on a fat basis) ranged from 195 ppt for OCDD to 2.9 ppt for TCDD, with the levels of the other congeners decreasing with decreasing chlorination. This is in contrast to the generally lower levels of CDFs in human milk, which range from 25.1 ppt for 2,3,4,7,8-PeCDF to 0.7 ppt for 1,2,3,7,8-PeCDF. An evaluation of the CDD and CDF levels in relation to the number of breast-fed children found that the concentrations in milk generally decreased with the greater number of children. The CDD and CDF levels in milk from mothers nursing their second child are on average 20%-30% lower than those for mothers breast-feeding their first child. CDD and CDF levels were also analyzed in one mother over a period of 1 year after delivery of her

second baby to assess the effect of duration of lactation. After breast-feeding for 1 year, the mother had CDD and CDF levels that were 30%-50% of the starting concentration. Levels in milkfat (ppt) at 1, 5, and 52 weeks after delivery were 251, 132, and 119 for OCDD; 7.9, 5.9, and 1.4 for TCDD; and 33.1, 24.5, and 10 for 2,3,4,7,8-PeCDF, respectively. The results suggest a more rapid mobilization of CDDs and CDFs and excretion into human milk during the first few weeks postpartum. Although further studies are necessary, the limited data suggest that there are time-dependent, isomer-specific differences in the excretion of CDDs and CDFs in human milk.

Schecter et al. (1998a) assess the decrease in the levels of CDDs, CDFs, PCBs, DDE, and HCB in the blood and milk lipid in a mother that nursed twins over a 38-month period. During the first 23 months of nursing, the CDD and CDF TEQ decreased 68% (15.7 to 5.0 ppt, lipid) for blood and decreased 77% (13.6 to 3.1 ppt, lipid) for breast milk. Thus, lactation results in a similar reduction in CDD and CDF concentrations in the lipid fractions of blood and milk. During the first 23 months of nursing, the PCB 126 (3,3',4,4',5-PeCB) milk concentration also decreased 71% (21.0 to 6.1 ppt, lipid). The authors estimate that approximately 115 ng TEQ (CDDs, CDFs, coplanar PCBs) was ingested by each infant from breast feeding for this extended period of time.

Abraham et al. (1996) investigated the intake, fecal excretion, and blood levels of CDDs, CDFs, and PCB 126 in two breast-fed and two formula-fed infants. At 1 month, the concentrations of CDDs and CDFs in breast milk were 19.7 and 22.2 TEQ (pg/g lipid), while the formula diet contained only 0.38 TEQ (pg/g lipid). At the age of 11 months, the breast-fed infants' blood CDD and CDF concentrations were 29.2 and 37.5 TEQ (pg/g lipid), whereas the formula-fed infants' blood CDD and CDF concentrations were 2.4 and 2.6 TEQ (pg/g lipid). At this time, the mothers that breast-fed had blood CDD and CDF concentrations of 12.3 and 10.5 TEQ, while the mothers that formula-fed had blood levels of 16.9 and 13.8 TEQ (pg/g lipid). Because PCB 126 has a TEF of 0.1, it is important to note that at 11 months, breast-fed infants also have much higher levels of PCB 126 (287 and 374 pg/g lipid) relative to formula-fed infants (24 and 18 pg/g lipid). PCB 126 levels in mothers that breast-fed were 105 and 86 relative to levels of 193 and 52 (pg/g lipid) in the mothers that formula-fed. Thus, when PCB 126 is included in the TEQ calculation, the breast-fed infants' total TEQ blood concentration (body burden) is more than doubled from that estimated on the basis of CDDs and CDFs alone. The results of this study provide direct, quantitative data showing that the body burden (blood level) of CDDs, CDFs, and PCB 126 is more than 10 times higher in 11-month-old breast-fed infants than in 11-month-old formula-fed infants.

Although data are more limited for the co-planar PCBs, 3,3′,4,4′-TCB, 3,3′,4,4′,5-PeCB, and 3,3′,4,4′,5,5′-HxCB have been detected in human milk from Swedish mothers, at concentrations of 16-32, 72-184, and 46-129 ppt on a fat basis, respectively (Noren et al., 1990).

Therefore, lactation appears to be an effective means for the excretion of co-planar PCBs from mothers and a major source of postnatal exposure of nursing infants. Because 3,3′,4,4′,5-PeCB and other co-planar PCBs are present in human milk at concentrations up to 60-fold higher than TCDD, it is important to consider the relative toxic potency of these dioxin-like compounds and their potential health impact on nursing infants.

Kreuzer et al. (1997) measured the levels of CDDs and CDFs in the lipids of adipose tissue and liver of 17 infants (0.43 to 44 weeks of age) who died of sudden infant death syndrome. As expected, the concentrations of these compounds in breast-fed infants were higher than those in non-breast-fed infants; however, the magnitude of this difference varied because of differences in the age of the subjects and the duration of breast-feeding. The TEQ concentrations in the livers of these subjects were slightly, but not significantly, higher than the respective levels measured in the adipose tissue lipids. The results also suggest that the higher chlorinated congeners preferentially accumulate in liver lipids, an observation made earlier for adults in a study by Thoma et al. (1990) (see Table 1-5).

Kreuzer et al. (1997) used data from the above study and other published results to validate a physiological toxicokinetic model they developed to describe the body burden of TCDD for the entire human lifetime and the influence of breast-feeding on the body burden. The model includes gender- and age-dependent changes in the following parameters: body weight; volumes of liver, adipose, and muscle tissue; food consumption; and excretion of feces. The model also assumes that TCDD exposure occurs primarily from the ingestion of contaminated food, that TCDD is distributed freely in lipids, and that TCDD is excreted unchanged in the lipids of the feces as well as following hepatic metabolism. More complex biochemical processes such as protein binding, saturation of metabolism at high TCDD concentrations, or induction of metabolism are not part of this model, which considers factors more relevant for low-level or background human exposures. With the basis assumption of this single-compartment model and the free distribution of TCDD in all body lipids, including the gastrointestinal tract, the half-life of the nonmetabolic elimination (tf1/2) is proportional to the ratio of volume of body lipids (V) to the mass of lipids in stool excreted per unit time (dFa/dt). During aging, V increases at least 40 times but dFa/dt only 1.7 times (from 3 g/day in infants to 5 g/day in adults). Consequently, the half-life of the nonmetabolic elimination (tf1/2) is calculated to be only 0.42 years in newborns and 9.5 years in 40-year-old adults. According to this model, most TCDD is eliminated as unchanged compound in children, with the role of metabolism-dependent elimination becoming more important with age. Thus, the half-life increases almost linearly from its starting value of about 4 months in newborns and reaches a value of 5 years at the age of 40. An age dependent elimination of TCDD has also been reported experimentally in the rhesus monkey (Bowman et al., 1989, 1990). Furthermore, the model of Kreuzer et al. (1997) predicts

that the relatively high TCDD concentrations that might be reached after 6 months of nursing do not lead to an elevated lifetime body burden of TCDD.

In a related study, Patandin et al. (1999) investigated dietary, including lactational, exposure to CDDs, CDFs, and PCBs from early childhood until the early reproductive age of 25 years in order to assess exposure risk to the next generation. Based on the analysis of 83 milk samples, previously reported analysis of food products, and food questionnaire data, the daily TEQ intake per kg body weight is 50 times higher in breast-fed than bottle-fed infants and 3 times higher in toddlers than in adults. Although exposures are relatively high in breast-fed infants, breast-feeding for 6 months contributes only 12% and 14% to the respective body burdens of men and women at the age of 25 years. After babies are weaned, dairy products, processed foods, and meat are major sources of exposure to these compounds.

1.4.6. Pharmacokinetics and Aging

The influence of aging on the intestinal absorption of TCDD was studied in 13-week-, 13-month-, and 26-month-old (senescent) male Fischer 344 rats (Hebert and Birnbaum, 1987). Absorption was measured by an in situ intestinal recirculation perfusion procedure. When absorption was calculated in terms of ng TCDD absorbed/g mucosal dry weight/hour, the decrease between the senescent rats and the two younger age groups, from 544 ng/g/hour (young) to 351 ng/g/hour (senescent), was not statistically significant ($p<0.05$). The results indicate that, as with other molecules that depend on diffusion for their absorption, aging does not affect the intestinal absorption of TCDD.

Banks et al. (1990) studied the effect of age on the dermal absorption and disposition of TCDD and 2,3,4,7,8-PeCDF in male Fischer 344 rats. When rats were administered the same dose per body weight, dermal absorption of TCDD at 3 days after exposure decreased from 17.7±2.7% (mean±SD) to 5.6±2.5% of the administered dose in 10- and 36-week-old rats, respectively. Dermal absorption in the 96-week-old rats was similar to that of the 36-week-old rats. Dermal absorption of 2,3,4,7,8-PeCDF also decreased from 22.2±0.2% to 14.7±3.8% of the administered dose in 10- and 36-week-old rats, respectively. Dermal absorption of both compounds was also decreased in older rats given the same total dose per surface area. Older animals may have decreased blood flow in the upper dermis, which will decrease the clearance of these compounds from the application site. Potential age-related changes in the intercellular stratum corneum lipids may also play a role in the decreased dermal absorption observed in older animals. Changes in the percentage of the administered dose detected in various depots reflected age-related changes in dermal absorption, whereas age-related changes in the tissue distribution of the absorbed dose reflected changes in the total mass of these tissues at various ages. Overall elimination of the absorbed dose was not affected by age. Although this investigation was

conducted with a lipophilic solvent system and an animal model with skin that is more permeable than human skin, the results suggest that systemic bioavailability after dermal exposure to TCDD or 2,3,4,7,8-PeCDF may be reduced in older age groups.

In a similar study, absorption, tissue distribution, and elimination were examined 72 hours after dermal application of a lower dose of 200 pmol (111 pmol/cm^2) TCDD to weanling (3-week-old), juvenile (5-week-old), pubescent (8-week-old), young adult (10-week-old), and middle-aged (36-week-old) rats (Anderson et al., 1993). Dermal absorption using acetone as the vehicle was greatest in 3-week-old rats (129 pmol; 64% of the administered dose), decreasing to ~80 pmol (40%) in 5-, 8-, and 10-week-old rats and to 45 pmol (22%) in 36-week-old rats. The results indicate that TCDD is absorbed to a greater degree through skin of very young animals and that a significant decrease in potential for systemic exposure may occur during maturation and again during aging.

1.5. SELECTION OF DOSE METRIC

Risk assessment requires the scaling of exposure/dose across endpoints and across species. Given the many responses to TCDD and its congeners, the selection of dose metrics for use in quantitative risk assessments is a complex problem. The biochemical and toxicological responses of TCDD and related chemicals are initiated by their interaction with the Ah receptor. Some responses, such as enzyme induction, require short periods (minutes to hours) of Ah receptor activation. Other responses, such as cancer, require prolonged (months to years) activation of this pathway. Still other responses, such as the developmental toxicities, require receptor activation during specific windows of sensitivity. Because of the different mechanisms involved in these diverse responses, it is unlikely that a single dose metric will be adequate for all of these endpoints. A number of studies have proposed a variety of dose metrics for a number of different responses. These studies have taken different approaches ranging from simple curve fitting exercises (Hurst et al., 2000; van Birgelen et al., 1996) to more complex PBPK modeling approaches (Jusko et al., 1995; Andersen et al., 1997; Kohn et al., 1993; Portier and Kohn, 1996). Area under the curve (AUC), a dose metric traditionally used in the pharmaceutical literature, has also been proposed as a dose metric for dioxin cancer risk estimates (Becher et al., 1998).

The choice of dose metric not only considers mechanistic data but must also consider pragmatic approaches as well. The use of the dose metric plays a role in its choice. Because of differences in life-span and uncertainties in the window of sensitivities for various endpoints, AUC may not be a useful dose metric for cross species extrapolation. However, AUC has been used in the analysis of the human cancer data (Becher et al., 1998) and may be a useful dose metric when applied to accidental or occupational exposures since cross species scaling is not

required. The choice of dose metric is also dependent upon the data available. A number of dose metrics, such as Ah receptor occupancy, induction of CYP1A2, and decreases in EGF receptor have been proposed based on PBPK models (Jusko et al. 1995; Andersen et al.1997; Kohn et al 1993; Portier and Kohn, 1996). While these dose metrics have been useful in hypothesis testing in experimental systems, they are not useful in animal to human extrapolations due to the difficulty in measuring these parameters in humans. In the following section, the strengths and weaknesses of a variety of proposed dose metrics will be presented.

1.5.1 Administered Dose

In experimental studies, animals are administered a defined dose through a variety of routes. A default method used by USEPA (USEPA, 1992; 1996) to estimate the human equivalent dose when scaling across species is to use allometric scaling based on the following equation:

$$Dose_{human} = Dose_{rat} (BW_{rat}/BW_{human})^{0.25}$$

Where BW is the body weight in kg and Dose is the daily administered dose in rats or the scaled human daily dose expressed as ng/kg/d. This method is thought to scale administered dose in such a way as to result in equivalent effective doses in humans and experimental animals (USEPA, 1992). Using this equation a dose of 1 ng TCDD/kg/d in a 0.35 kg rat would result in a scaled human dose of 0.27 ng TCDD/kg/d for a 70 kg human. If this scaling method applies to TCDD and related chemicals, then 1 ng TCDD/kg/d in the rat should produce similar effective dose in a human exposed to 0.27 ng TCDD/kg/d, some 3.8 times lower. Assuming similar sensitivity between rats and humans at the tissue level, effective doses should be a function of tissue concentration. Tissue concentrations of TCDD and related chemicals are directly related to the concentration of TCDD in the body. The steady-state concentration of TCDD in the body, or steady-state body burden, can be estimated in rats and humans using the following equation.

$$\text{Steady-state body burden (ng/kg)} = (Dose*F) * (t_{½}/Ln(2))$$

where Dose is the daily administered dose, F is the fraction absorbed, and $t_{½}$ is the species-specific half-life of TCDD. In the present example, we will assume F is 50% and the species specific half-life of TCDD is 25 days for rats and 2593 days for humans. Starting with an administered dose of 1 ng/kg/d in rats and the scaled human dose of 0.27 ng/kg/d, the steady-

state body burdens are presented in Table 1-14. The steady-state body burden of TCDD using the scaled human dose is approximately 28 times that of the steady-state body burden in the rat (Table 1-14). Using the equation above, the estimated steady-state body burden in rats exposed to 1 ng TCDD/kg/day is 18 ng/kg. An equivalent administered dose in humans that results in a body burden of 18 ng/kg is estimated at 0.0096 ng/kg/day. It should be noted that when body burden is used as the dose metric, an equivalent human dose is over 100 times less than the human equivalent dose estimated using the EPA default scaling method.

Using administered dose as a dose metric has additional uncertainties when route and duration of exposures are varied. Tissue concentrations of a chemical are influenced by the route and duration of exposure. For example, the time course and peak tissue concentrations for the distribution of a dose of TCDD is different when the dose is administered orally, dermally or intratracheally (Diliberto et al., 1994). The dosing vehicle can also influence the absorption and distribution of a chemical (Dix et al., 1997). The amount and rate of absorption of a chemical in an oil vehicle can be very different when the chemical is dissolved or suspended in an aqueous vehicle or bound to soil (Olson et al., 1994). Using administered dose as the metric for exposures occurring through the same route, rate and dosing vehicle within the same species clearly is appropriate. However, in cases where these parameters vary across dosing scenarios, there is increasing uncertainty in the extrapolation.

Clearly, the default scaling method results in an estimated human equivalent dose that produces a much greater estimated steady-state body burden (505 ng/kg) than the rat's. One reason for the discrepancy of the scaling method is that the half-life of TCDD in rodents and humans is much larger than is typically observed for other xenobiotics (Bachmann et al., 1996; Sarver et al., 1997). The half-life of TCDD in humans is approximately 100 fold greater than in rats. The EPA default scaling methodology would estimate human half-lives at approximately 3.8 times greater than in rats. This exercise demonstrates that administered dose does not provide a useful dose metric for cross species extrapolation even if the dose is scaled using the EPA default methodology. However, administered dose can be used to compare exposures between human populations in order to describe potential human health risks, because the species differences in half-life would not exist in this case.

1.5.2 Area Under the Curve

Area under the curve or AUC is frequently used as a dose metric for reversible responses of pharmaceutical agents. Typically, these agents have half-lives on the order of minutes to hours. In the pharmaceutical literature, AUC is most frequently used for drugs with a rapid onset of action and that are rapidly reversed following cessation of exposure (Goodman and Gilman). In addition, the pharmacological actions of the drugs and the length of time of the response is

clearly defined in both animals and humans. In essence, plasma concentrations are readily determined and the time span is easily defined. In cases where repeated doses of a drug is used, the steady-state plasma concentration is the preferred measure of dose. Also, when using drugs with a slow onset (i.e., a week or more), such as the tricyclic antidepressants, dose is typically expressed as steady-state blood concentrations.

Mechanistic considerations also suggest that AUC can be a useful dose metric for chemical carcinogenesis. AUC has been applied as a dose metric in chemical carcinogenesis for DNA reactive chemicals. In these cases, the DNA reactive chemicals, increases in the mutational rates are expected to be related to the integrated tissue exposure to the critical DNA reactive species (Krewski et al., 1994). What is less certain about AUC as a dose metric is whether the risk across species for DNA reactive chemicals should be normalized based on integrated daily tissue concentration or an integrated lifetime tissue concentration. In any event, the dose metric would be the integrated tissue concentration of DNA reactive chemical over the appropriate period of the animal or human life span (Krewski et al., 1994).

There are some concerns over applying AUC as a cancer dose metric for TCDD. TCDD and related chemicals are thought to induce tumors non-genotoxic mechanisms. The evidence supporting the use of lifetime AUC calculations for cancer risk involves genotoxic chemicals and radiation. TCDD lacks direct acting genotoxicity and is considered a tumor promoter. This promotional process requires sustained tissue concentrations of TCDD sufficient to maintain increased gene expression. It is likely that AUC would be an appropriate dose metric for cancer and may also involve the incorporation of a threshold concentration (Hays et al., 1997). Chemicals for which AUC has been applied as a dose metric are DNA reactive chemicals. DNA reactive chemicals produce DNA adducts and the probability of a mutational event occurring from adduct formations increases with the number of adduct formed. Adduct formation is associated with an integrated measure of dose. Because of the difference in mechanism of action, there no evidence supporting or refuting the use of AUC as a cancer dose metric for TCDD.

The need for species extrapolation in toxicology further complicates the use of AUC as a dose metric. While blood or plasma concentrations of TCDD can be determined in both human and animals, the determination of the time span for which the AUC is to be calculated is much less certain. For some of the toxic responses of TCDD, the window of sensitivity is clearly defined in rodents and humans, such as induction of cleft palate. For other responses, such as the developmental reproductive alterations observed in male and female rats, the window of sensitivity has been narrowed to exposures between gestational day 15 and 20 in the rats, but the human window of sensitivity is uncertain. For carcinogenesis, the length of time required to induce the response remains uncertain in both experimental animals and humans. In order to

apply AUC for species comparisons of the sensitivity to TCDD, one must have a better understanding of the species differences in the windows of sensitivity to the various biological effects of TCDD.

Another of the uncertainties in risk assessment is time scaling across species. The difficulty is that there does not appear to be a consistent method of time scaling between species for different biological processes. If we were to compare the length of time of several common biological phenomena in rats and humans, we would observe different ratios of these time frames. For example, rats live approximately 2-2.5 years, while the average human life span is estimated at 70 years. The gestation period is approximately 21 days in a rat and 270 days in humans. The age at the time of puberty in rats is between postnatal days 29-45 and in humans occurs between 8 and 14 years old. In contrast, some processes, such as diurnal cycles or cell replication, have equivalent time spans between species. Due to uncertainties in how to properly account for the differences in time span for different biological responses, lifetime average daily dose is recommended as the default dose metric (Rhomberg, 1990).

In addition, differences in life-span also must be considered. Brody and Reid (1967) proposed that the biological activity of a drug is related to its plasma concentrations. If animals and humans had the same plasma concentrations for their entire lives, the human AUC would be greater because humans have a longer half-life. However, because the plasma concentrations were the same, according to Brody and Reid (1967) the responses should be similar. Hence, in order to use AUC for chronic toxicities, such as cancer, a correction for the difference in life-span must be applied. Typically, this involves the derivation of an average daily AUC (Alyward et al., 1996). An estimation of the average daily AUC is directly related to steady-state body burdens. Hence, once the AUC is corrected for life-span differences, these values are equivalent to steady-state body burdens.

While AUC may not be an appropriate dose metric for animal to human extrapolations, it is a use tool for comparing populations exposed to high concentrations of dioxins over a short period of time to the background population. Becher et al (1998) successfully used this approach to examine dose response relationships for cancer in an occupationally exposed cohort. One difficulty in determining AUC is the accuracy of the intake measurements. Past exposures through the diet are uncertain, although they have been estimated (Pinsky and Lorber, 1998). Future exposures are thought to be decreasing, although the exact magnitude of this decrease are uncertain. Hence, determination of AUC carries a number of uncertainties that must be considered.

1.5.3 Plasma or Tissue Concentrations

Brodie and Reid (1967) have argued that the response to a drug is determined by the amount bound to its biological receptor and since the drug receptor complex is in dynamic equilibrium with the free drug in the plasma, the biological response of a drug will be related to its plasma concentrations. There is no reason to believe that this relationship will not be true for TCDD and related chemicals. However, there are several data gaps that may prohibit the use of plasma or blood concentrations for species extrapolation. First, few animal studies determined blood or plasma concentrations of TCDD, particularly in the subchronic, chronic and lifetime exposures. PBPK models can be used to estimate blood concentrations and should provide reasonable estimates of these values. In contrast, the human exposure data is based predominately on blood, serum or plasma dioxin concentrations. One limitation of the human data is that it is mostly presented on a lipid adjusted basis. Hence in order to compare the human and animal plasma or blood concentrations, one would have to first estimate the blood concentrations in the animals using a PBPK model. Then either the animal data would have to be expressed as a lipid basis or the human data would have to be expressed as a wet weight basis. In either case, assumptions of the percent lipid in the blood would have to be applied as well as a number of assumptions used in the PBPK models.

The use of tissue concentrations as a dose metric has been examined by Van Birgelen et al., (1996) and Hurst et al., (1999). Van Birgelen and coworkers (1996) presented data demonstrating tissue that concentrations provided an accurate prediction of enzyme induction regardless of the exposure scenario (i.e. acute vs subchronic). The use of alternative dose metrics, such as AUC and total administered dose, failed to demonstrate predictive relationships for enzyme induction and immunotoxicity (van Birgelen, 1996). Similarly, Hurst et al. (1999) presented data demonstrating that fetal tissue concentrations of TCDD on gestation day 16 predicted decreases in sperm counts, delays in puberty in males, urethra-phallus distance and the incidence of vaginal threads in rats prenatally exposed to TCDD on either gestational day 9 or 15. These data suggest that target tissue concentrations may be a reasonable dose metric for these responses.

While tissue concentrations may aid in estimating risks, these data are unlikely to be collected in humans in sufficient numbers to be useful, particularly for fetal concentrations. Plasma concentrations are also a useful tool to compare exposures in different human populations. Application of plasma concentrations as a dose metric for species extrapolation require some level of assumptions as described above, but reasonable comparisons could be made, particularly for comparing steady-state exposures in humans and animals. Comparing plasma or blood concentrations following acute exposures in experimental animals to steady-state human blood or plasma concentrations would not be appropriate. One limitation of the use

of either plasma, blood, or target tissue concentrations as dose metrics is the lack of human PBPK models to predict these values based on changes in intake patterns.

1.5.4 Steady-State Body Burdens

Body burden is defined as the concentration of TCDD and related chemicals in the body and is typically expressed as ng/kg. Steady-state body burden is defined as the concentration of TCDD and related chemicals in the body under steady-state exposure conditions and is also expressed as ng/kg. Humans generally reach exposures approximating steady-state between the ages of 20 and 30, with body burdens increasing slightly with age over the course of the next several decades. Humans steady-state body burdens and are estimated based on an intake rate and the half-life of TCDD in humans. Alternatively, body burdens in humans are estimated based on lipid adjusted serum or adipose tissue TCDD or TEQ concentrations. In animals, these values are calculated from studies at or approaching steady-state and are associate with either biochemical or toxicological responses. In addition, these values are calculated based on either knowledge of the species-specific half-life and the exposure regimen or they are estimated based on the TCDD tissue concentration, the size of the tissues and the weight of the animal.

Steady-state body burdens provide a useful dose metric for several reasons. First, tissue and blood concentrations are directly related to body burdens. Thus, body burdens are surrogates for tissue concentrations. Second, the differences in the half-life of TCDD between species is accounted for because these body burdens are estimated at steady-state conditions. Third, DeVito et al. (1995) have demonstrated that for some biochemical responses, chloracne and cancer, species have similar rates of responses when dose is expressed on a body burden basis. Finally, body burdens provide flexibility because they can be estimated based on either intake rates or on measured tissue concentrations.

Body burdens also have some limitations. In order to estimate body burdens from lipid adjusted tissue concentrations, an assumption of the percent body fat must be used. In the reassessment, a value of 25% has been used. It should be noted that there are human populations with body fat compositions less than 10% and greater than 35%. Also when estimating the body burden based on intake rates and half-lives, the uncertainty of these parameters should be considered. In the reassessment, the estimated steady-state body burden of approximately 5 ng TEQ/kg is based on measured serum concentrations from several populations in the mid 1990's. While measured concentrations should eliminate some of the uncertainties around estimates using intake rates and half-life assumptions, it is likely that these measured values represent a past history of higher exposure and we must anticipate a continued downward trend to present a “true” lifetime average concentration. Caution must be used when using body burden in conditions other than steady-state. Under these short-term exposures conditions in experimental

animals, the relationship between tissue concentrations and body burden may not be the same as under steady-state conditions.

1.5.5. Mechanistic Dose Metrics

Several groups have proposed a variety of dose metrics based on mechanistic considerations, such as concentration of occupied AhR (Jusko, 1995), induced CYP1A2 (Andersen et al., 1997; Kohn et al., 1993) and reduced epidermal growth factor receptor (EGFR) (Portier and Kohn, 1996). While these dose metrics are intellectually appealing, it must be kept in mind that they are still hypothesized dose metrics and require further research to demonstrate their utility for cross-species extrapolations. In addition, these dose metrics are unlikely to be measured in sufficient human samples to be useful.

1.5.6. Summary

A variety of dose metrics have been proposed for estimating potential human health effects following exposure to dioxins. Many of these dose metrics have limitations that prohibit their use, such as tissue concentrations and the mechanistic dose metrics. Other dose metrics, such as AUC have limited utility for species extrapolations because of our limited understanding of the concept of physiological time. Some dose metrics can be used to compare different human exposures, such as AUC and administered dose, but are not suitable for species extrapolations. Other dose metrics, such as steady-state body burdens or blood concentrations, are useful dose metric because they are easily estimated, and are directly related to tissue concentrations and can be estimated in both animals and humans. The use of any of these dose metrics requires a number of assumptions discussed above. The choice of dose metric requires an understanding of the data available and their application of the dose metric. Future research efforts on the issue of dose metrics could provide better guidance in choosing the dose metrics for dioxins and related chemicals. However, in the mean time, the use of steady-state body burdens can provide a basis for species extrapolations.

Table 1-1. Gastrointestinal absorption of TCDD and related compounds following a single oral exposure by gavage

Chemical	Species (Sex)	Dose (μmol/kg)	Dose (μg/kg)	Vehicle	% Administered Dose Absorbed[a] [Mean (Range)]	Reference
CDDs						
2,3,7,8-TCDD	Sprague-Dawley rat (M)	0.16	50	acetone:corn oil (1:7)	70	Piper et al., 1973
2,3,7,8-TCDD	Sprague-Dawley rat (M/F)	0.003	1.0	acetone:corn oil (1:25)	84 (66-93)	Rose et al., 1976
2,3,7,8-TCDD	Hartley guinea pig (F)	0.005	1.45	acetone:corn oil (1:45)	50	Nolan et al., 1979
2,3,7,8-TCDD	Golden Syrian hamster (M)	2.0	650	olive oil	74	Olson et al., 1980
2,3,7,8-TCDD	Human (M)	0.000003	0.001	corn oil	87	Poiger and Schlatter, 1986
1,2,3,7,8-PeCDD	Sprague-Dawley rat (M/F)	0.03	9.2	corn oil	NR (19-71)	Wacker et al., 1986
OCDD	Fischer 344 rat (M)	0.11 1.1 1.1 11	50 500 500 5000	o-dichlorobenzene:Emulphor (1:1) o-dichlorobenzene:corn oil (1:1) corn oil suspension corn oil suspension	12 15 2 5	Birnbaum and Couture, 1988

Table 1-1. Gastrointestinal absorption of TCDD and related compounds following a single oral exposure by gavage (continued)

Chemical	Species (Sex)	Dose (μmol/kg)	Dose (μg/kg)	Vehicle	% Administered Dose Absorbed[a] [Mean (Range)]	Reference
BDDs						
2,3,7,8-TBDD	Fischer 344 rat (M)	0.001 0.01 0.1 0.5	0.5 5 50 500	Emulphor:ethanol:water (1:1:3)	78 82 60 47	Diliberto et al., 1990
CDFs						
2,3,7,8-TCDF	Fischer 344 rat (M)	0.1 1.0	30.6 306	Emulphor:ethanol (1:1)	90 90	Birnbaum et al., 1980
2,3,7,8-TCDF	Hartley guinea pig (M)	0.02	6	Emulphor:ethanol:water (1:1:8)	90	Decad et al., 1981a
2,3,4,7,8-PeCDF	Fischer 344 rat (M)	0.1 0.5 1.0	34 170 340	corn oil	~70 ~70 ~70	Brewster and Birnbaum, 1987
PCBs						
3,3′4,4′-T4CB	C57BL mouse (F)	34.5	10,000	corn oil	77	Wehler et al., 1989

[a]Absorption is generally estimated as the difference between the administered dose (100%) and the percent of the dose that was not absorbed. The unabsorbed fraction is estimated as the recovery of parent compound in feces within 48 hours of exposure.
NR = Not reported.

Table 1-2. Percentage of TCDD in the liver of rats 24 hours after oral administration of 0.5 mL of various formulations containing TCDD

Formulation	TCDD Dose (ng)	No. of Animals	Percentage of Dose in the Liver
50% ethanol	14.7	7	36.7±1.2
Aqueous suspension of soil (37%, w/w) that had been in contact with TCDD for:			
10–15 hours	12.7, 22.9	17	24.1±4.8
8 days	21.2, 22.7	10	16.0±2.2
Aqueous suspension of activated carbon (25%, w/w)	14.7	6	≤0.07

w/w = Weight by weight.

Source: Poiger and Schlatter, 1980.

Table 1-3. Dermal absorption of 2,3,7,8-TCDD and related compounds in the rat

Chemical	Dose		% Administered Dose	
	(μmol/kg)	(μg/kg)	Skin Site[a]	Absorbed
2,3,7,8-TCDD	0.00015	0.05	61.73±4.37	38.27±4.37
	0.001	0.32	59.71±1.90	40.29±1.89
	0.01	3.2	72.60±0.41	27.40±0.41
	0.1	32	82.21±2.85	17.78±2.85
	0.5	160	80.92±2.74	19.08±2.74
	1.0	321	82.68±3.69	17.30±3.67
2,3,7,8-TCDF	0.1	31	51.18±11.95	48.84±11.95
	0.5	153	82.14±11.22	17.86±11.22
	1.0	306	88.70±5.17	11.32±5.17
1,2,3,7,8-PeCDF	0.1	34	74.72±3.58	25.27±3.58
	0.5	170	91.67±2.46	8.33±2.46
	1.0	340	84.23±5.44	15.76±5.44
2,3,4,7,8-PeCDF	0.1	34	65.77±4.80	34.19±4.78
	0.5	170	75.50±1.81	24.50±1.80
	1.0	340	81.84±1.67	18.16±1.67

[a]Values are the mean±SD of three to four animals and represent the amount of administered dose of radiolabeled congener remaining at the application site 3 days after dermal exposure.

Source: Brewster et al., 1989.

Table 1-4. Tissue distribution of [^{14}C]-2-3,7,8-TCDD in female Wistar rats[a]

Tissue	Range of 2,3,7,8-TCDD Concentrations (ng/g)
Liver	29.23–30.99
Adipose tissue	3.72–4.14
Adrenal glands	0.89–1.08
Ovaries	0.76–0.96
Thymus	0.60–1.05
Skin	0.64–0.68
Lung	0.32–0.33
Kidney	0.27–0.29
Pancreas	0.21–0.31
Spleen	0.18–0.23
Serum	0.16–0.18
Bone (with marrow)	0.16–0.16
Muscle	0.08–0.12
Brain	0.07–0.09

[a]Distribution was assessed 7 days after a single subcutaneous exposure (3 μg/kg bw).

Source: Abraham et al., 1988.

Table 1-5. 2,3,7,8-Substituted PCDDs and PCDFs in human liver and adipose tissue

	Tissue Concentrations on a Lipid Basis (ppt)			Tissue Concentrations on a Wet Weight Basis (ppt)	
	Fat	Liver	Liver/Fat	Liver[a]	Liver/Fat
TCDD	8.0	16.4	2.05	1.1	0.14
PeCDD	16.4	20.1	1.22	1.4	0.09
HxCDD	94.7	166.8	1.76	11.7	0.12
HpCDD	106.7	1,002.4	9.39	70.2	0.66
OCDD	373.2	4,416.2	11.83	309.1	0.83
TCDF	2.5	5.5	2.20	0.4	0.15
PeCDF	35.2	173.7	4.93	12.2	0.35
HxCDF	41.5	389.5	9.38	27.3	0.66
HpCDF	14.2	218.9	15.42	15.3	1.08
OCDF	4.0	29.7	7.43	2.1	0.52

Values are the mean of 28 people from the Munich area.
[a]Estimated from the % fat in the liver (7.02±5.33%, mean±SD)

Source: Thoma et al., 1990.

Table 1-6. Elimination of 2,3,7,8-TCDD and related compounds from major tissue depots

Chemical	Species (Sex)	Dose	Tissue	Half-Life (days)	Remarks	Reference
CDDs						
2,3,7,8-TCDD	Wistar rat (F)	0.3 µg/kg, s.c.	liver liver liver adipose	11.5 16.9 13.6 24.5	95% Confidence interval (time period investigated): 10.7-12.3 (10-49 days) 14.0–21.4 (49–91 days) 12.8–14.4 (10–91 days) 22.4–26.8 (14-91 days)	Abraham et al., 1988
2,3,7,8-TCDD	Wistar rat (M)	1.0 µg//kg, i.p.	liver adipose	37.1 53.2	Tissue levels were measured for 20 weeks following exposure	Lakshmanan et al., 1986
2,3,7,8-TCDD	Sprague-Dawley rat (M)	7 or 20 ppb in diet for 42 days	liver	11	85% total dose	Fries and Marrow, 1975
2,3,7,8-TCDD	Sprague-Dawley rat (F)	7 or 20 ppb in diet for 42 days	liver	13	70% of total dose	Fries and Marrow, 1975
2,3,7,8-TCDD	C57BL/6J mice (M) Ah^b/Ah^d	0.5 µg/kg, i.p.	liver adipose skin	8.5 10.3 16.0	Pool size (% of total dose): 36.8 23.6 7.6	Birnbaum, 1986
2,3,7,8-TCDD	C57BL/6J mice (M) Ah^d/Ah^d	0.5 µg/kg, i.p.	liver adipose skin	7.1 7.6 14.9	Pool size (% of total dose): 20.6 31.3 10.2	Birnbaum, 1986
2,3,7,8-TCDD	DBA/2J mice (F) Ah^b/Ah^d	0.5 µg/kg, i.p.	liver adipose skin	12.4 13.3 13.2	Pool size (% of total dose): 29.2 30.9 21.4	Birnbaum, 1986

Table 1-6. Elimination of 2,3,7,8-TCDD and related compounds from major tissue depots (continued)

Chemical	Species (Sex)	Dose	Tissue	Half-Life (days)	Remarks	Reference
2,3,7,8-TCDD	DBA/2J mice (F) Ah^d/Ah^d	0.5 µg/kg, i.p.			Pool size (% of total dose):	Birnbaum, 1986
			liver	11.9	20.2	
			adipose	11.8	42.3	
			skin	12.8	26.6	
2,3,7,8-TCDD	rhesus monkey (F)	25 ppt in diet	adipose	391±88	Mean±SE (n=7)	Bowman et al., 1989
OCDD	Fischer 344 rat (M)	50 µg/kg, i.v.			Pool size (% of total dose):	Birnbaum and Couture, 1988
			liver	84	72.7	
			adipose	38	7.1	
			skin	3	9.0, 1st component	
				69	0.3, 2nd component	
BDDs						
2,3,7,8-TBDD	Fischer 344 rat (M)	0.5 µg/kg, i.v. (0.001 µmol/kg)	liver	4.5	1st component	Kedderis et al., 1991a
				16.5	2nd component	
			adipose	57.8		
			skin	2.5	1st component	
				57.8	2nd component	
			muscle	1.6	1st component	
				26.7	2nd component	
			blood	18.2		
CDFs						

Table 1-6. Elimination of 2,3,7,8-TCDD and related compounds from major tissue depots (continued)

Chemical	Species (Sex)	Dose	Tissue	Half-Life (days)	Remarks	Reference
2,3,7,8-TCDF	Fischer 344 rat (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	liver adipose skin muscle blood	0.10 1.25 3.75 0.45 11.09 0.02 0.72 0.02 1.14	Pool size (% of total dose) 29.09 1st component 31.39 2nd component 17.85 6.84 1st component 1.22 2nd component 24.85 1st component 6.73 2nd component 1.31 1st component 0.89 2nd component	Birnbaum et al., 1980
2,3,7,8-TCDF	C57BL/6J mice (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	liver adipose skin muscle	1.9 1.6 0.15 4.0 0.015 1.1	 1st component 2nd component 1st component 2nd component	Decad et al., 1981b
2,3,7,8-TCDF	DBA/2J mice (M)	30.6 µg/kg, i.v. (0.1 µmol/kg)	liver adipose muscle	1.8 7.0 0.02 4.0	 1st component 2nd component	Brewster and Birnbaum, 1988

Table 1-6. Elimination of 2,3,7,8-TCDD and related compounds from major tissue depots (continued)

Chemical	Species (Sex)	Dose	Tissue	Half-Life (days)	Remarks	Reference
1,2,3,7,8-PeCDF	Fischer 344 rat (M)	34 µg/kg, i.v. (0.1 µmol/kg)	liver adipose skin muscle adrenal blood	1.36 25.72 12.91 1.32 14.53 0.03 6.96 0.14 2.36 0.07 12.42	Pool size (% of total dose): 42.59 1st component 1.27 2nd component 10.19 7.14 1st component 1.49 2nd component 34.81 1st component 7.42 2nd component 0.26 1st component 0.02 2nd component 5.33 1st component 1.29 2nd component	Brewster and Birnbaum, 1988
1,2,3,7,8-PeCDF	Sprague-Dawley rat (F)	4.0 µg/kg, p.o.	liver	3.3	69.8% of total dose	Van den Berg et al., 1989a,b
2,3,4,7,8-PeCDF	Fischer 344 rat (M)	34 µg/kg, i.v. (0.1 µmol/kg)	liver adipose skin muscle blood	193 69 0.62 1.23 0.04 0.51 9.84 0.04 1.32 55	Pool size (% of total dose): 67.71 10.53 3.54 1st component 1.37 2nd component 29.40 1st component 2.01 2nd component 0.78 3rd component 3.18 1st component 0.37 2nd component 0.008 3rd component	Brewster and Birnbaum, 1987

Table 1-6. Elimination of 2,3,7,8-TCDD and related compounds from major tissue depots (continued)

Chemical	Species (Sex)	Dose	Tissue	Half-Life (days)	Remarks	Reference
2,3,4,7,8-PeCDF	Sprague-Dawley rat (F)	5.6 µg/kg, p.o.	liver	108	78.3% of total dose	Van den Berg et al., 1989b
1,2,3,6,7,8-HxCDF	Sprague-Dawley rat (F)	6.0 µg/kg, p.o.	liver	73	63.4% of total dose	Van den Berg et al., 1989b
PCBs						
3,3′,4,4′-TCB	Sprague-Dawley rat (F)	5 mg/kg/day, p.o., for 21 days	liver adipose	0.8 2.5	21-day exposure produced steady state with 300 ng/g in liver and 8 µg/g in adipose tissue. Elimination was assessed over a 22-day postexposure period.	Clarke et al., 1984
3,3′,4,4′-TCB	ICR mice (M)	8 mg/kg, p.o., every other day for 10 doses	liver adipose serum	2.15 2.60 1.07	Steady-state tissue concentrations: 1.5 µg/g 19.2 µg/g 0.04 µg/mL	Clevenger et al., 1989

i.v. = intravenous; s.c. = subcutaneous; i.p. = intraperitoneal; p.o. = per os.

Table 1-7. Elimination constants and half-lives of various 2,3,7,8-Substituted CDDs and CDFs in hepatic and adipose tissue of marmoset monkeys[a,b]

Congener	Hepatic Tissue			Adipose Tissue		
	K_e ($weeks^{-1}$)	Half-Life (weeks)	95% Conf. Interval (weeks)	K_e ($weeks^{-1}$)	Half-Life (weeks)	95% Conf. Interval (weeks)
2,3,7,8-TCDD[c]	0.0841±0.0109	8.3	6.6–11.1	0.0658±0.0072	10.5	8.7–13.4
1,2,3,7,8-PeCDD[c]	0.0649±0.0101	10.7	8.2–15.4	0.0490±0.0057	14.2	11.5–18.3
1,2,3,4,7,8-HxCDD	0.0702±0.0059	9.9	8.4–11.8	0.0411±0.0083	16.9	12.1–27.9
1,2,3,6,7,8-HxCDD	0.0558±0.0046	12.4	10.7–14.9	0.0373±0.0073	18.6	13.4–30.2
1,2,3,7,8,9-HxCDD	0.0767±0.0078	9.0	7.5–11.3	0.0525±0.0089	13.2	9.9–19.7
1,2,3,4,6,7,8-HpCDD	0.0518±0.0081	13.4	10.2–19.3	0.0372±0.0060	18.6	14.2–27.2
OCDD	0.0089±0.0084	78	27–∞[d]	0.0122±0.0093	101	20–∞[d]
2,3,7,8-TCDF	0.8012±0.0549	<0.87[e]	-<1.00	0.4986±0.0829	1.39	1.05–2.06
1,2,3,7,8-/1,2,3,4,8-PeCDF	0.7476±0.0294	0.93	0.86–1.00	0.4735±0.0408	1.46	1.25–1.76
2,3,4,7,8-PeCDF	0.0786±0.0048	8.8	7.9–10.0	0.0563±0.0059	12.3	10.2–15.5
1,2,3,4,7,8-/1,2,3,4,7,9-HxCDF	0.0307±0.0039	23	18–30	0.0103±0.0074	68	28–∞[d]
1,2,3,6,7,8-HxCDF	0.0486±0.0037	14.3	12.4–16.7	0.0290±0.0091	24	15–62
1,2,3,7,8,9-HxCDF	0.0848±0.0057	8.2	7.2–9.4	not analyzed[f]	NA	NA
2,3,4,6,7,8-HxCDF	0.0373±0.0057	18.6	14.3–26.5	0.0182±0.0082	38	20–327

Table 1-7. Elimination constants and half-lives of various 2,3,7,8-Substituted CDDs and CDFs in hepatic and adipose tissue of marmoset monkeys[a,b] (continued)

Congener	Hepatic Tissue			Adipose Tissue		
	K_e ($weeks^{-1}$)	Half-Life (weeks)	95% Conf. Interval (weeks)	K_e ($weeks^{-1}$)	Half-Life (weeks)	95% Conf. Interval (weeks)
1,2,3,4,6,7,8-HpCDF	0.0186±0.0072	37	21–152	-0.0140±0.0137	∞[d]	54–∞[d]
1,2,3,4,7,8,9-HpCDF	0.0088±0.0127	79	20–∞[d]	0.0011±0.0112	660	30–∞[d]
OCDF	0.0040±0.0096	174	30–∞[d]	-0.0042±0.0148	∞[d]	28–∞[d]

[a]Source: Neubert et al., 1990.
[b]Animals were treated subcutaneously with a single dose of a defined CDD/CDF mixture, and the tissues were analyzed at different times following treatment. Half-lives were calculated from tissue concentrations of the 2,3,7,8-substituted congeners in hepatic and adipose tissue. Values are given as elimination rate constant K_e including estimated SD and half-life including 95% confidence intervals.
[c]Calculated from the time period: >6 weeks after injection.
[d]Calculated half-life is apparently infinite. Data for OCDD and OCDF are unreliable due to delayed absorption.
[e]Not detected in hepatic tissue 6 weeks after treatment; limits of detection used for calculation.
[f]Due to interference.
NA = Not applicable.

Table 1-8. TCDD concentrations in liver and adipose tissue following different doses and calculated concentration ratios (liver/adipose tissue)[a]

Dose (ng/kg)	Number	TCDD Concentration Liver (ng/g)	TCDD Concentration Adipose Tissue (ng/g)	Concentration Ratio: Liver/Adipose Tissue
1	6	0.0031±0.0009	ND	NA
3	6	0.0102±0.0020	0.0139±0.0015	0.74±0.15
10	12	0.0406±0.0121	0.0494±0.0084	0.82±0.20
30	6	0.162±0.032	0.139±0.021	1.16±0.07
100	6	0.699±0.130	0.335±0.065	2.10±0.27
300	6	3.38±0.22	0.819±0.075	4.14±0.31
1000	6	10.7±2.2	2.02±0.17	5.27±0.96
3000	5	27.9±2.4	3.66±0.31	7.65±0.64

[a]Concentrations were measured 7 days after injection.
ND = Not detectable; NA = not applicable.

Source: Abraham et al., 1988.

Table 1-9. Metabolism and excretion of 2,3,7,8-TCDD and related compounds[a]

Chemical	Species	Dose	Chemical Nature of Excretion Products (% Metabolites)			Ratio of % of Dose Excreted (Feces/Urine)	Half-Life[b] (days)	Comment	Reference
			Urine	Bile	Feces				
CDDs									
2,3,7,8-TCDD	Sprague-Dawley rat (M)	50 µg/kg, p.o.	NA	NA	NA	4.0	17.4±5.6[c]	NC	Piper et al., 1973
2,3,7,8-TCDD	Sprague-Dawley rat (M)	7 or 72 ppb in diet for 42 days	NA	NA	NA	NA	12	NC	Fries and Marrow, 1975
2,3,7,8-TCDD	Sprague-Dawley rat (F)	7 or 72 ppb in diet for 42 days	NA	NA	NA	NA	15	NC	Fries and Marrow, 1975
2,3,7,8,-TCDD	Sprague-Dawley rat (M, F)	1.0 µg/kg, p.o	NA	NA	NA	9.9	31±6[d]	NC	Rose et al., 1976
2,3,7,8-TCDD	Sprague-Dawley rat (M, F)	0.1 and 1.0 µg/kg/day, 5 days/week for 7 weeks	NA	NA	NA	8.5	23.7	NC	Rose et al., 1976
2,3,7,8-TCDD	Han/Wistar rat (M)	5 µg/kg, i.p.	>90	NA	~70–90	14.1	21.9	NC	Pohjanvirta et al., 1990
2,3,7,8-TCDD	Long-Evans rat (M)	5 µg/kg, i.p.	>90	NA	~20-90	12.0	20.8	NC	Pohjanvirta et al., 1990
2,3,7,8-TCDD	Sprague-Dawley (M)	500 µg/kg, i.p.	100	100	NA	NA	NA	NC	Neal et al., 1982
2,3,7,8-TCDD	C57BL/6J mice (M)	10 µg/kg, i.p.	100	100	85	2.7	11.0±1.2[d]	NC	Gasiewicz et al., 1983a

Table 1-9. Metabolism and excretion of 2,3,7,8-TCDD and related compounds[a] (continued)

Chemical	Species	Dose	Chemical Nature of Excretion Products (% Metabolites)			Ratio of % of Dose Excreted (Feces/Urine)	Half-Life[b] (days)	Comment	Reference
			Urine	Bile	Feces				
2,3,7,8-TCDD	DBA/2J mice (M)	10 µg/kg, i.p.	100	100	82	1.2	24.4±1.0[d]	NC	Gasiewicz et al., 1983a
2,3,7,8-TCDD	B6D2F1J mice (M)	10 µg/kg, i.p.	100	100	86	2.5	12.6±0.8[d]	NC	Gasiewicz et al., 1983a
2,3,7,8-TCDD	C57BL/6J mice Ah^b/Ah^d (M)	500 ng/kg, i.p.	NA	NA	NA	3.1	9.42	NC	Birnbaum, 1986
2,3,7,8-TCDD	C57BL/6J mice Ah^d/Ah^d (M)	500 ng/kg, i.p.	NA	NA	NA	2.1	9.74	NC	Birnbaum, 1986
2,3,7,8-TCDD	DBA/2J Ah^b/Ah^d (F)	500 ng/kg, i.p.	NA	NA	NA	5.3	10.40	NC	Birnbaum, 1986
2,3,7,8-TCDD	DBA/2J Ah^d/Ah^d (F)	500 ng/kg, i.p.	NA	NA	NA	6.8	11.11	NC	Birnbaum, 1986
2-Iodo-3,7,8-TCDD	C57BL/6J mice (F)	[^{125}I] 0.1 nmol/kg, i.p.	NA	NA	NA	NA	14.2	whole body counting was used to estimate body burden over 30-day period	Leung et al., 1990b
2-Iodo-3,7,8-TCDD	C57BL/6J mice (F)	[^{125}I] 0.1 nmol/kg, i.p., 3 days following pretreatment with 2,3,7,8-TCDD (0.1 µmol/kg, i.p.)	NA	NA	NA	NA	8.0	whole body counting was used to estimate body burden over 30-day period	Leung et al., 1990b
2,3,7,8-TCDD	Hartley guinea pig (M)	0.5 µg/kg, i.p.	NA	NA	NA	15.7	30.2±5.8[d]	NC	Gasiewicz and Neal, 1979
2,3,7,8-TCDD	Hartley guinea pig (M)	0.56 µg/kg, i.p.	100	100	19	11.2	93.7±15.5[d]	NC	Olson, 1986
2,3,7,8-TCDD	Golden Syrian hamster (M)	[^{3}H] 650 µg/kg, i.p.	NA	NA	NA	1.4	11.95±1.95[d]	NC	Olson et al., 1980; Neal et al., 1982

Table 1-9. Metabolism and excretion of 2,3,7,8-TCDD and related compounds[a] (continued)

Chemical	Species	Dose	Chemical Nature of Excretion Products (% Metabolites)			Ratio of % of Dose Excreted (Feces/Urine)	Half-Life[b] (days)	Comment	Reference
			Urine	Bile	Feces				
2,3,7,8-TCDD	Golden Syrian hamster (M)	[^{14}C] 650 µg/kg, i.p.	100	100	55-75	NA	10.82±2.35	NC	Olson et al., 1980; Neal et al., 1982
2,3,7,8-TCDD	Golden Syrian hamster (M)	[^{3}H] 650 µg/kg, p.o.	NA	NA	NA	NA	14.96±2.53	NC	Olson et al., 1980; Neal et al., 1982
2,3,7,8-TCDD	human (M)	1.14 ng/kg, p.o.	NA	NA	~50	>3.1	2120[c]	NC	Poiger and Schlatter, 1986; Wendling et al., 1990
2,3,7,8-TCDD	rainbow trout	494 ppt in diet for 13 weeks	NA	~75	NA	NA	105	elimination followed for 13 weeks following exposure	Kleeman et al., 1986b
2,3,7,8-TCDD	yellow perch	494 ppt in diet for 13 weeks	NA	~90	NA	NA	126	elimination followed for 13 weeks following exposure	Kleeman et al., 1986a
1,2,3,7,8-PeCDD	Sprague-Dawley rat (M, F)	8.42–10.06 µg/kg, p.o.	NA	100	NA	12	29.5±2.7	NC	Wacker et al., 1986
OCDD	Fischer 344 rat (M)	50 µg/kg, iv	<33	0	0	>65	~70	whole body $t_{1/2}$ estimated from body burden in liver, skin, and adipose tissue over 56-day period	Birnbaum and Couture, 1988
OCDD	Fischer 344 rat (M)	50 µg/kg/day, p.o., for 10 days	NA	NA	NA	NA	~173	whole body $t_{1/2}$ estimated from body burden in liver, skin, and adipose tissue over 112-day period	Birnbaum and Couture, 1988
BDDs									

Table 1-9. Metabolism and excretion of 2,3,7,8-TCDD and related compounds[a] (continued)

Chemical	Species	Dose	Chemical Nature of Excretion Products (% Metabolites)			Ratio of % of Dose Excreted (Feces/Urine)	Half-Life[b] (days)	Comment	Reference
			Urine	Bile	Feces				
2,3,7,8-TBDD	Fischer 344 rat (M)	0.001 µmol/kg, iv	NA	100	80–90	11.1	0.7 2.9 17.8	Pool size (% of dose): 11.63 1st component 2.78 2nd component 1.45 3rd component	Kedderis et al., 1991a
2,3,7,8-TBDD	Fischer 344 rat (M)	0.1 µmol/kg, iv	NA	100	80-90	9.2	0.6 17.8	Pool size (% of dose): 22.47 1st component 2.35 2nd component	Kedderis et al., 1991a

Table 1-9. Metabolism and excretion of 2,3,7,8-TCDD and related compounds[a] (continued)

Chemical	Species	Dose	Chemical Nature of Excretion Products (% Metabolites)			Ratio of % of Dose Excreted (Feces/Urine)	Half-Life[b] (days)	Comment	Reference
			Urine	Bile	Feces				
CDFs									
2,3,7,8-TCDF	Fischer 344 rat (M)	0.1 µmol/kg, iv	100	>96	99	31.4	1.8 0.3	fecal excretion urinary excretion	Birnbaum et al., 1980
2,3,7,8-TCDF	C57BL/6J mice (M)	0.1 µmol/kg, iv	100	NA	80	6.5	2.8 1.8 2.0	urine feces urine and feces	Decad et al., 1981b
2,3,7,8-TCDF	DBA/2J mice (M)	0.1 µmol/kg, iv	100	NA	80	2.8	4.9 5.4 4.0	urine feces urine and feces	Decad et al., 1981b
2,3,7,8-TCDF	Hartley guinea pig (M)	0.02 µmol/kg, iv	>90	NA	<10	1.0	20	animal exhibited body weight loss	Decad et al., 1981a
2,3,7,8-TCDF	Hartley guinea pig (M)	4 µg/kg, p.o.	NA	NA	NA	NA	40	no observable toxicity	Ioannou et al., 1983
2,3,7,8-TCDF	rhesus monkey (M)	0.1 µmol/kg, iv	100	>92	>92	5.4	6.24 10.30 ~8	urine feces urine and feces	Birnbaum et al., 1981
1,2,3,7,8-PeCDF	Fischer 344 rat (M)	0.1 µmol/kg, iv	~90	100	NA	12.8	 0.92 3.32 1.26 17.32 1.12 6.30	Pool size (% of dose): feces: 57.79 1st component 6.92 2nd component urine: 2.68 1st component 0.16 2nd component feces and urine: 59.97 1st component 2.51 2nd component	Brewster and Birnbaum, 1988

Table 1-9. Metabolism and excretion of 2,3,7,8-TCDD and related compounds[a] (continued)

Chemical	Species	Dose	Chemical Nature of Excretion Products (% Metabolites)			Ratio of % of Dose Excreted (Feces/Urine)	Half-Life[b] (days)	Comment	Reference
			Urine	Bile	Feces				
2,3,4,7,8-PeCDF	Fischer 344 rat (M)	0.1 µmol/kg, iv	NA	>90	>90	>100	1.27 63.82	Pool size (% of dose): feces 1.22 1st component 0.57 2nd component	Brewster and Birnbaum, 1987
2,3,4,7,8-PeCDF	rhesus monkey (M)	0.1 µmol/kg, iv	NA	NA	63–70	~34	38–49	$t_{1/2}$ represents minimum value; all animals lost body weight and exhibited other signs of toxicity	Brewster et al., 1988
CBs									
3,3'4,4'-TCB	CD rat (M, F)	0.6 mg/kg, iv	>90	NA	>90	42	~1.3–1.5	NC	Abdel-Hamid et al., 1981
3,3'4,4'-TCB	rhesus monkey (F)	0.6 mg/kg, iv	97	NA	97	7.2	~8–10	NC	Abdel-Hamid et al., 1981

[a]All studies measure the excretion of radiolabeled parent compound and metabolites following exposure to a single congener labeled with ^{3}H, ^{14}C, or ^{125}I.
[b]Half-life for excretion estimates assume first-order elimination kinetics.
[c](mean±SE).
[d](mean±SD).
[e]n=1.
i.p. = intraperitoneal; i.v. = intravenous; NA = not available; NC = no comment; p.o. = per os.

Table 1-10. Half-life estimates for 2,3,7,8-TCDD and related compound in humans

Chemical	Exposure Incident	Number of Individuals	Sample	Time Period Between First and Last Analysis	Number of Time Points	Half-Life (years)	Reference
CDDs							
2,3,7,8-TCDD	Male volunteer	1	fecal excretion	125 days	28	5.8	Poiger and Schlatter, 1986
2,3,7,8-TCDD	Male volunteer	1	adipose tissue	6 years	5	9.7	Schlatter, 1991
2,3,7,8-TCDD	Ranch Hand Vietnam veterans	36	serum	5 years	2	7.1[a]	Pirkle et al., 1989
2,3,7,8-TCDD	Ranch Hand Vietnam veterans	337	serum	5 years	2	11.3[b]	Wolfe et al., 1994
1,2,3,6,7,8-HxCDD	technical pentachlorophenol in wood of home	1	adipose tissue	28 months	2	3.5	Gorski et al., 1984
1,2,3,4,6,7,8-HpCDD	technical pentachlorophenol in wood of home	1	adipose tissue	28 months	2	3.2	Gorski et al., 1984
OCDD	technical pentachlorophenol in wood of home	1	adipose tissue	28 months	2	5.7	Gorski et al., 1984
CDFs							
2,3,4,7,8-PeCDF	Binghamton, New York, state office building	1	adipose tissue blood combined	initial 43 months final 29 months total 6 years	4 4 7	4.7 7.2 4.5	Schecter et al., 1990b
1,2,3,4,7,8-HxCDF	Binghamton, New York, state office building	1	adipose tissue blood combined	initial 43 months final 29 months total 6 years	4 4 7	2.9 4.4 4.0	Schecter et al., 1990b
1,2,3,6,7,8-HxCDF	Binghamton, New York, state office building	1	adipose tissue blood combined	initial 43 months final 29 months total 6 years	4 4 7	3.5 4.3 4.9	Schecter et al., 1990b

Table 1-10. Half-life estimates for 2,3,7,8-TCDD and related compound in humans (continued)

Chemical	Exposure Incident	Number of Individuals	Sample	Time Period Between First and Last Analysis	Number of Time Points	Half-Life (years)	Reference
1,2,3,4,6,7,8-HpCDF	Binghamton, New York, state office building	1	adipose tissue blood combined	initial 43 months final 29 months total 6 years	4 4 7	6.5 4.1 6.8	Schecter et al., 1990a
2,3,4,7,8-PeCDF	Yu-Cheng	4 3 2	blood	initial 2.9 years final 2.7 years total 5.6 years	2 2 3	1.3 2.9 1.7	Ryan and Masuda, 1989
1,2,3,4,7,8-HxCDF	Yu-Cheng	4 3 2	blood	initial 2.9 years final 2.7 years total 5.6 years	2 2 3	2.1 5.1 2.4	Ryan and Masuda, 1989
1,2,3,4,6,7,8-HpCDF	Yu-Cheng	4 3 2	blood	initial 2.9 years final 2.7 years total 5.6 years	2 2 3	1.6 6.1 2.4	Ryan and Masuda, 1989
2,3,4,7,8-PeCDF 1,2,3,4,7,8-HxCDF 1,2,3,4,6,7,8-HpCDF	Yu-Cheng	3	blood	9 years	5-6	2-3	Ryan and Masuda, 1991
2,3,4,7,8-PeCDF 1,2,3,4,7,8-HxCDF	Yusho	9	blood	7 years	3-5	>5	Ryan and Masuda, 1991
1,2,3,4,6,7,8-HpCDF	technical pentachlorophenol in wood of home	1	adipose tissue	28 months	2	<1.7	Gorski et al., 1984
OCDF	technical pentachlorophenol in wood of home	1	adipose tissue	28 months	2	1.8	Gorski et al., 1984
PCBs							
3,3',4,4',5-PeCB	Yu-Cheng	NA	blood	NA	NA	<1	Ryan and Masuda, 1991
3,3',4,4',5,5'-HxCB	Yu-Cheng	NA	blood	NA	NA	10	Ryan and Masuda, 1991

[a]95% confidence interval about the median of 5.8–9.6 years.
[b]95% confidence interval about the median of 10.0-14.1 years.
NA = Not applicable.

Table 1-11. Calculated daily intakes for TCDD

Half-life (yrs)	Fat vol. (L)	Fat conc. (ppt)	Calculated daily intake (PG/KG/Day)
5.8	14.0	6.72	0.44
7.0	14.0	6.72	0.37
5.8	14.0	5.00	0.33
7.0	14.0	5.00	0.27
5.8	7.0	6.72	0.22
7.0	7.0	6.72	0.18
5.8	7.0	5.00	0.16
7.0	7.0	5.00	0.14

Table 1-12. Half-life calculations

Chemical	Food-ppt[a]	Body-ppt[b]	$t_{1/2}$[c] years	$t_{1/2}$[d] years
2378-TCDD	0.23	6.72	7.0	6.0
2378-TCDF	0.84	3.9	1.11	1.3
12378-PeCDD	0.7	21.5	7.35	5.0
23478-PeCDF	1.4	36.8	7.94	6.3
OCDD	19.2	653.0	8.14	50.0

[a]Concentrations in food for TCDD, TCDF, and OCDD were obtained as discussed in Part I, Volume 3; those for PCDD and PCDF were taken from Schlatter (1991).
[b]Concentrations in body (adipose tissue) were all taken from Schecter (1991).
[c]Calculated using Equation 1-19, except for TCDD.
[d]Calculated by Schlatter (1991), except for TCDD.

Table 1-13. Half-life estimates taken from Flesch-Janys et al. (1996)

Compound	N individuals	Median half-life estimate (years)
2,3,7,8-TCDD	48	7.2
1,2,3,7,8-PeCDD	40	15.7
1,2,3,4,7,8-HCDD	41	8.4
1,2,3,6,7,8-HCDD	40	13.1
1,2,3,7,8,9-HCDD	39	4.9
1,2,3,4,6,7,8-HpCDD	26	3.7
OCDD	32	6.7
2,3,4,7,8-PeCDF	5	19.6
1,2,3,4,7,8-HCDF	42	6.2
1,2,3,6,7,8-HCDF	31	6
2,3,4,6,7,8-HCDF	6	5.8
1,2,3,4,6,7,8-HpCDF	22	3
1,2,3,4,7,8,9-HpCDF	6	3.2

Table 1-14. Comparison of administered dose and body burden in rats and humans.

	(A) Rat Daily Administered Dose/Body Burden	(B) Human Scaled Administered Dose/Body Burden[1]	(C) Human Equivalent Administered Dose/Body Burden[2]	(A/B) Ratio of Rat to Human Scaled Dose	(A/C) Ratio of Rat to Human Equivalent Dose
Dose (ng/kg/d)	1	0.27	0.0096	3.7	104
Body Burden (ng/kg)	18	505	18	0.036	1

1. Assumes administered dose scales across species as a function of $BW^{3/4}$
2. Assumes administered dose scales across species as a function of equivalent body burdens

Figure 1-1. Time course of the connection of 14C-TCDD in rat liver and adipose tissue after a single subcutaneous injection of 300 ng TCDD/kg bw to female rats (M±SD).

Source: Abraham et al., 1988.

Figure 1-2. Dose dependency of the percentage of the administered dose of 14C-TCDD/g of tissue recovered in liver and adipose tissue after single subcutaneous doses (values from animals treated with 3000 ng TCDD/kg bw were corrected for 84% adsorption). Concentrations were measured 7 days after the injection.

Source: Abraham et al., 1988.

$$D = \left(\frac{ln2}{t_{1/2}} \right) V_F \, C_F \left(\frac{1}{70KG} \right)$$

$$D = \left(\frac{ln2}{5.8years} \right) \left(14L \;\; 1000 \; \frac{ml}{L} \right) \left(6.72 \frac{pg}{ml} \right) \left(\frac{1}{70KG} \right) \left(\frac{1year}{365days} \right)$$

$$D = 0.44 \;\; pg/kg/day$$

Figure 1-3. Sample calculation of daily intake for TCDD.

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2. MECHANISM(S) OF ACTION*

2.1. INTRODUCTION

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) is the prototype for a class of halogenated aromatic hydrocarbons (HAHs) that produce similar patterns of toxicity and appear to have a common mechanism of action, although they differ in potency (Poland and Knutson, 1982; Safe, 1986). Because it is the most potent, TCDD has been studied much more extensively than other structurally related compounds (Figure 2-1). TCDD achieved notoriety in the 1970s, when it was discovered to be a contaminant in the herbicide Agent Orange and was shown to produce birth defects in rodents. Subsequently, dioxin has continued to generate concern because of its widespread distribution, its persistence as an environmental contaminant, its accumulation within the food chain, and its toxic potency. In animals, TCDD elicits a wide range of biological effects, including alterations in metabolic pathways, immunological changes, reproductive and developmental abnormalities, and neoplasia (Poland and Knutson, 1982; Safe, 1986; Birnbaum, 1994b). In humans, dioxin and related compounds can produce the skin condition known as chloracne. Increased cancer rates have also been associated with exposures to dioxin-like chemicals (International Agency for Research on Cancer, 1997). The possibility that dioxins also produce birth defects and developmental abnormalities is a particular public health concern. Many individuals have been exposed to TCDD, primarily from dietary sources, although occupational and accidental exposures have also occurred. TCDD is a poor substrate for detoxification systems such as the microsomal cytochrome P450 enzymes, which oxygenate other lipophilic compounds to inactive derivatives during their metabolic processing. Because of its relative resistance to metabolism, TCDD persists in the body, with a half-life in humans on the order of 7 to 10 years (Pirkle et al., 1989; Michalek et al., 1996; Michalek and Tripathi, 1999). Therefore, dioxin tends to accumulate in human tissues over time, raising concern that repeated exposures, even to "low" concentrations, may evoke adverse health effects. Epidemiological studies performed to date have not produced well-defined estimates of the health risk that dioxin poses to humans. There has been hope that knowledge of the mechanism of dioxin action will bring about a greater understanding of these issues (Andersen et al., 1994; Denes et al., 1996).

Mechanistic studies can reveal the biochemical pathways and types of biological and molecular events that contribute to dioxin's adverse effects. For example, much evidence indicates that TCDD acts via an intracellular protein (the aryl hydrocarbon receptor; Ah receptor), which functions as a ligand-dependent transcription factor in partnership with a second protein (known as the Ah receptor nuclear translocator; Arnt). Therefore, from a mechanistic standpoint, TCDD's adverse effects appear likely to reflect alterations in gene expression that occur at an inappropriate time and/or for an inappropriately long time. Mechanistic studies also indicate that several other proteins contribute to TCDD's gene regulatory effects and that the response to TCDD probably involves a relatively complex interplay between multiple genetic and environmental factors. If TCDD operates through such a mechanism, as all evidence indicates, then there are certain constraints on the possible models that can plausibly account for TCDD's biological effects and, therefore, on the assumptions used during the risk assessment process (e.g. Poland, 1996; Limbird and Taylor, 1998). Mechanistic knowledge of dioxin action may also be useful in other ways. For example, a further understanding of the ligand specificity and structure of the Ah receptor will likely assist in the identification of other chemicals to which humans are exposed that may either add to, synergize, or block the toxicity of TCDD. Knowledge of genetic polymorphisms that influence TCDD responsiveness may also allow the identification of individuals at greater risk from exposure to dioxin. In addition, knowledge of the biochemical pathways that are altered by TCDD may help identify novel targets for the development of drugs that can antagonize dioxin's adverse effects.

As described below, biochemical and genetic analyses of the mechanisms by which dioxin may modulate particular genes have revealed the outline of a novel regulatory system whereby a chemical signal can alter cellular regulatory processes. Future studies of dioxin action have the potential to provide additional insights into mechanisms of mammalian gene regulation that are of a broader interest. Additional perspectives on dioxin action can be found in several recent reviews (Birnbaum, 1994a,b; Schecter, 1994; Hankinson, 1995; Schmidt and Bradfield, 1996; Gasiewicz, 1997; Rowlands and Gustafsson, 1997; Denison et al., 1998; Hahn, 1998; Wilson and Safe, 1998; Gu et al., 2000).

2.2. THE "RECEPTOR" CONCEPT

The idea that a drug, hormone, neurotransmitter, or other chemical produces a physiological response by interacting with a specific cellular target molecule, i.e., a "receptor," evolved from several observations. First, many chemicals elicit responses that are restricted to specific tissues. This observation implies that the responsive tissue (e.g., the adrenal cortex) contained a "receptive" component whose presence is required for the physiologic effect (e.g., cortisol secretion). Second, many chemicals are quite potent. For example, picomolar to

nanomolar concentrations of numerous hormones and growth factors elicit biological effects. This observation suggests that the target cell contains a site(s) to which the particular chemical binds with high affinity. Third, stereoisomers of some chemicals (e.g., catecholamines, opioids) differ by orders of magnitude in their ability to produce the same biological response. This observation indicates that the molecular shape of the chemical strongly influences its biological activity. This, in turn, implies that the binding site on or in the target cell also has a specific, three-dimensional configuration. Together, these types of observations predict that the biological responses to some chemicals involve stereospecific, high-affinity binding of the chemicals to specific receptor sites located on or in the target cell.

The availability of compounds of high specific radioactivity has permitted quantitative analyses of their binding to cellular components in vitro. To qualify as a potential "receptor," a binding site for a given chemical must satisfy several criteria: (1) the binding site must be saturable, i.e., the number of binding sites per cell should be limited; (2) the binding should be reversible; (3) the binding affinity measured *in vitro* should be consistent with the potency of the chemical observed *in vivo*; (4) if the biological response exhibits stereospecificity, so should the *in vitro* binding; (5) for a series of structurally related chemicals, the rank order for binding affinity should correlate with the rank order for biological potency; and (6) tissues that respond to the chemical should contain binding sites with the appropriate properties.

The binding of a chemical ("ligand") to its cognate receptor is assumed to obey the law of mass action; that is, it is a bimolecular, reversible interaction. The concentration of the liganded, or occupied, receptor [RL] is a function of both the ligand concentration [L] and the receptor concentration [R]:

$$[L] + [R] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [RL]$$

Inherent in this relationship is that the fractional occupancy (i.e. $[RL] / [R_t]$) is a function of ligand concentration [L] and the apparent equilibrium dissociation constant K_D, which is a measure of the binding affinity of the ligand for the receptor, that is, $[RL] / [R_t] = [L] / (K_D + [L])$, where $K_D = [L] [R_t] / [LR] = k_2 / k_1$. Therefore, the relationship between receptor occupancy and ligand concentration is hyperbolic. At low ligand concentrations (where $[L] << K_D$), a small increase in [L] produces an approximately linear increase in fractional receptor occupancy. At high ligand concentration (where $[L] >> K_D$), the fractional occupancy of the receptor is already very close to 1, that is, almost all receptor sites are occupied. Therefore, a small increase in [L] is likely to produce only a slight increase in receptor occupancy.

Ligand binding constitutes only one aspect of the receptor concept. By definition, a receptor mediates a response, and the functional consequences of the ligand-receptor binding represent an essential aspect of the receptor concept. Receptor theory attempts to quantitatively relate ligand binding to biological responses. The classical "occupancy" model of Clark (1933) postulated that (1) the magnitude of the biological response is directly proportional to the fraction of receptors occupied and (2) the response is maximal when all receptors are occupied. However, analyses of numerous receptor-mediated effects indicate that the relationship between receptor occupancy and biological effect is not as straightforward as Clark envisioned. In certain cases, no response occurs even when there is some receptor occupancy. This suggests that there may be a threshold phenomenon that reflects the biological "inertia" of the response (Ariens et al., 1960). In other cases, a maximal response occurs well before all receptors are occupied, a phenomenon that reflects receptor "reserve" (Stephenson, 1956). Therefore, one cannot simply assume that the relationship between fractional receptor occupancy and biological response is linear. Furthermore, for a ligand (such as TCDD) that elicits multiple receptor-mediated effects, one cannot assume that the binding-response relationship for a simple effect (such as enzyme induction) will necessarily be identical to that for a different and more complex effect (such as cancer). The cascades of events leading to different complex responses (e.g., altered immune response to pathogens or development of cancer) are likely to be different, and other rate-limiting events likely influence the final biological outcome resulting in different dose-response curves. Thus, even though ligand binding to the same receptor is the initial event leading to a spectrum of biological responses, ligand-binding data may not always mimic the dose-effect relationship observed for particular responses.

Another level of complexity is added when one considers different chemical ligands that bind to the same receptor. Relative potencies are determined by two properties of the ligand: affinity for the receptor, and capacity to confer a particular response in the receptor (e.g., a particular conformational change), also called efficacy (Stephenson, 1956). Ligands with different affinities and the same degree of efficacy would be expected to produce parallel dose-response curves with the same maximal response within a particular model system. However, ligands of the same affinity with different efficacies may result in dose-response curves that are not parallel or that differ in maximal response.

2.3. THE Ah (DIOXIN) RECEPTOR

The unusual toxic potency of TCDD suggested the possible existence of a receptor for dioxin. Poland and coworkers, using radiolabeled TCDD as a ligand, demonstrated that the cytosolic fraction of C57BL/6J mouse liver contained a protein that bound the dioxin saturably (i.e., ~10^5 binding sites per cell), reversibly, and with high affinity (i.e., in the nanomolar range,

consistent with TCDD's biological potency in vivo). Competition binding studies with congeners of TCDD revealed that ligands with the highest binding affinity were planar and contained halogen atoms in at least three of the four lateral positions; thus, ligand binding exhibited stereospecificity. In addition, the ligand-receptor binding relationship resembled a rectangular hyperbola and, therefore, appeared to obey the law of mass action. Together, these findings demonstrated that the intracellular TCDD-binding protein had the ligand binding properties expected for a "dioxin receptor." The protein has been designated as the "Ah receptor" because it binds and mediates the response to other aromatic hydrocarbons (such as 3-methylcholanthrene) in addition to TCDD (Poland and Knutson, 1982).

Inbred mouse strains differ quantitatively in their responsiveness to TCDD and other aromatic hydrocarbons. For example, TCDD elicits its effects at about 10-fold lower concentrations in the more responsive mouse strains (typified by C57BL/6) than in the less responsive strains (typified by DBA/2). This polymorphism in responsiveness is genetic in origin, and, in crossbreeding studies, the more responsive phenotype segregates as an autosomal dominant trait. Numerous responses to TCDD (e.g., enzyme induction, thymic involution, cleft palate formation, hepatic porphyria) exhibit a segregation pattern identical to that for the binding of TCDD to the Ah receptor. Thus, the genetic locus (designated *Ah*) that governs this receptor polymorphism also governs the biological responses to TCDD. These findings implicate the Ah receptor in the mechanism of dioxin action (Poland and Knutson, 1982; Nebert et al., 1991). The resistance of recently developed Ah receptor null-allele ("knockout") mice to the enzyme inductive and toxic effects of very high doses of TCDD further corroborates the role of this protein in these responses (Fernandez-Salguero et al., 1996; Schmidt et al., 1996; Mimura et al., 1997; Hundeiker et al., 1999; Peters et al., 1999).

Studies of structure-activity relationships (SARs) reveal that, within groups of structurally-related compounds, a ligand's receptor-binding affinity often correlates with its potency in eliciting a biological response(s). Such SAR analyses are useful for assessing possible participation of the AhR in ligand-induced responses in experimental systems where genetic polymorphisms of the receptor are not available. Such SAR studies constitute biochemical evidence that implicates the Ah receptor in the mechanism of dioxin action. In general, the rank order binding affinity of TCDD and related chemicals to the Ah receptor has been demonstrated to be similar to their rank order of potency to elicit a broad spectrum of biochemical, morphologic, immunologic, neoplastic, developmental, and reproductive effects (Poland and Knutson, 1982; Safe, 1986, 1990). This rank order appears largely dependent on several structural constraints. For example, relatively planar aromatic compounds with approximate van der Waals dimensions of 14 x 12 x 5 Å with few bulky substituent groups have, in general, the highest ligand binding affinity and are the most potent for eliciting biological

effects (Poland and Knutson, 1982; Gillner et al., 1993; Waller and McKinney, 1995). However, it is becoming increasingly recognized that some Ah receptor ligands have both agonist and antagonist activity (Harris et al., 1989b; Kurl et al., 1993; Lu et al., 1996; Henry et al., 1999), suggesting that not all Ah receptor ligands have the same degree of efficacy (Hestermann et al., 2000).

The cloning of receptor cDNA (Burbach et al., 1992; Ema et al., 1992) has added important new insights into Ah receptor structure and function (reviewed in Hankinson, 1995; Rowlands and Gustafsson, 1997). The deduced amino acid sequence reveals that the Ah receptor has several features in common with a class of transcription factors known as basic helix-loop-helix (bHLH) proteins. The Ah receptor contains a bHLH domain, located towards the N-terminal end of the receptor. An analysis of this and other bHLH proteins indicates that the basic region mediates DNA binding, whereas the helix-loop-helix domain is necessary for dimerization with other proteins. Two other receptor regions function in dimerization. These are designated as "PAS" regions due to their sequence homology with Per (a *Drosophila* circadian rhythm protein), Arnt (another protein that contributes to dioxin responsiveness, described below), and Sim (a regulatory protein that participates in *Drosophila* central nervous system development) (Huang et al., 1993). In the AhR, the PAS domain consists of approximately 300 amino acid residues containing two copies of a repeat of about 50 amino acids, referred to as the PAS-A and PAS-B repeats. In the absence of an agonist, the PAS-B region associates with one heat shock protein 90 (hsp90) molecule, permitting binding of a second hsp90 to the HLH region (Whitelaw et al., 1993; Antonsson et al., 1995; Coumailleau et al., 1995; Whitelaw et al., 1995; Fukunaga et al., 1995). TCDD has been shown to interact with a ligand-binding pocket near the PAS-B region, the conformation of which is maintained by hsp90. Dimerization between AhR and Arnt is mediated through their HLH regions, but is further stabilized by PAS-PAS interactions (Reisz-Porszasz et al., 1994; Fukunaga et al., 1995). Immunohistochemical studies, using anti-receptor antibodies, reveal that the unliganded receptor resides in the cytoplasm; exposure of cells to (under in vitro conditions) TCDD leads to the accumulation of the receptor within the nucleus (Pollenz et al., 1994). Association with hsp90 is also thought to limit nuclear uptake of the receptor by blocking a N-terminal nuclear localization sequence (Pongratz et al., 1992; Ikuta et al., 1998). The carboxyl end of the protein contains a glutamine-rich region, which resembles certain "activation domains" present in some other transcription factors; by analogy, this region could interact with coactivator proteins that have yet to be characterized. Thus, like many proteins, the Ah receptor appears to be composed of several different functional domains. It is notable that the TCDD-bound Ah receptor does not, by itself, bind strongly to DNA; acquisition of DNA-binding capability appears to require that the receptor interact with another factor (such as the Arnt protein). Thus, the active form of the

receptor is heteromeric. The bHLH proteins identified to date are involved in transcriptional regulation and have a variety of roles in tissue growth and differentiation processes (Murre et al., 1994; Schmidt and Bradfield, 1996).

Human cells also contain an intracellular protein whose ligand-binding and hydrodynamic properties resemble those of the Ah receptor identified in other species (see Cook and Greenlee, 1989; Harris et al., 1989a; Roberts et al., 1990; Lorenzen and Okey, 1991; Harper et al., 1991; Ema et al., 1994). Furthermore, the sequence of this protein shows homology with that of other mammalian species (Dolwick et al., 1993; Ema et al., 1994; Hahn, 1998). Compared with the rat or mouse Ah receptor, however, the human Ah receptor appears, at least under cell-free conditions, to have a several-fold lower affinity for TCDD (Manchester et al., 1987; Ema et al., 1994). Some data also suggest that the human Ah receptor may be many times less sensitive in terms of eliciting a response. For example, cultured human embryonic palatal cells were approximately 200 times less sensitive than mouse palatal cells with respect to the inducibility of *CYP1A1* by TCDD (Abbott et al., 1999a). Although these data might imply that human tissues would be less sensitive to the toxic effects of TCDD, the Ah receptor in human cells has also been shown to exist in more than one form (Perdew and Hollenbeck, 1995). The relative sensitivity and function of these different forms have not been evaluated. Furthermore, these observed differences may be related to the greater lability of the human receptor during tissue preparation and cell fractionation procedures (Manchester et al., 1987). Data also suggests considerable heterogeneity of Ah receptor concentrations and characteristics in the human population (e.g., Roberts et al., 1986, 1990, 1991). However, a limited analysis for human AhR polymorphisms identified only one amino acid exchanging polymorphism, and this is thought to have little or no functional significance (Wanner et al., 1999). Additional studies of the human receptor should increase our knowledge of its functional properties and role in mediating altered cell- and tissue-specific responses elicited by TCDD and related chemicals.

Evidence indicates that the Ah receptor evolved prior to the introduction of HAHs into the environment (Czuczwa et al., 1984; Hahn et al., 1997). Furthermore, what is known about the structure, regulation, and expression of the Ah receptor in different tissues indicates a purposeful regulation for some normal function. The ontogenically related and tissue-specific expression of the receptor (e.g., Abbott et al., 1995; Jain et al., 1998), as well as the conservation of its presence and protein sequence in diverse groups of vertebrates, implies an essential function (Hahn, 1998). Furthermore, the level and activity of the Ah receptor appear to be regulated by changes in cell differentiation stages, growth factors, cell activation, diurnal cycle, and prior exposure to receptor agonists (Vaziri et al., 1996; Crawford et al., 1997; Shimba et al., 1998; Hayashi et al., 1995; Wanner et al., 1995; Liu et al., 1996; Pollenz, 1996; Richardson et al., 1998). These aspects might, at least in part, contribute to the ability of TCDD to cause

tissue- and developmental stage-specific effects. The best evidence for a normal physiological function of the Ah receptor comes from studies with Ah receptor-deficient animals. These mice have altered hepatic growth and development, immune system abnormalities, development of vasculature, adverse reproductive outcomes and reproductive tissue development, and abnormal processes in a variety of tissues (Fernandez-Salguero et al., 1995; Schmidt et al., 1996; Fernandez-Salguero et al., 1997; Abbott et al., 1999b; Hushka et al., 1998; Thurmond et al., 2000; Robles et al., 2000; Benedict et al., 2000; Lahvis et al., 2000).

Several reports have indicated stimulation of Ah receptor-dependent responses under certain conditions in the absence of added ligand (Sadek and Allen-Hoffman, 1994; Ma and Whitlock, 1996; Weiss et al., 1996; Crawford et al., 1997; Chang and Puga, 1998). However, it is not yet clear whether this occurs via an endogenously present ligand or some other process. Nevertheless, it has been postulated that some other compound(s) must represent the "natural" ligand(s) for the receptor (Poellinger et al., 1992). Naturally occurring high-affinity ligands for the receptor exist in the environment, particularly in plants (Gillner et al., 1985, 1989; Rannung et al., 1987; Bjeldanes et al., 1991). Other candidates for endogenous ligands include tryptophan derivatives (Helferich and Denison, 1991), carotinoids (Gradelet et al., 1996), arachidonic acid metabolites (Schaldach et al., 1999), and tetrapyrroles or their derivatives (Sinal and Bend, 1997). Thus, it is possible that the Ah receptor might have evolved as part of a substrate-inducible system designed to metabolize and/or activate dietary lipophilic substances, and TCDD may mimic the binding of such substances to the receptor. TCDD has been observed to produce changes in the proliferative/differentiated phenotype of a variety of cell types (Knutson and Poland, 1980; Blankenship et al., 1993; Gaido and Maness, 1994; Gierthy et al., 1994; Brodie et al., 1996; Yang et al., 1999). Thus, an additional possibility is that TCDD mimics an endogenous Ah receptor ligand involved in the regulation of such tissue-specific phenotypes. Several reports have also suggested a role of the Ah receptor in cell cycle control (Ma and Whitlock, 1996; Weiss et al., 1996; Kolluri et al., 1999), possibly through regulation of tissue growth factors such as transforming growth factor-β (Zaher et al., 1998).

2.4. THE ARNT PROTEIN

Biochemical and hydrodynamic findings suggest that more than one protein participates in the response to TCDD. In particular, overwhelming evidence indicates that the Ah receptor interacts with the Arnt protein to form a heteromeric, DNA-binding protein complex that can activate gene transcription (reviewed in Hankinson, 1995; Schmidt and Bradfield, 1996; Rowlands and Gustafsson, 1997; Denison et al., 1998; Whitlock, 1999).

The human Arnt cDNA encodes a protein of about 86 kDa, which has several features in common with the Ah receptor. Like the Ah receptor, it contains a bHLH domain, which

contributes both to DNA binding and to protein-protein interactions (Hoffman et al., 1991; Li et al., 1994; Reisz-Porszasz et al., 1994). Furthermore, the Arnt protein contains PAS domains homologous to Per and Sim, and C-terminal domains functional in transcriptional activation (Huang et al., 1993; Reisz-Porszasz et al., 1994; Lindebro et al., 1995) . The Arnt protein does not bind TCDD. Furthermore, it does not bind to Ah receptor recognition sites on DNA (termed dioxin or xenobiotic response elements; DREs or XREs) on DNA in the absence of the liganded Ah receptor protein (Whitelaw et al., 1993). Immunohistochemical studies, using anti-Arnt antibodies, reveal that the Arnt protein resides in the nucleus in uninduced mouse hepatoma cells and that TCDD exposure of cells produces no change in its intracellular distribution (Pollenz et al., 1994). Thus, Arnt appears to be a nuclear protein. Furthermore, the nuclear accumulation of the Ah receptor occurs in Arnt-defective cells. Together, these findings argue against a primary role for Arnt in the translocation per se of the receptor from cytoplasm to nucleus. Instead, it has been suggested that Arnt interacts with the liganded Ah receptor to form a heteromeric, DNA-binding protein complex that can activate gene transcription. Experiments in vitro support this idea. For example, immunoprecipitation experiments reveal that the liganded Ah receptor and the Arnt protein can interact in solution. The liganded receptor alone does not exhibit substantial DNA-binding activity in the absence of Arnt; rather, the presence of both proteins is required to generate a specific DNA-binding species and to activate the expression of a dioxin-responsive reporter gene. Furthermore, deletion of the bHLH domain of Arnt abrogates its functional interaction with the liganded Ah receptor (Whitelaw et al., 1993). Together, these findings imply that the transcriptionally active component of the dioxin-responsive system is a protein heteromer consisting of (at least) the liganded Ah receptor and Arnt. Although both proteins contain a C-terminal transactivation domain, the Ah receptor appears to provide the dominant activation function, and the relative contribution of the Arnt domain largely depends on the availability of other cell-specific factors (Corton et al., 1996; Ko et al., 1996).

Multiple forms of Arnt have been detected in several species (Drutel et al., 1996; Hirose et al., 1996; Pollenz et al., 1996). In mice and rats, Arnt1 and Arnt2 are 83% identical in amino acid sequence, and have the ability to dimerize with the AhR and bind to specific DNA elements in vitro (Hirose et al., 1996). However, the expression patterns for these two isoforms are quite different. Arnt1 is widely expressed in a variety of tissues, whereas Arnt2 is detected primarily in adult brain and kidney (Drutel et al., 1996; Hirose et al., 1996). In addition, each protein has a distinct expression pattern in the developing mouse (Jain et al., 1998). The respective roles of these proteins in contributing to the variety of TCDD-elicited responses are not yet clear.

Both the Ah receptor and Arnt protein belong to the bHLH class of transcription factors, which function as heterodimers and contribute to the control of numerous genes (Kadesch, 1993). The dimerization capabilities of bHLH proteins provides a potential mechanism for

generating regulatory diversity. For example, different heterodimers may exhibit different stabilities, may have different DNA-binding affinities, or may recognize different DNA sequences. The bHLH structure of the Ah receptor raises the possibility that it might form heterodimeric complexes with proteins other than Arnt, generating regulatory molecules with potentially novel properties. By analogy with other bHLH systems, both the absolute amount of each partner and their relative ratios could influence the extent and type of response to TCDD. Thus, diversity in heteromer formation might contribute to the diversity of responses that typifies dioxin action. Arnt1 has been shown to be a dimerization partner for several proteins including the Ah receptor, single-minded (Sim), hypoxia inducible factor-1α, and endothelial PAS protein 1, and several other as yet uncharacterized proteins (Ema et al., 1997; Hogenesch et al., 1997; Probst et al., 1997). In addition, Arnt1 has been shown to have an essential role in development (Kozak et al., 1997; Maltepe et al., 1997). However, Arnt is the only protein that has been demonstrated to be a functional partner for the Ah receptor in terms of conferring specificity of DNA binding and transactivation. Some HLH proteins, which lack a basic region (typified by Id), may act as dominant negative regulators of transcription by dimerizing with bHLH proteins and inhibiting their DNA binding ability (Kadesch, 1993). There is evidence for an inducible dominant negative regulator of the Ah receptor, termed the Ah receptor repressor, that interacts with Arnt (Mimura et al., 1999). It is possible that the tissue-specific presence or absence of this factor regulates Ah receptor function and thus its response to xenobiotics by competing with the receptor for Arnt. In any case, the bHLH structure of the Ah receptor and the Arnt protein suggests that some of the diversity in TCDD's biological effects might reflect differential gene regulation by a mechanism involving formation of different protein heterodimers. Future mechanistic studies should aid in elucidating how such processes regulate dioxin action.

2.5. OTHER PROTEINS THAT PARTICIPATE IN THE RESPONSE TO DIOXIN

Attempts to purify the unliganded Ah receptor under nondenaturing conditions revealed that it tends to associate with other proteins in vitro, in particular the 90-kDa heat shock protein (hsp90). The hsp90 protein is an abundant factor that can interact with numerous other proteins and that may have multiple functions (Buchner, 1999). Immunoprecipitation studies and immunosedimentation experiments using anti-hsp90 antibodies reveal that the unliganded Ah receptor associates with hsp90 in vitro (Denis et al., 1988; Perdew, 1988). In view of previous findings implicating hsp90 in glucocorticoid receptor function (Picard et al., 1990), the association between the Ah receptor and hsp90 in vitro may be more than fortuitous. Hsp90 may be needed to maintain the unliganded receptor in a configuration that facilitates ligand binding. It might have a role in regulating nuclear translocation and DNA binding of the Ah receptor (Pongratz et al., 1992; Antonsson et al., 1995; Coumailleau et al., 1995; Phelan et al., 1998).

Studies in yeast have demonstrated the requirement for hsp90 in the formation of a functional Ah receptor (Carver et al., 1994). However, since complete hsp90 dissociation does not appear to be essential for nuclear localization (Heid et al., 2000), the dissociation of the two hsp90 molecules may occur during separate events in the cytosol and the nucleus, initiated by ligand binding and Arnt association, respectively. An additional protein, ARA9/AIP/XAP2, has been shown to enhance the transcriptional activity of the AhR-Arnt complex (Ma and Whitlock, 1997; Carver et al., 1998; Meyer et al., 1998). Although this protein does not appear to be required for AhR-hsp90 interaction, it apparently stabilizes this interaction and has some function in regulating the rate of AhR turnover in the cytosol or intracellular localization (Meyer and Perdew, 1999; LaPres et al., 2000; Petrulis et al., 2000; Bell and Poland, 2000). Recently, a 23-kDa protein has been shown to associate with the ligand-binding form of the Ah receptor. This protein is thought to play a role in stabilizing the complex containing receptor and hsp90 (Kazlauskas et al., 1999). Given the important functions of these proteins in stabilizing an Ah receptor form that can bind ligand and transduce the ligand-initiated signal to the nuclear compartment, the relative presence of these proteins might play an important role in the tissue-specific sensitivity to Ah receptor ligands like TCDD.

Several lines of evidence suggest that phosphorylation/dephosphorylation of the Ah receptor and the Arnt protein may contribute to the function of the dioxin-responsive system. Treatment of nuclear extracts with potato acid phosphatase, which dephosphorylates proteins, inhibits the binding of the liganded receptor heteromer to its DNA recognition sequence in vitro (Pongratz et al., 1991). Modulation of protein kinase C (PKC) activity is also associated with a reduction in DNA-binding capability of the receptor heteromer in vitro and alteration of Ah receptor-dependent transcriptional function in vivo (Carrier et al., 1992; Okino et al., 1992; Berghard et al., 1993; Chen and Tukey, 1996; Long et al., 1998). Furthermore, immunoprecipitation experiments using anti-receptor antibodies reveal that the receptor can undergo phosphorylation in vivo (Berghard et al., 1993; Mahon and Gasiewicz, 1995). Additional experiments in vitro suggest that phosphorylation of the Arnt protein is required for its heterodimerization with the Ah receptor; however, phosphorylation of the receptor is not required (Berghard et al., 1993). Together, these findings suggest that PKC and other protein kinases might influence heterodimerization, binding of the receptor-Arnt heteromer to DNA, or transcriptional activation of the Ah receptor. Although tyrosine phosphorylation in particular appears to be important for regulation of DNA binding of the AhR-Arnt complex (Park et al., 2000), the exact amino acid residue, the mechanism of regulation, and if this, or other, phosphorylation may be partially responsible for tissue- and developmental stage-specific regulation of AhR activity, have yet to be determined. It is known that many mammalian transcription factors undergo cycles of phosphorylation and dephosphorylation; however, in

most cases, the physiological significance of the modification is unknown (Hunter and Karin, 1992). Additional research is necessary to fully delineate the role of protein phosphorylation in the biological response to TCDD, and to identify the particular protein kinases and phosphatases that participate in the regulation of Ah receptor and Arnt protein.

The Ah receptor has been shown to physically interact with both retinoblastoma and NF-kB proteins (Ge and Elferink, 1998; Tian et al., 1999; Puga et al., 2000a). Both proteins are known to function in the regulation of cell cycle and cell differentiation in response to a variety of cytokines and growth factors (e.g., Beg and Baltimore, 1996; Van Antwerp et al., 1996; Zacksenhaus et al., 1996). It is reasonable to speculate that these interactions contribute to the noted ability of TCDD and related xenobiotics to affect cell cycle and cellular differentiation states, but the exact pathways that lead to these cell- and tissue-specific responses have yet to be determined. Nevertheless, this certainly represents a promising area of future research.

It appears likely that additional proteins, which remain to be identified and characterized, also contribute to the dioxin-response system. Both the Ah receptor and Arnt activate gene expression, at least in part, through direct interaction with basal transcription factors (Rowlands et al., 1996). Furthermore, there appears to be considerable cross-regulation of the Ah receptor with other signaling proteins including hypoxia inducible factor, estrogen receptors, and the retinoic acid and thyroid hormone receptors (e.g., Caruso et al., 1999; Chan et al., 1999; Duan et al., 1999; Kumar et al., 1999; Nguyen et al., 1999). There is evidence to indicate that protein-protein interactions have an important part in regulating the transcriptional activity of several nuclear receptors (e.g., Chen and Evans, 1995). Likewise, Ah receptor-Arnt complex-mediated transcriptional activities may be modulated by coactivator/corepressor proteins in a cell- and gene-specific manner (Watson and Hankinson, 1988; Watson et al., 1992; Ma et al., 1995; Kobayashi et al., 1997; Kress and Greenlee, 1997; Gradin et al., 1999; Kumar et al., 1999; Nguyen et al., 1999; Eltom et al., 1999). The relative importance of these interactions in the dose-related and tissue-specific responses elicited by TCDD are unknown.

2.6. ACTIVATION OF GENE TRANSCRIPTION BY DIOXIN

2.6.1. In Vitro Studies

Much of our current understanding of the mechanism of dioxin action is based on analyses of the induction of particular enzyme activities by TCDD. Aryl hydrocarbon hydroxylase activity reflects the action of the cytochrome P4501A1 (*CYP1A1*) enzyme, which catalyzes oxygenation of polycyclic aromatic substrates as the initial step in their metabolic processing to water-soluble derivatives (Conney, 1982). TCDD induces *CYP1A1* activity in many tissues. In particular, the relatively strong induction of *CYP1A1* activity by TCDD in cultured cells has facilitated the application of molecular genetic techniques to the analysis of the

induction mechanism (Whitlock, 1999). Table 2-1 and Figure 2-2 summarize some of the molecular events involved in this induction response.

In mouse hepatoma cells, nuclear transcription experiments reveal that TCDD induces hydroxylase activity by stimulating transcription of the corresponding *CYP1A1* gene. The response to TCDD occurs within a few minutes and is direct in that it does not require ongoing protein synthesis. Thus, the regulatory components required for the activation of *CYP1A1* transcription are present constitutively within the cell. TCDD fails to activate *CYP1A1* transcription in Ah receptor-defective cells and in Arnt-defective cells, indicating that the response requires both the Ah receptor and Arnt.

Observations that TCDD activates transcription and the liganded Ah receptor binds to DNA led to the discovery of a dioxin-responsive regulatory DNA sequence upstream of the *CYP1A1* gene. Recombinant DNA methods were used to construct chimeric genes in which potential regulatory DNA sequences from the *CYP1A1* gene were ligated to a heterologous "reporter" gene. After transfection of the recombinant genes into mouse hepatoma cells, TCDD was observed to activate the expression of the reporter gene. Additional transfection experiments defined the size of the dioxin-responsive domain and revealed that it had the properties of a transcriptional enhancer (Jones et al., 1986; Neuhold et al., 1986; Fujisawa-Sehara et al., 1987; Fisher et al., 1990). Furthermore, the recombinant gene responded poorly when transfected into Ah receptor-defective cells or Arnt-defective cells. Thus, both the receptor protein and the Arnt protein are required for enhancer function. Analyses of stable transfectants revealed that the dioxin-responsive enhancer can function in a chromosomal location distinct from that of the *CYP1A1* gene (Fisher et al., 1989). Therefore, in principle, an analogous enhancer element could mediate the transcriptional response of other genes to TCDD.

The DNA upstream region of the *CYP1A1* gene contains a second control element, a transcriptional promoter, that functions to ensure that transcription is initiated at the correct site. The promoter binds proteins that are expressed constitutively by the cell; however, the promoter contains no binding sites for the liganded Ah receptor heteromer. Transfection experiments indicate that neither the enhancer nor the promoter functions in the absence of the other (Jones and Whitlock, 1990). On might question how the enhancer and promoter, which are separated by hundreds of nucleotides, function in concert. TCDD-induced alterations in the chromatin structure of the *CYP1A1* gene play an important part in this process, as described later.

As indicated above, enhancer function requires both Ah receptor and Arnt proteins. Furthermore, the liganded, heteromeric form of the receptor exhibits an increased affinity for DNA. Together these data indicate that activation of *CYP1A1* transcription involves binding of the receptor heteromer to the enhancer. Analyses of protein-DNA interactions in vitro by gel retardation were done using enhancer DNA sequences and nuclear extracts from uninduced and

TCDD-induced cells. These studies revealed the existence of an inducible, receptor-dependent, and Arnt-dependent protein-DNA interaction, whose characteristics were those expected for the binding of the receptor heteromer to DNA (Denison et al., 1989; Hapgood et al., 1989; Saatcioglu et al., 1990a,b). The receptor heteromer recognizes the specific core nucleotide sequence

5'-NTGCGTG-3'
3'-NACGCAC-5'

present in multiple copies within the enhancer. These are often referred to as a DRE or XRE. Studies with a [^{125}I]-labeled dioxin indicate that the receptor heteromer binds in a 1:1 ratio to its DNA recognition sequence (Denison et al., 1989). Methylation protection and interference experiments in vitro reveal that the receptor heteromer lies within the major DNA groove and contacts the four guanines of the recognition sequence (Neuhold et al., 1989; Shen and Whitlock, 1989; Saatcioglu et al., 1990a, b). Transfection analyses of the six enhancer binding sites (in the mouse) for the receptor heteromer, as well as several mutated sites synthesized in vitro, reveal that nucleotides adjacent to the core recognition sequence contribute to enhancer function because the core nucleotides alone fail to exhibit enhancer activity (Denison et al., 1988). Studies of protein-DNA interactions reveal that there is no strict relationship between the affinity of the receptor heteromer for DNA and the extent of enhancer activation (Shen and Whitlock, 1992; Neuhold et al., 1989). These latter observations suggest that the protein-DNA interaction per se does not suffice to activate transcription and that an additional event (such as DNA bending--see below) is necessary. Mutational analyses reveal that the four base-pair sequence

5'-CGTG-3'
3'-GCAC-5'

is required for the receptor heteromer to bind to DNA in vitro (Shen and Whitlock, 1992; Yao and Denison, 1992; Lusska et al., 1993). Six distinct DRE sites have been identified within the mouse *CYP1A1* promoter (Lusska et al., 1993), whereas the rat and human *CYP1A1* gene promoters contain two and three copies of the core DRE sequence, respectively (Swanson and Bradfield, 1993). Thus, the homologous gene from different species may have different regulatory units. It is inappropriate to assume that the relative sensitivity of these genes to modulation by TCDD may be increased or decreased based on the number of DREs or their relative position in the upstream regulatory region, because this is also influenced by a variety of other regulatory factors. It is also possible that additional transcription factors, activators or

repressors, may have overlapping DNA binding specificities with that of the Ah receptor-Arnt complex (e.g., Duan et al., 1999; Klinge et al., 1999).

The DNA recognition sequence for the receptor heteromer contains two CpG dinucleotides. Studies in other systems have revealed that cytosine methylation at CpG is associated with decreased gene expression, often in tissue-specific fashion. Cytosine methylation of the CpG dinucleotides within the recognition sequence diminishes both the binding of the receptor heteromer to the enhancer (as measured by gel retardation) and the functional activity of the enhancer element (as determined by transfection experiments). Therefore, given that the TCDD-responsive receptor/enhancer system can regulate the transcription of genes other than *CYP1A1*, methylation of the enhancer may constitute one mechanism for controlling expression of such genes in a tissue-specific fashion (Shen and Whitlock, 1989).

An extensive analysis of the manner in which other bHLH proteins dimerize and bind to their respective DNA recognition sequences has been performed (reviewed in Swanson et al., 1995; Schmidt and Bradfield, 1996; Wilson and Safe, 1998). The bHLH/PAS family can be subdivided based on the basic region amino acid sequence and the DNA recognition sequence of its members. Arnt-like proteins recognize a 3'-half-site GTG, whereas heterodimer partners for Arnt, such as the Ah receptor, are more selective with unique basic domains. This suggests that although the Arnt-like component may function as a generic coregulator, specificity may be designated by Arnt's dimerization partner. These data are consistent with the finding that Arnt can dimerize with several other bHLH proteins; to date, the Ah receptor has been found to dimerize only with Arnt. Thus the family of bHLH/PAS proteins may exhibit a multitude of possible dimerizations, each complex recognizing a unique DNA sequence. The relative presence and state of activation of these proteins represent a novel mechanism to determine diversity of tissue-, cell-, and gene-specific regulation.

Promoter regions of TCDD-responsive genes have also been found to contain negative regulatory elements (Hines et al., 1988; Walsh et al., 1996; Piechocki and Hines, 1998). Superinducibility of *CYP1A1* by TCDD has been observed following the treatment of cells with cycloheximide, a protein synthesis inhibitor, suggesting that constitutively bound proteins are involved in negative regulation of *CYP1A1* (Lusska et al., 1992). The function and regulation of these negative elements are not completely understood and are likely to be gene-, cell-, and species-specific.

Gel retardation analyses also reveal that binding of the receptor heteromer to its recognition sequence bends the DNA in vitro. The site of the bend is at, or very near, the site of the protein-DNA interaction (Elferink and Whitlock, 1990). These findings suggest that binding

of the receptor heteromer to chromatin might also alter the configuration of the enhancer DNA in vivo.

2.6.2. In Vivo Studies

Studies that use transfection and in vitro techniques for analyzing protein-DNA interactions provide important clues about the functional components of the TCDD-responsive system. However, such experimental approaches necessitate removing the DNA regulatory elements from their native context within the chromosome and, therefore, have the potential to generate misleading results. For example, in the intact cell, nuclear DNA is complexed with histones and other chromosomal proteins, and the structure of the nucleoprotein complex (chromatin) makes important contributions to the control of gene transcription (Grunstein, 1990; Felsenfeld, 1992; Kornberg and Lorch, 1992). Transfection experiments and studies of protein-DNA interactions in vitro do not adequately control for this variable. For this reason, the protein-DNA interaction at the dioxin-responsive enhancer was analyzed in intact cells (Wu and Whitlock, 1993). These experiments revealed that the inactive (i.e., uninduced) enhancer binds few, if any, proteins within the major DNA groove. This finding implies that the inactive enhancer is relatively inaccessible to DNA-binding proteins in vivo. In addition, from a mechanistic standpoint, the absence of protein-enhancer interactions in uninduced cells argues against the idea that, at least for the *CYP1A1* gene, a specific repressor protein maintains the enhancer in an inactive configuration. Exposure of cells to TCDD leads to rapid binding of receptor heteromers, and a few other proteins, to the enhancer in the regulatory region of the *CYP1A1* gene. Therefore, in isolated hepatoma cells the liganded receptor heteromer appears to activate transcription of *CYP1A1* by a mechanism that does not require other enhancer-binding proteins (Wu and Whitlock, 1993).

Proteins that bind to the *CYP1A1* promoter are expressed constitutively, and TCDD has no effect on their interactions with promoter DNA in vitro, as measured by DNase footprinting (Jones and Whitlock, 1990). However, in intact cells, these proteins fail to bind to the inactive (i.e., uninduced) promoter. Thus, the promoter, like the enhancer, is inaccessible in uninduced cells. Exposure of cells to TCDD induces a rapid conformational change at the promoter region, such that it becomes accessible to the constitutively expressed proteins. This change represents a primary effect of TCDD that does not require transcription since it is insensitive to actinomycin D. In addition, it is receptor dependent and Arnt dependent, because it does not occur in Ah receptor- and Arnt-deficient cells. These observations indicate that the receptor-enhancer interaction increases accessibility of the downstream promoter to transcription factors (Durrin and Whitlock, 1989; Wu and Whitlock, 1992).

Studies of *CYP1A1* gene chromatin structure reveal that, in the transcriptionally inactive state, the enhancer/promoter region assumes a nucleosomal structure that is specifically positioned at the promoter (Morgan and Whitlock, 1992). Its organization into nucleosomes plausibly accounts for the inaccessibility of the enhancer/promoter region to DNA-binding proteins in uninduced cells. Exposure to TCDD produces a rapid and actinomycin D-insensitive loss of the positioned nucleosomes at the promoter; this change in chromatin structure accounts for the TCDD-induced increase in promoter accessibility and increased *CYP1A1* transcription in vivo (Morgan and Whitlock, 1992). However, studies indicate that Ah receptor-Arnt binding to DNA and increased chromatin accessibility at the enhancer are not sufficient to induce *CYP1A1* gene expression, but that enhancer-promoter communication is also required. This is postulated to be mediated, at least in part, by the ability of the C-terminal region of the Ah receptor to interact with other proteins (Okino and Whitlock, 1995; Ko et al., 1996).

The mechanism by which binding of liganded receptor heteromers to the enhancer alters chromatin structure is unknown. One possibility is that the DNA-bound receptor complex affects histones (e.g., by recruiting other proteins possessing and/or activating histone acetylase activity), thereby weakening histone-DNA interactions and destabilizing nucleosomes. Studies using trichostatin A, a histone deacetylase inhibitor, show that histone acetylation plays an important role in Ah receptor-elicited activation of the *CYP1A1* and *1A2* genes (Xu et al., 1997). The Ah receptor-Arnt complex has been shown to interact with several coactivator proteins that may enhance transcription under some contexts (Kobayashi et al., 1996; Kumar et al., 1999; Nguyen et al., 1999). Furthermore, several coactivators have been identified that contain regions homologous to the PAS domain of the Ah receptor, Arnt and other bHLH proteins (Kamei et al., 1996; Voegel et al., 1996). Under in vitro conditions, AhR and Arnt have been found to directly interact with several proteins that make up the basal transcriptional machinery, such as TBP (TATA-box binding protein), TFIIF, and TFIID, which has acetyltransferase activity (Rowlands et al., 1996; Swanson and Yang, 1998). A second possibility is that the receptor-enhancer interaction alters the DNA structure of the enhancer/promoter region, thereby stabilizing it in a non-nucleosomal configuration. This idea is consistent with the observation that the receptor heteromer bends DNA in vitro (Elferink and Whitlock, 1990).

The six binding sites for the receptor heteromer on the *CYP1A1* enhancer in mice are arranged in an irregular pattern. The absence of regular spacing between sites suggests that enhancer activation does not require protein-protein interactions between adjacent DNA-bound receptor heteromers. Instead, irregular spacing of binding sites may reflect constraints imposed by chromatin structure because the receptor heteromer must bind to nucleosomes. For example, as the DNA helix wraps around the histone core of the nucleosome, the major groove (which contains the binding sites for the receptor heteromer) is periodically accessible. Increasing the

number of binding sites at irregular intervals increases the probability that at least one site will be accessible even when the DNA is nucleosomal. In addition, the receptor heteromer contacts a relatively short (six base-pair) DNA segment, increasing the probability that the entire binding site in the nucleosome will be accessible. Thus, the multiplicity, irregular distribution, and small size of the binding sites may have evolved as a mechanism for overcoming the steric constraint imposed by the nucleosomal organization of the inactive enhancer in vivo.

2.7. EVIDENCE FOR DIFFERENT MECHANISMS OF TOXICITY.

As indicated above, much of our understanding of the possible mechanisms by which TCDD and related chemicals may act has been elucidated through analyses of how they induce *CYP1A1* gene expression. Based on this model, it is logical to hypothesize that the binding of TCDD to the Ah receptor, receptor-Arnt dimerization, binding of this complex to DREs present in 5' promoter regions of responsive genes, and inappropriate modulation of gene expression, represent the initial steps in a series of biochemical, cellular, and tissue changes that result in the toxicity observed. This hypothesis is further supported by numerous studies evaluating structure-activity relationships of various Ah receptor ligands, the genetics of mutant Ah receptor genes, receptor-deficient mice, and the molecular events contributing to and regulating expression of the Ah receptor and its activity. For example, it is striking that dosages of TCDD, that produce a variety of toxic effects in normal mice, produce no effects in Ah receptor knockout mice. Although the promoter regions of many genes, including *CYP1A1*, contain DREs (Lai et al., 1996), only a few of these are known to be directly regulated by the Ah receptor-Arnt complex (reviewed in Denison et al., 1998). However, the modulated expression of these genes does not completely explain (at least not as yet) the diversity of toxic effects elicited by TCDD in numerous animal species. By analogy, it is predicted that other genes have inappropriate expression (or repression) directly related to particular toxic events. The findings that many Ah receptor-modulated genes are regulated in a species-, cell-, and developmental stage-specific manner suggest that molecular and cellular pathways leading to any particular toxic event are extremely complex. Recent work demonstrated the modulation of at least 310 known genes in human hepatoma cells exposed to TCDD (Puga et al., 2000b). Indeed, precise dissection of these events represents a considerable challenge, especially in that a toxic response may depend on timely modulation of several genes rather than of just one particular gene, and possibly modulation of these genes in several rather than just one cell type.

As our understanding of the receptor and the molecular events that regulate its activity has progressed, it has become apparent that biochemical and biological outcomes of TCDD exposure can be modulated by numerous other proteins with which the Ah receptor interacts. Thus, it is possible that dioxin could modulate gene expression by pathways that do not involve

interaction of the receptor with either Arnt or DREs. Although conditional disruption of the Arnt gene results in the inability of TCDD to induce several responsive genes including CYP1A1 (Tomita et al., 2000), there are, in fact, no data proving that Arnt is required for any toxic effects elicited by dioxin. No other functional heterodimer partner for the Ah receptor has been identified. Thus, it is conceivable that, through interaction with other proteins, the receptor could bind to DNA elements that are uniquely different from the consensus DRE identified. This possibility seems even more plausible given the multiple dimerization partners identified for Arnt and other bHLH-PAS proteins.

It is also reasonable to hypothesize that the Ah receptor might modulate gene expression by a mechanism that does not require its direct interaction with DNA. It is plausible, for example, that the Ah receptor and the Ah receptor-Arnt complex could divert other proteins and transcription factors from other signaling pathways. Several studies provide evidence to support this possibility. For example, direct interaction between the Ah receptor and retinoblastoma protein has been shown (Ge and Elferink, 1998; Puga et al., 2000a). Progression of the cell cycle through G1 phase is regulated, in part, by the retinoblastoma protein (Weinberg, 1995). TCDD exposure has been shown to arrest cells in G1 (Weiss et al., 1996; Kolluri et al., 1999), and the Ah receptor appears to be necessary for progression of mouse hepatoma cells through G1 (Ma and Whitlock, 1996). These observations are consistent with a hypothesis that the dioxin-activated Ah receptor may disrupt normal retinoblastoma protein-mediated differentiation processes. Notably, another protein, p27Kip1, which is important for regulating the progression of cells from G1 to S phase, has been shown to be induced by TCDD (Kolluri et al., 1999). Furthermore, the Ah receptor is expressed in cells in a cycle-dependent manner, with expression peaking in the late S phase (Vaziri et al., 1996). Similarly, recently described interactions between the Ah receptor and the transcription factor NF-kB could potentially explain several biological effects associated with TCDD exposure (Tian et al., 1999). Data suggests that activation of the AhR may increase the activity of specific NF-kB subunits (Kim et al., 2000; Schlezinger et al., 2000). For example, the AhR has been shown to associate with the RelA subunit of NF-kB to activate the C-myc gene promoter in human breast cancer cells (Kim et al., 2000). Likewise, dioxin treatment has been shown to inhibit progesterone receptor signaling (Kuil et al., 1998). This might be due to the sequestration of common accessory factors or coactivator proteins used by other transcription factors. It has been demonstrated that overexpression of one steroid hormone receptor can decrease transcriptional activity of another, presumably through this mechanism (Meyer et al., 1989). It is also possible that because Arnt (or other as yet unidentified partners for the Ah receptor) can dimerize with other proteins, some of the biological effects of the dioxins could be related to recruitment of Arnt by the Ah receptor away from these other pathways. Thus, toxicity could result from loss of Arnt function. At this

point, there is no evidence for this mechanism. In fact, recent data suggest that the noted functional interference between hypoxia-induced pathways and Ah receptor-mediated signaling (Gradin et al., 1996) does not occur through competition between the Ah receptor and HIF-1α for Arnt (Pollenz et al., 1999). Data also suggest that ligand binding to the Ah receptor initiates a phosphorylation/dephosphorylation cascade resulting in modulated activity of other transcription factors (Enan and Matsumura, 1996; Blankenship and Matsumura, 1997). Precise components and events of these modulated pathways have yet to be delineated. How or whether any of these interactions in fact lead to any or all of the toxic effects elicited by dioxin exposure has yet to be established. Nevertheless, it is clear that inappropriate activation of the Ah receptor could have profound effects on regulation of a variety of signal transduction pathways; disruption of these could have serious consequences on a number of cell and tissue processes.

Despite the wealth of evidence to indicate a role of the Ah receptor in the toxicity elicited by the dioxins, it also seems possible that these chemicals may cause toxic effects through mechanisms involving their interaction with biological effector molecules other than the receptor. Clearly, a causal link between Ah receptor-regulated gene expression (regardless of the mechanism of gene modulation) and any of the demonstrated toxic effects has not been established. Furthermore, even though data from structure activity relationship and genetic studies are consistent with the notion that the Ah receptor mediates some toxic effects, not all effects have been thoroughly examined by these parameters. Similarly, Ah receptor knockout mice have not been thoroughly examined for the ability of dioxin to elicit all of its known toxic effects. Finally, although the Ah receptor is present in human cells and tissues, and studies using human cells are consistent with the hypothesis that the Ah receptor mediates effects of the dioxins, it is not known whether these same relationships would exist following exposure of intact humans. Thus, it seems possible that dioxin might cause effects in people and animals by a mechanism involving macromolecules other than the Ah receptor. Furthermore, within the same organism some effects may involve the receptor and others may not. To date, there is, however, no relevant evidence to support these possibilities.

It has been demonstrated that Ah receptor-deficient mice show no signs of toxicity at doses of TCDD (200 µg/kg) approximating the LD50 dose in mice containing the Ah receptor (Fernandez-Salguero et al., 1996). However, a single exposure of 2000 µg/kg to Ah receptor-deficient animals produced several minor lesions including scattered necrosis and vasculitis in the liver and lungs. These data suggest that a pathway leading to toxicity exists, albeit at very high doses, that is independent of the Ah receptor. However, these data also clearly indicate that the major in vivo effects of TCDD are mediated, at least in mice, through the Ah receptors. Notably, the level of TCDD exposure in these Ah receptor-deficient animals is well beyond that known to occur in any human population.

There is much evidence to indicate that the immunotoxic effects of TCDD are mediated by the Ah receptor (Luster et al., 1985; Silkworth and Antrim, 1985; Davis and Safe, 1988, 1989, 1990; Safe, 1990; Ackerman et al., 1989; Pavylak et al., 1989; Kerkvliet et al., 1990; Silkworth et al., 1993). These studies primarily investigate structure-activity relationships following a single dose, and compare mouse strains that are sensitive or less sensitive to TCDD because of alterations in the amino acid sequence of the Ah receptor. However, the results of other investigations using repeated dosing schedules could be interpreted to indicate that the Ah receptor is not involved in some immunotoxic responses. When TCDD was administered to mice daily for 2 weeks, no differences in the inhibition effects of TCDD on antibody-forming cells in the spleen were observed between sensitive and less sensitive strains of mice (Morris et al., 1992). A simple interpretation of these results might be that molecules other than the Ah receptor may mediate the effects of TCDD following multiple or chronic exposures. However, the authors did observe differences in sensitivity between different control groups, and when the data were expressed as a percentage of the appropriate control, strain differences in response to TCDD were observed. It also seems likely that relative sensitivity to TCDD contributes to strain differences in the pharmacokinetics of this chemical. TCDD and related chemicals have been shown to induce expression of cytochrome P4501A2 (CYP1A2) in the liver, and the presence or absence of this protein has been shown to influence tissue distribution of TCDD (Poland et al., 1989; Kedderis et al., 1993; Diliberto et al., 1997). Thus, it is likely that, because of the induction of CYP1A2 and greater sequestration of dioxin in the livers of responsive animals, less is available to other tissues compared with less responsive animals. Data have been presented that indicate this (Diliberto et al., 1999).

Several other studies performed in isolated cells might also be interpreted to indicate that some of the immunotoxic effects of the dioxins are Ah receptor independent (Tucker et al., 1986; Davis and Safe, 1991; Morris et al., 1991; Morris and Holsapple, 1991). However, these data appear to conflict with results obtained in vivo and have been shown to be dependent on culture conditions (Morris and Holsapple, 1991). Furthermore, actual cellular concentrations of chemicals used in several of these in vitro studies were much higher than those known to occur in vivo where immunotoxic effects are observed (Neumann et al., 1992).

Several biochemical responses have been shown to occur rapidly in isolated cells following exposure to TCDD and related dioxins. These include increases in protein kinase and phospholipase C activities, and affects on plasma membranes (Bombick et al., 1984; Bombick et al., 1985; Beebe et al., 1990; Ma et al., 1992; Puga et al., 1992; Ashida et al., 2000b). Some of these responses occur in cells lacking Arnt and in cells with highly reduced levels of Ah receptor (Puga et al., 1992), implying either a non nuclear role of the Ah receptor in mediating these events or an Ah receptor-independent process. Blankenship and Matsumura (1997) have shown

that TCDD, directly or indirectly, activates protein tyrosine kinase activity in murine hepatic cytosol, also suggesting non-nuclear activity of this chemical. In another recent study, TCDD was shown to stimulate c-fos activity in CV-1 cells in which no Ah receptor could be detected by immunoblot analysis or by the induction of *CYP1A1* activity (Hoffer et al., 1996). However, this study failed to completely rule out the presence of very low levels of receptor. Notably, certain bone marrow stromal cell lines lack immunodetectable Ah receptor and fail to show induction of *CYP1A1* following treatment with TCDD. However, in these same cell lines, Ah receptor mRNA transcripts could be detected and *CYP1B1* mRNA was clearly inducible by TCDD (Lavin et al., 1998).

Thus, at present the wealth of evidence available indicates that most, if not all, of the biological and toxic effects of dioxins are mediated by the Ah receptor. Although the receptor may be necessary for the occurrence of these events, clearly it is not sufficient because other proteins and conditions are known to affect activity of the receptor and its ability to alter gene expression. There is some evidence to support mechanisms involving pathways for Ah receptor action that do not involve Arnt, although the exact steps involved in these pathways have yet to be fully detailed. Certain studies could be interpreted to indicate Ah receptor-independent mechanisms, although these have not clearly ruled out involvement of the Ah receptor. The only consistent, but limited, evidence for dioxin-elicited effects that do not involve the Ah receptor comes from studies using Ah receptor-deficient animals. Here however, observed minor effects occurred only following treatment with extremely high doses of TCDD. Notably, these doses are well beyond that which any humans are known to have been exposed.

2.8. FUTURE RESEARCH

The cloning of cDNAs encoding the Ah receptor and Arnt proteins, and the development of anti-receptor and anti-Arnt antibodies, open the way for additional mechanistic studies of dioxin action. It is now practical to analyze the structure and function of these proteins using mutagenesis techniques, to analyze the structure and regulation of the corresponding genes, to determine whether different forms of the receptor and Arnt exist, and to directly analyze the role of posttranslational modifications on receptor and Arnt function. In vitro transcription can be used to study the functional components of the dioxin-responsive pathway.

The observation that the Ah receptor and Arnt proteins heterodimerize via HLH motifs raises the likelihood that they may also dimerize with other partners (perhaps in a tissue-specific fashion) to generate different protein combinations that may have novel regulatory properties. The types of protein complexes formed may depend on the relative amount of each potential partner protein present in different cell types and at different times of tissue development/differentiation, as well as on the stability of each type of heterodimer. This

combinational mechanism for regulating dioxin responses may also allow for functional interactions with other signal transduction pathways, increasing the potential diversity of dioxin-induced responses even further (see, e.g., Pimental et al., 1993; Hogenesch et al., 1997; Caruso et al., 1999; Chan et al., 1999; Nebert et al., 2000). These are promising areas for future research, and are likely to provide novel insights into the mechanism of dioxin action, in particular, and the regulation of mammalian gene transcription (especially by bHLH proteins), in general. If such studies reveal new proteins (and corresponding genes) that influence rate-limiting steps in the response to dioxin, the findings might also prove useful from a risk assessment standpoint.

The teratogenic and tumor-promoting effects of TCDD, its effects on differentiation of a variety of cell types, and results from Ah receptor deficient animals suggest that the Ah receptor and other components of the dioxin-responsive system contribute to important developmental and proliferative pathways. Further study of transgenic animals, in which both alleles for the Ah receptor or the Arnt protein have been permanently or conditionally inactivated, will provide new insights into such pathways. In addition, the use of transgenic animals in toxicological studies might be helpful to assess what cellular components participate in the adverse responses to particular chemicals.

Chromatin structure and nucleosome positioning have important effects on mammalian gene expression (Grunstein, 1990; Felsenfeld, 1992; Kornberg and Lorch, 1992). The TCDD-responsive *CYP1A1* gene is an interesting model system that can be used to analyze the mechanism by which a protein complex, such as the liganded receptor heteromer, can trigger chromatin structural changes that increase DNA accessibility. Such studies may also provide novel insights into the function of the dioxin-responsive system.

Some dioxin-responsive genes (e.g., *CYP1A2*, *CYP1B1*, *glutathione S-transferase Ya*) exhibit substantial constitutive ("basal") transcription, which is increased further upon TCDD treatment. The constitutive expression of these genes implies that the promoter must be maintained in an accessible configuration even in the absence of dioxin; therefore, TCDD may induce the transcription of such genes by a mechanism that does not involve major changes in chromatin structure. As such, the liganded receptor heteromer may be able to increase gene transcription by both chromatin-dependent and chromatin-independent mechanisms. This may be an interesting area for future research.

The overall evidence indicates that the Ah receptor participates in every biological response to TCDD (Poland and Knutson, 1982; Safe, 1986; Birnbaum, 1994). Thus, through its interaction with Arnt and other transcription factors, TCDD likely activates transcription of other genes via a receptor- and enhancer-dependent mechanism analogous to that described for the *CYP1A1* gene. For example, TCDD induces the expression of genes encoding CYP1A2,

CYP1B1, glutathione S-transferase Ya subunit, aldehyde dehydrogenase, prostaglandin endoperoxide H synthase 2, and quinone reductase. In some cases, induction has been shown to occur at the transcriptional level, to be Ah receptor and Arnt dependent, and to involve a DNA recognition sequence analogous to that found upstream of the *CYP1A1* gene (Dunn et al., 1988; Quattrochi and Tukey, 1989; Favreau and Pickett, 1991; Takimoto et al., 1992; Pimental et al, 1993; Rushmore and Pickett, 1993; Sutter et al., 1994; Kraemer et al., 1996). Other observations reveal that TCDD activates the transcription of several other genes by unknown mechanisms (see Denison et al., 1998). For dioxin-responsive genes other than *CYP1A1*, and especially for genes that respond in a tissue-specific fashion, the presence of the receptor/enhancer system may not be sufficient for dioxin action. Rather, other tissue-specific regulatory components may play a dominant role in governing the response to TCDD. For example, estrogens (presumably via estrogen receptors) influence TCDD-induced liver neoplasia in rats (Lucier et al., 1991). In addition, in vitro experiments suggest that, in some cell types, a repressor protein inhibits the response to TCDD by competing for the receptor binding site(s) on DNA (Gradin et al., 1993; Walsh et al., 1996; Piechocki and Hines, 1998). Future research may reveal the existence of additional stimulatory or inhibitory gene regulatory components that can modulate the activity of the dioxin-responsive receptor/enhancer system. Further research is also needed to determine whether Ah receptor-dependent modulation of gene expression is exclusively dependent on Arnt. Other heterodimeric partners for the Ah receptor may be identified and these complexes may recognize unique DNA response elements that are involved in the control of a variety of genes. In addition, it is also possible that the Ah receptor controls certain activities, such as phosphorylation/dephosphorylation, through pathways that do not directly involve nuclear localization and transcriptional activation.

The potential teratogenic, developmental, and neoplastic effects of TCDD have raised particular concerns about the human health effects of dioxin. In particular, experimental studies in animals suggest that developing tissues are especially sensitive. These effects have been characterized by altered cell proliferation, metaplasia, and modified terminal differentiation, and can occur at dosages that have no overt toxicity to the pregnant dam (see Theobald and Peterson, 1994; Gray and Ostby, 1995; Roman et al., 1995). Concentrations of TCDD as low as 0.8 ng/g in the murine embryonic palate have been shown to result in cleft palate (Abbott et al., 1996). These responses may reflect complicated cascades of biochemical changes that are difficult to analyze mechanistically; therefore, a major challenge for the future will be to establish experimental systems in which such complex phenomena are amenable to study at the molecular level.

The actual molecular mechanisms underlying differences in sensitivity between species, tissues, and periods of development have yet to be determined. Indeed, this is a central issue for

relating animal studies to human exposures and sensitivity. A major obstacle has been our lack of understanding of the direct tissue and cell targets, critical periods of increased sensitivity, and actual dose to the target cell type. Even with the same dosage per cell, it is not difficult to envision that given the multitude of regulatory controls for any particular gene at a particular period of cellular development, different dose-dependent response curves for these genes would be observed. For example, rat *UDP glucuronosyltransferase 1A6* gene is about 1000 times less sensitive than the *CYP1A1* gene to induction of transcription by dioxin (Vanden Heuvel et al., 1994). Furthermore, considering the likely multitude of additional molecular events that contribute to the ultimate biological/toxic response following initial gene modulation, it is also not difficult to envision that different endpoints might have very different sensitivities, even though binding to the same receptor is the common initial trigger. Considering this complexity, it remains a particular challenge to develop appropriate model systems that accurately mimic the in vivo effects associated with exposure. It is also important to consider that a particular response to TCDD may be mediated through effects on multiple cells. Evidence was recently presented to indicate that Ah receptor activation in both hepatic parenchymal and hematopoietic cells contributes to the hepatic lesions induced by TCDD in mice (Thurmond et al., 1999).

Clearly, most data are consistent with the belief that the Ah receptor has some normal cellular function. We can now appreciate that the Ah receptor is a member of a family of proteins that are conserved through evolution and involved in growth and differentiation processes. The expression and activity of the Ah receptor appear to be well regulated in a differentiation and cell cycle stage-specific manner. Furthermore, we now know that the genes regulated by the receptor are involved in not only xenobiotic metabolism, but also in cell growth and differentiation processes. Further identification of other Ah receptor-regulated genes and their function, as well as factors that may control the ability of the receptor to regulate these in a cell-specific manner, will undoubtedly assist in our understanding of its normal function and how aberrant function may lead to toxicity. For example, recognition that the Ah receptor influences cell cycle regulation, and a further dissection of the pathways involved, will likely help us understand how dioxins affect developmental and neoplastic processes. In addition, further research to characterize and identify possible endogenous ligands for the receptor, and its role in regulating cellular processes, will have a great impact in these areas. It seems plausible that the spectrum of genes regulated by the receptor may mediate both endogenous ligand function and prevention of its inappropriate action through metabolism (Nebert et al., 2000).

2.9. MECHANISTIC INFORMATION AND RISK ASSESSMENT

A substantial body of evidence from investigations using experimental animals indicates that the Ah receptor mediates the biological effects of TCDD. Although studies using human

tissues are much less extensive, it appears reasonable to assume that dioxin's effects in humans are also receptor mediated. Studies using human organs and cells in culture are consistent with this hypothesis. A receptor-based mechanism would predict that, except in cases where the concentration of TCDD is already high (i.e., [TCDD]~K_D), incremental exposure to TCDD will lead to some increase in the fraction of Ah receptors occupied. However, it cannot be assumed that an increase in receptor occupancy will necessarily elicit a proportional increase in all biological response(s), because numerous molecular events (e.g., cofactors, other transcription factors, genes) contributing to the biological endpoint are integrated into the overall response. That is, the final biological response should be considered as an integration of a series of dose-response curves with each curve dependent on the molecular dosimetry for each particular step. Dose-response relationships that will be specific for each endpoint must be considered when using mathematical models to estimate the risk associated with exposure to TCDD. It remains a challenge to develop models that incorporate all the complexities associated with each biological response. Furthermore, the parameters for each mathematical model may only apply to a single biological response within a given tissue and species.

Given TCDD's widespread distribution, its persistence, and its accumulation within the food chain, it is likely that most humans are exposed to some level of dioxin; thus, the population at potential risk is large and genetically heterogeneous. By analogy with the findings in inbred mice, polymorphisms in the Ah receptor probably exist in humans. Therefore, a concentration of TCDD that elicits a particular response in one individual may not do so in another. For example, studies of humans exposed to dioxin following an industrial accident at Seveso, Italy, fail to reveal a simple and direct relationship between blood TCDD levels and development of chloracne (Mocarelli et al., 1991). These differences in responsiveness to TCDD may reflect genetic variation either in the Ah receptor or in some other component of the dioxin-responsive pathway. Therefore, analyses of human polymorphisms in the Ah receptor and Arnt genes have the potential to identify genotypes associated with higher (or lower) sensitivities to dioxin-related effects. Such molecular genetic information may be useful in the future for accurately predicting the health risks dioxin poses to humans.

Complex responses (such as cancer) probably involve multiple events and multiple genes. For example, a homozygous recessive mutation at the *hr* (hairless) locus is required for TCDD's action as a tumor promoter in mouse skin (Poland et al., 1982). Thus, the *hr* locus influences the susceptibility of a particular tissue (in this case skin) to a specific effect of dioxin (tumor promotion). An analogous relationship may exist for the effects of TCDD in other tissues. For example, TCDD may produce porphyria cutanea tarda only in individuals with inherited uroporphyrinogen decarboxylase deficiency (Doss et al., 1984). Such findings suggest

that, for some adverse effects of TCDD, the population at risk may be limited to individuals with a particular genetic predisposition.

Other factors can influence an organism's susceptibility to TCDD. For example, female rats are more prone to TCDD-induced liver neoplasms than are males; this phenomenon is related to the hormonal status of the animals (Lucier et al., 1991). In addition, hydrocortisone and TCDD synergize in producing cleft palate in mice. Retinoic acid and TCDD produce a similar synergistic teratogenic effect (Couture et al., 1990). These findings indicate that, in some cases, TCDD acts in combination with hormones or other chemicals to produce adverse effects. Such phenomena might also occur in humans. If so, the difficulty in assessing risk is increased, given the diversity among humans in hormonal status, lifestyle (e.g., smoking, diet), and chemical exposure. For example, several compounds present in the diet have been found to inhibit activation of the AhR induced by TCDD (Ashida et al., 2000a).

Dioxin's action as a tumor promoter and developmental toxicant presumably reflects its ability to alter cell proliferation and differentiation processes. There are several plausible mechanisms by which this could occur. First, TCDD might activate a gene (or genes) that is directly involved in tissue proliferation. Second, TCDD-induced changes in hormone metabolism may lead to tissue proliferation (or lack thereof) and altered differentiation secondary to altered secretion of a trophic hormone. Third, TCDD-induced changes in the expression of growth factor or hormone receptors may alter the sensitivity of a tissue to proliferative stimuli. Fourth, TCDD-induced toxicity may lead to cell death, followed by regenerative proliferation. These mechanisms likely differ among tissues and periods of development, and might be modulated by different genetic and environmental factors. As such, this complexity increases the difficulty associated with assessing the human health risks form dioxin exposure.

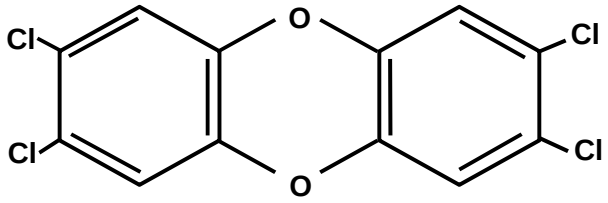
Under certain circumstances, exposure to TCDD may elicit beneficial effects. For example, TCDD protects against the carcinogenic effects of PAHs in mouse skin, possibly reflecting induction of detoxifying enzymes (Cohen et al., 1979; DiGiovanni et al., 1980). In other situations, TCDD-induced changes in estrogen metabolism may alter the growth of hormone-dependent tumor cells, producing a potential anticarcinogenic effect (Spink et al., 1990; Gierthy et al., 1993). However, several recent studies in mice indicate that the Ah receptor has an important role in the genetic damage and carcinogenesis caused by components in tobacco smoke such as benzo[a]pyrene through its ability to regulate *CYP1A1* gene induction (Dertinger et al., 1998, 2000; Shimizu et al., 2000). These issues complicate the risk assessment process for dioxin.

TCDD's biological effects likely reflect a complicated interplay between genetic and environmental factors. Thus, it may be overly simplistic to use mechanistic information derived

largely from the relatively simple responses described in this chapter (i.e., *CYP1A1* induction) as the basis for developing a quantitative approach to dioxin risk assessment in humans. While this approach represents a start toward incorporating mechanistic information into risk assessment, future biologically based dose-response models will require a better understanding not only of the TCDD-induced biochemical alterations that produce disease, but also of the relationships between genetic and environmental factors that influence an individual's susceptibility to TCDD. Molecular toxicology and mechanistic studies have great potential to provide new insights into such issues in the future.

Table 2-1. Events in the activation of *CYP1A1* gene transcription by dioxin

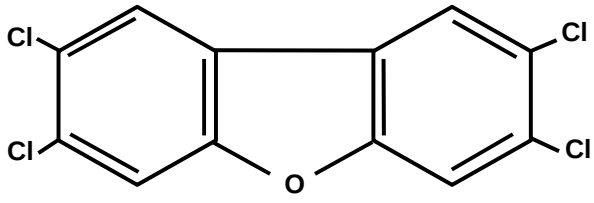
●	Diffusion into the cell
●	Binding to the Ah receptor protein
●	Conversion of liganded receptor to the DNA-binding form
●	Dissociation from hsp90
●	Active translocation from cytoplasm to nucleus
●	Association with Arnt protein
●	Binding of liganded receptor heteromer to enhancer DNA
●	Enhancer activation
●	Altered DNA configuration
●	Histone modification
●	Recruitment of additional proteins
●	Nucleosome disruption
●	Increased accessibility of transcriptional promoter
●	Binding of transcription factors to promoter
●	Enhanced mRNA and protein synthesis



2,3,7,8-Tetrachlorodibenzo-p-dioxin

Polychlorinated dibenzopara-dioxins

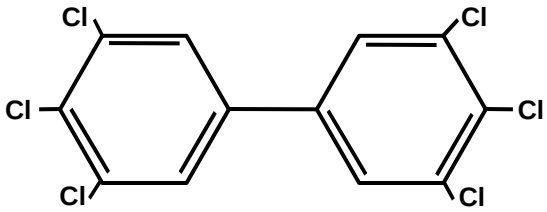
75 congeners



2,3,7,8-Tetrachlorodibenzofuran

Polychlorinated dibenzofurans

135 congeners



3,3',4,4',5,5'-Hexachlorobiphenyl

Figure 2-1. Chemical structure of dioxin and smiliar compounds.

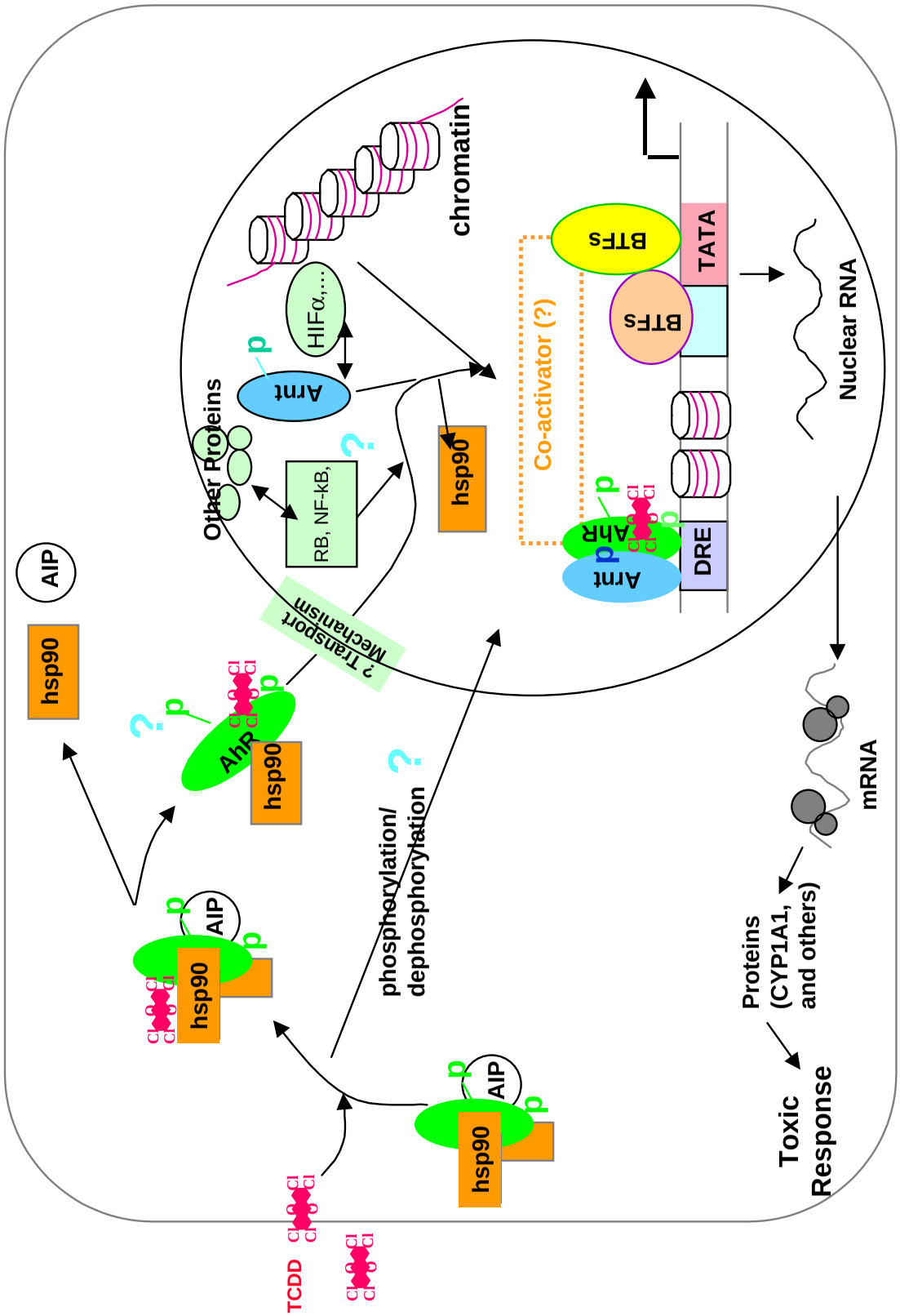


Figure 2-2. Cellular Mechanisms for Ah Receptor Action

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3. ACUTE, SUBCHRONIC, AND CHRONIC TOXICITY

3.1. SCOPE AND LIMITATIONS

The acute, subchronic, and chronic toxicology of the chlorinated dioxins, dibenzofurans, biphenyls, and related compounds have been reviewed extensively in recent years. This chapter summarizes knowledge on the toxicology of tetrachlorodibenzo-*p*-dioxin (TCDD), but also includes references to other dioxin-like compounds when relevant data are available. Included are selected various data that are considered to be of importance to risk assessment, particularly experimental animal data. Immunotoxicity, reproductive/developmental toxicity, carcinogenicity, toxicity to humans, and epidemiology are all covered in other chapters. Ecotoxicology is not covered in this chapter, but examples from mammalian and avian laboratory species are included.

3.2. ACUTE TOXICITY

The range of doses of TCDD that are lethal to animals varies extensively with both species and strain, as well as with sex, age, and the route of administration within a single strain (Table 3-1). One of the characteristics of TCDD-induced toxicity is delayed manifestation of lethality after acute exposure, with the time to death after exposure being several weeks. Death usually occurs as a consequence of loss of body weight (wasting syndrome) from TCDD-induced inhibition of gluconeogenesis and appetite suppression. Deaths within the first week after exposure—an unusually rapid course for TCDD toxicity—have been observed in guinea pigs (Schwetz et al., 1973), rabbits (Schwetz et al., 1973), and Syrian Golden hamsters (Olson et al., 1980). A more than 8,000-fold difference exists between the dose of TCDD reported to cause 50% lethality (LD_{50}) in male Hartley guinea pigs, the most sensitive species tested (Schwetz et al., 1973), and the LD_{50} dose in male Syrian Golden hamsters (Henck et al., 1981). Another animal with extremely high sensitivity is the mink (*Mustela vision)*; for the female, the calculated 28-day LC_{50} value is 0.264 µg TCDD/kg bw/day (Hochstein et al., 1998), which is an order of magnitude less than the 28-day LD_{50} of 4.2 µg TCDD/kg bw/day for male mink (Hochstein et al., 1988).

The rat seems to be the third most sensitive species among experimental animals, although there is a >300-fold variability in LD_{50} values among different strains. The Han/Wistar (H/W) Kuopio strain of rat has been shown to be particularly resistant to TCDD exposure (Pohjanvirta and Tuomisto, 1987). Among the five-rats-per-dose group (0, 1,500, 2,000, 2,500, or 3,000 µg TCDD/kg bw), only one animal died within the 40-day observation period. The DBA/2 male mouse has also been shown to have a high resistance to TCDD toxicity (Chapman and Schiller, 1985).

Data on gender differences in sensitivity to the lethal effects of TCDD are conflicting. The gender differences in the acute toxicity of TCDD are likely due to differences in toxicokinetics, i.e., higher tissue concentrations and longer half-life in females than in males (Li et al., 1995). Acute toxicity data that address the effect of age at the time of exposure to TCDD are scarce, and comparisons are hampered by either the absence or inadequacy of information on the age and body weight of the tested animals. As demonstrated with other chemicals, the acute toxicity of TCDD may vary several-fold depending on the vehicle used or the presence of other substances that affect uptake.

Differences in sensitivity toward TCDD among various strains of mice have been shown to depend on a genetic variability in the Ah locus (see Chapter 2). In two strains of male C57B/6J mice that differ only at the Ah locus, Birnbaum et al. (1990) found LD_{50} values of 159 and 3,351 µg/kg for wild-type mice ($Ah^{b/b}$) and congenic mice ($Ah^{d/d}$), respectively. The mean time to death, 22 days, was independent of dose and genotype. Signs of toxicity were similar in the two strains, and it was concluded that the spectrum of toxicity is independent of the allele at the Ah locus. The relative dose needed to bring about various acute responses, however, is ~8-24 times greater in congenic mice homozygous for the "d" allele than in the wild-type mice carrying two copies of the "b" gene.

The DBA/2 mouse strain requires 10 to 20 times higher doses of 2,3,7,8-TCDD than does the C57BL/6 strain for lethality (Chapman and Schiller, 1985). The reason for this difference between the two strains is the low TCDD-binding affinity to the Ah receptor in the DBA/2 strain (Okey et al., 1994). The difference in ligand-binding affinity, associated with susceptibility to TCDD-induced lethality that segregates with the Ah locus (Chapman and Schiller, 1985), is due to a point mutation (translated as alanine to valine) in the ligand-binding domain of codon 375 (Poland et al., 1994; Ema et al., 1994).

Wasting, hemorrhage, and anemia are the three primary causes for dioxin-induced lethality in rats, and a body weight loss of 25% is considered to be the minimum threshold to assign the presence of wasting syndrome for rats (Viluksela et al., 1997a,b, 1998).

1,2,3,4,5,6,7,8-HeptaCDD (HpCDD)-induced dose-response for wasting and hemorrhage overlap in female Sprague-Dawley rats (Rozman, 1999). Death from wasting and hemorrhage occur within the first few weeks of exposure. Animals that did not exhibit wasting or hemorrhage died from anemia, which did not start before day 126 postexposure (Rozman, 1999). Furthermore, unlike rats dying of wasting syndrome, the ones dying of anemia or hemorrhage had fat depots in the body, suggesting that increased body fat may aid them in surviving beyond the 30-day mark (Rozman,1999), only to succumb later to hemorrhage and anemia.

Long-Evans (L-E) *Turku* AB strain rats are around 1000-fold more sensitive to TCDD-induced acute lethality (LD_{50} about 10 µg/kg) than H/W Kuopio strain rats (LD_{50} > 9,600 µg/kg)

(Pohjanvirta et al., 1999). This feature of the H/W rat being highly resistant to acute TCDD toxicity, yet sensitive to enzyme induction, may be due in part to differences in AhR types between rat strains. The H/W strain has point mutations at exon 10 and at the first invariant nucleotide at the 5' end of intron 10 in the AhR gene. These cause alterations in AhR protein structure, leading to loss and alteration of multiple amino acid sequences at the carboxyl terminal region of the transactivation domain (Pohjanvirta et al., 1998). The homozygous AhR $^{hw/hw}$ type fails to mediate some endpoints of TCDD toxicity that parallel lethality. At lethal doses, H/W rats show only slight changes in bilirubin and body weight, while L-E rats show a five-fold increase in bilirubin and a 20% to 30% decrease in body weight as early as 6 days postexposure (Unkila et al., 1994a). Furthermore, at lethal doses H/W rats manifest only slight or transient inhibition of daily food intake and body weight gain, whereas in L-E rats progressive decrease in daily feed intake and body weight gain occur within 4 to 7 days postexposure (Unkila et al., 1994a).

Tuomisto et al. (1999) suggested that an uncharacterized gene, other than AhR, determines resistance of H/W Kuopio rats to TCDD-induced acute toxicity.

Geyer et al. (1990) utilized both their own and other data to determine a correlation between total body fat content and acute toxicity in various species and strains of laboratory mammals. They found a correlation of 0.834, and suggested that the reason for this correlation was that an increased total body fat content (TBF) may enhance the capacity to remove TCDD from the systemic circulation. This factor may be important, but it almost certainly does not explain all of the interspecies differences. Geyer et al. (1997) have determined that there is a linear relationship in mammals independent of strain and species between the logarithm of the oral 30-day LD_{50} in units of µg/kg bw and the mammal's TBF in percent via the regression equation:

$$\log LD_{50} = 5.30 \times \log TBF - 3.22$$

Data from studies of H/W Kuopio rats, which are extremely resistant to TCDD-induced lethality (Pohjanvirta and Tuomisto, 1987), were not included in this equation.

In chickens, acute toxicity is characterized by clinical signs such as dyspnea, reduced body weight gain, stunted growth, subcutaneous edema, pallor, and sudden death (chick edema disease). The disease first gained attention in 1957, but the causal agents were not identified as CDDs until much later (Firestone, 1973). Chick edema occurred in birds given oral doses of 1 or 10 µg TCDD/kg/day or 10 or 100 µg hexaCDD/kg/day, but it was not observed in chicks maintained on a diet containing 0.1% or 0.5% OCDD (Schwetz et al., 1973).

The female mink (*Mustela vision)* is more sensitive than the male mink to TCDD-induced lethality. Hochstein et al. (1998) fed 2- or 3-year-old adult female mink diets

supplemented with 0, 0.001, 0.01, 0.1, 1, 10, or 100 ppb TCDD for up to 125 days. Feed consumption was significantly depressed in the 10 and 100 ppb groups beginning in weeks 4 and 3, respectively. When adjusted for body weight (g food intake/100 g bw/day), the feed intake in TCDD-exposed groups was not significantly different from the control, except in the 10 ppb-dosed group during week 5. Significant body weight loss associated with classic symptoms of wasting syndrome resulting in mortality was observed in the 1, 10, and 100 ppb-dosed groups, respectively, from the third, second, and first week of exposure. Mortality reached 12.5%, 62.5% and 100% by day 28 in the 1, 10, and 100 ppb-dosed groups, respectively. By day 125, mortality increased to 62.5% and 100% in the 1 and 10 ppb groups. Based on the average feed intake of 5.5 g/100 g bw/day for the control mink, the dietary LC_{50} values of 4.8 and 0.85 ppb approximate 0.264 and 0.047 µg TCDD/kg bw/day, respectively, for 28 and 125 days of exposure.

3.2.1. Signs and Symptoms of Toxicity

TCDD affects a variety of organ systems in different species. It should be noted that much of the comparative database is derived from high-dose effects. The liver is the organ primarily affected in rodents and rabbits, while atrophy of the thymus and lymphatic tissues seems to be the most sensitive marker of toxicity in guinea pigs (WHO/IPCS, 1989; U.S. EPA, 1984, 1985). It is not possible to specify a single organ whose dysfunction accounts for lethality. Dermal effects are prominent signs of toxicity in nonhuman primates, and changes in epithelial tissues dominate both cutaneously and internally. This is most apparent in nonhuman primates in which the TCDD-induced cutaneous lesions closely mimic the chloracne and hyperkeratosis observed in humans. The histopathological alterations observed in epithelial tissues include hyperplastic and/or metaplastic alterations, as well as hypoplastic responses. The toxic responses of various species to TCDD are summarized in Table 3-2.

Loss of body weight, or wasting syndrome, is a characteristic sign observed in most animals exposed to TCDD. The weight loss usually manifests itself within a few days after exposure, and results in a substantial reduction of the adipose (Peterson et al., 1984) and muscle tissue (Max and Silbergeld, 1987) observed at autopsy. With sublethal doses of TCDD, a dose-dependent decrease in body weight gain occurs.

The greatest species-specific differences in toxicity concern pathological alterations in the liver. Administering lethal doses to guinea pigs does not result in liver damage comparable to the liver lesions observed in rabbits and rats, or to the liver changes observed in mice (McConnell et al., 1978a; Moore et al., 1979; Turner and Collins, 1983). In the hamster, manifest liver lesions do not occur even after fatal doses of TCDD; however, the ED_{50} for increased hepatic weight is only ~15 µg/kg (Gasiewicz et al., 1986). Liver-related enzyme

activities in serum are elevated in those animal species where liver damage is a prominent sign of TCDD toxicity. In animal species where hepatotoxicity is not as apparent, such as monkeys and guinea pigs, these enzyme activities are nearly normal.

Thymic atrophy has also been found in all animal species given lethal doses of TCDD. Treatment with TCDD inhibits bone marrow hematopoiesis in mice, both in vivo and in vitro, by directly altering the colony growth efficiency of stem cells (Chastain and Pazdernik, 1985; Luster et al., 1980, 1985).

Among other signs and symptoms that have been demonstrated in various species, the following should be noted: hepatic porphyria, hemorrhages in various organs, testicular atrophy, reduced prostate weight, reduced uterine weight, increased thyroid weight, lesions of the adrenal glands, inhibited bone marrow hematopoiesis, decreased serum albumin, and increased serum triglycerides and free fatty acids. The details of all underlying studies for these observations have been extensively reviewed (U.S. EPA, 1984, 1985; WHO/IPCS, 1989).

Effects on heart muscle have also been observed in guinea pigs and rats (Brewster et al., 1987; Kelling et al., 1987; Canga et al., 1988). Five days after a single lethal dose of TCDD (10 µg/kg intraperitoneally) was administered, a significantly decreased beta-adrenergic responsiveness was observed in the right ventricular papillary muscle of the guinea pig (Canga et al., 1988). In the TCDD-treated animals, a decrease in the positive inotropic effects of isoproterenol at 0.03-0.3 µM, but not at 0.1-10 nM, was also demonstrated. Additionally, enhanced responsiveness to low-frequency stimulation and increases in extracellular calcium were observed in these animals. Based on these findings, the authors suggest that the heart may be a major target for TCDD lethality at acutely toxic doses.

In the monkey, several additional symptoms have been registered, such as periorbital edema, conjunctivitis, and thickening of the meibomian glands followed by loss of the eyelashes, facial hair, and nails (McConnell et al., 1978b). These symptoms are similar to those observed in cases of human intoxication, such as from occupational exposure, the Seveso incident, and the Yusho and Yu-Cheng toxic oil intoxications, the latter involving exposure to PCBs and CDFs (see Chapter 7).

3.2.2. Studies In Vitro

Over 30 cell types, including primary cultures and cells from established and transformed cell lines derived from various tissues of at least six animal species, have been examined for their general cellular responses to TCDD (Beatty et al., 1975; Knutson and Poland, 1980a; Niwa et al., 1975; Yang et al., 1983a). The effects studied were changes in viability, growth rate, and morphology. Overall, there were few effects documented on these general cellular parameters in early studies.

Other in vitro studies, using more specific endpoints of toxicity, have clearly indicated effects of TCDD at comparatively low concentrations. For example, several studies have shown that TCDD affects cultured epidermal keratinocytes through interactions with differentiation mechanisms, and that this effect may be regulated by the modulation of epidermal growth factor (EGF) binding to the cells (Hudson et al., 1986). Additionally, in epithelial cells of human origin, TCDD has been shown to alter differentiation (Hudson et al., 1985), while aryl hydrocarbon hydroxylase (AHH) and 7-ethoxyresorufin O-deethylase (EROD) activity have been induced in vitro (see Section 3.5.4).

TCDD was found to inhibit high-density growth arrest in human squamous carcinoma cells in culture (Hebert et al., 1990a). Wiebel et al. (1991) identified a cell line (H4IIEC3-derived 5L hepatoma cells) that responds with decreased proliferation at low TCDD concentrations. In this cell line, half-maximum inhibition of proliferation occurs at a concentration of 0.1-0.3 nM. The onset of the effect is fairly rapid, manifesting itself as early as 4-8 hours after treatment. Further studies demonstrated that insensitive variants of this cell line were deficient in cytochrome P-4501A1 activity and lacked measurable amounts of the Ah receptor (Göttlicher et al., 1990). In addition, 3,3',4,4'-TCB inhibited proliferation in the sensitive cell line, although at higher concentrations.

3.2.3. Appraisal

Numerous studies of acute toxicity in various mammalian species have demonstrated dramatic species- and strain-specific differences in sensitivity. However, most species and strains respond at some level with a spectrum of symptoms that is generally the same, although species differences do exist.

Lethality is typically delayed by several weeks, and there is a pronounced wasting syndrome in almost all laboratory animals. Studies in congenic mice differing in their Ah responsiveness indicate that the sensitivity to acute toxicity of TCDD segregates with the Ah locus. Furthermore, studies of other CDDs, CDFs, and coplanar PCBs demonstrate that the potency for inducing lethality correlates with their ability to bind to the Ah receptor. In contrast, studies in various other species, including various strains of rats, have demonstrated a wide range of sensitivities regardless of rather comparable levels of the Ah receptor. This in no way obviates the necessary, but not sufficient, role of AhR.

3.3. SUBCHRONIC TOXICITY

Available studies on the subchronic toxicity of TCDD have been reviewed by the U.S. EPA (1984, 1985) and WHO/IPCS (1989). Overall, the signs and symptoms observed are in agreement with those observed after administration of single doses.

The study of Kociba et al. (1976) is of special interest, as it has been used for comparisons of the relative toxicities of other CDDs and CDFs (Plüess et al., 1988a,b). Adult male and female SD rats, in groups of 12, were given 0, 0.001, 0.01, 0.1, and 1.0 µg TCDD/kg bw by gavage 5 days/week for 13 weeks. At the end of the treatment period, five rats of each sex were sacrificed for histopathological examination. The remaining animals were observed for postexposure effects. The highest dose caused five deaths among the females, three during the treatment period and two after, while two deaths occurred in males in the posttreatment period. The rats given 0.01 µg TCDD/kg did not differ overtly from the controls except for a slight increase in the mean liver-to-body weight ratio.

A 13-week dietary study of SD rats given 1,2,3,4,8-PeCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, or 1,2,3,6,7,8-HxCDF demonstrated that both subchronic toxicity and the depletion of hepatic vitamin A followed the rank order of the ability of the compounds to bind to the Ah receptor and to cause induction of AHH (Plüess et al., 1988a,b; Håkansson et al., 1990). Direct comparisons of the effects are hampered, however, by differences in the toxicokinetic behavior of the compounds. Slightly different relationships with regard to toxicity were observed in a tumor promotion study, where an initial loading dose (subcutaneous) of 2,3,4,7,8-PeCDF was given, followed by repeated lower doses (subcutaneous), in order to obtain a steady-state concentration (Wærn et al., 1991a). Both of these studies support the assumption that most signs and symptoms obtained may be mediated through the Ah receptor.

In another study primarily aimed at investigating TCDD-induced porphyria (Goldstein et al., 1982), groups of eight female SD rats were exposed to 16 weekly oral doses of 0, 0.01, 0.1, 1.0, and 10.0 µg TCDD/kg bw. The animals were killed and studied 1 week after the last treatment. Additional groups of rats received doses of 0 or 1.0 µg/kg/week for 16 weeks and were allowed to recover for 6 months. The high-dose level was lethal to all animals within 12 weeks, while the only other gross sign of toxicity was a decrease in body weight gain in the group receiving 1.0 µg/kg/week. After 16 weeks of exposure to TCDD, liver porphyrins were elevated ~1,000-fold in 7 of 8 animals receiving 1.0 µg/kg/week. Only 1 of 8 animals in the 0.1 µg/kg/week group had elevated porphyrin levels. The no-effect dose for porphyria was 0.01 µg/kg/week. After a 6-month recovery period, the porphyrin level in animals exposed to 1.0 µg/kg/week was still 100-fold higher than the values in the control group. A similar pattern was observed for urinary excretion of uroporphyrin. A 6-month recovery period was not sufficient for complete reversal of TCDD-induced porphyria.

Two studies were conducted (Harris et al., 1973; Vos et al., 1973) in which four weekly oral doses of 0.2, 1, 5, or 25 µg TCDD/kg bw were given to male C57Bl/6 mice in corn oil. No effects were noted at 1 µg/kg/week, which corresponds to ~0.1 µg/kg bw/day. In a subchronic exposure study, van Birgelen et al. (1996a) observed a synergistic effect of PCBs and TCDD on

hepatic porphyrin in rats at levels comparable with those found in human milk and fat samples. Coadministration of TCDD with 2,2',4,4',5,5'-PCB (PCB 153) resulted in elevated hepatic porphyrin levels not observed in TCDD cotreated with 3,3',4,4',5-PCB (PCB126) or 2,3,3',4,4',5-PCB (PCB156) groups. In this experiment, LOAELs for hepatic porphyrin accumulation for TCDD, PCB126, and PCB 156 were found to be 0.047, 3.18, and 365 µg/kg/d, respectively. van Birgelen et al. (1996b) have further extended the observation on hepatic porphyrin activity in female B6C3F1 mice after subchronic exposure to individual PCDD, PCDF, and PCB congeners. A dose-response relationship with potencies, relative to TCDD, for increased hepatic porphyrin accumulation was observed for all of the individual congeners studied. The relative potencies of PCDDs and PCDFs tested, based on hepatic porphyrin and enzymatic activities associated with hepatic CYP1A1 and CYP1A2, were found to be in a comparable range.

A 90-day TCDD feeding study of male and female Hartley guinea pigs was performed by DeCaprio et al. (1986), in which surviving animals were subjected to extensive pathologic, hematologic, and serum chemical analyses. The diets contained 0, 2, 10, 76, or 430 ng TCDD/kg bw. The two lowest doses, 2 and 10 ng/kg, produced no dose-related alterations. Based on this study, a no-observed-adverse-effect level (NOAEL) of 0.6 ng TCDD/kg bw/day in guinea pigs was estimated. At the highest dose, severe body weight losses and mortality were observed. No dose-related mortality occurred at 76 ng/kg.

A cumulative dose of 0.2 µg TCDD/kg bw, which was divided into nine oral doses 3 times/week during days 20-40 of gestation, produced no clinical signs of toxicity in pregnant rhesus monkeys (Macaca mulatta) (McNulty, 1984). Signs of toxicity such as body weight loss, epidermal changes, and anemia did occur, however, in monkeys that received cumulative doses of 1.0 and 5.0 µg TCDD/kg bw over the same time period.

3.3.1. Appraisal

Utilizing the above data, subchronic no-observable-adverse-effect levels (NOAELs) for rats, mice, and guinea pigs are estimated to be 1 ng, 100 ng, and 0.6 ng TCDD/kg bw/day, respectively. These studies cannot be directly compared with each other, however, and these subchronic NOAELs cannot be used for extrapolating human risk. None of the studies utilized initial loading doses and, due to the long half-life of TCDD, steady-states may not have been reached in the animals except toward the end of the study periods. Distribution between tissues in the animals depends on both time of exposure and dose level (see Chapter 1), which further complicates any comparisons.

In spite of this, the limited data available seem to indicate that signs and symptoms of subchronic toxicity follow the same rank order as Ah receptor-mediated effects, such as induction of AHH.

3.4. CHRONIC TOXICITY

The results of chronic toxicity studies performed on laboratory animals exposed to TCDD are summarized in Table 3-3. Details have been reviewed by the U.S. EPA (1984, 1985) and WHO/IPCS (1989).

The most important study in rats is the chronic toxicity study of Kociba et al. (1978, 1979). Groups of 50 male and 50 female SD rats were fed diets providing daily doses of 0.001, 0.01, and 0.1 µg TCDD/kg bw for 2 years. Control rats, 86 males and 86 females, received diets containing the vehicle alone. Increased mortality was observed in females given 0.1 µg/kg/day, while increased mortality was not observed in male rats at this dose or in animals receiving doses of 0.01 or 0.001 µg/kg/day. From month 6 to the end of the study, the mean body weights of males and females decreased at the highest dose and, to a lesser degree, in females given 0.01 µg/kg/day. During the middle of the study, lower-than-normal body weights were also occasionally recorded in the low-dose group, although during the last quarter of the study the body weights were comparable with those of the controls.

Increased urinary coproporphyrin and uroporphyrin were noted in female rats, but not in males, given TCDD at a dose rate of 0.01 and 0.1 µg/kg/day. Analyses of blood serum collected at terminal necropsy revealed increased enzyme activities related to impaired liver function in female rats given 0.1 µg TCDD/kg/day. Necropsy examination of the rats surviving TCDD exposure until the end of the study revealed that effects in the liver constituted the most consistent alteration in both males and females. Histopathological examination revealed multiple degenerative, inflammatory, and necrotic changes in the liver that were more extensive in females. Multinucleated hepatocytes and bile-duct hyperplasia were also noted. Liver damage was dose related, and no effect was observed at the low-dose rate. The NOAEL was estimated to be 0.001 µg/kg/day. At the end of the study, the fat and liver concentration of TCDD at this dose was 540 ppt.

In male Swiss mice, weekly oral doses of 0, 0.007, 0.7, and 7.0 µg TCDD/kg bw for 1 year resulted in amyloidosis and dermatitis (Toth et al., 1979). The incidence of these lesions was 0 of 38, 5 of 44, 10 of 44, and 17 of 43 in the control-, low-, medium-, and high-dose groups, respectively. The LOAEL in this study was estimated to be 0.001 µg/kg/day (=1 ng/kg/day).

In the National Toxicology Program (NTP, 1982) gavage study of B6C3F1 male and female mice, no adverse effects were seen at the lowest dose tested (0.01 and 0.04 µg/kg bw/week for males and females, respectively; corresponding to ~1.4 and 6 ng/kg bw/day).

The limited studies (9-20 months) available in rhesus monkeys (Allen et al., 1977; Barsotti et al., 1979; Schantz et al., 1979) revealed signs and symptoms similar to those recorded

in more short-term studies. Adverse effects were noted down to the lowest dose tested (~2-3 ng/kg bw/day for 20 months) (Schantz et al., 1979).

3.4.1. Appraisal

From different long-term studies on TCDD, it can be estimated that the NOAEL for the rat is 1 ng/kg bw/day, corresponding to a fat and liver concentration (NOAEL) of 540 ppt. For the male Swiss mouse, dermatitis and amyloidosis in 5 of 44 animals were noted at the lowest dose tested (the LOAEL was 1 ng/kg bw/day). NOAELs of 1.4 and 6 ng/kg/day were obtained for male and female B6C3F1 mice, respectively. The reported studies on rhesus monkeys are problematic for use in such a determination, because adverse effects were observed at the lowest dose tested, ~2-3 ng/kg bw/day.

3.5. SPECIFIC EFFECTS

3.5.1. Wasting Syndrome

TCDD at high doses (lethal or near lethal) causes a starvation-like effect, or wasting syndrome, in several animal species. In young animals, or following a sublethal dose to adults, this response is manifested as a cessation of weight gain. Animals exposed to near lethal or higher doses characteristically lose weight rapidly. Numerous studies utilizing pair-feeding, total parenteral nutrition, and everted intestinal sacs have been performed to elucidate the mechanisms behind the wasting syndrome (U.S. EPA, 1984, 1985; WHO/IPCS, 1989), but no single explanation has been obtained thus far. No generalized impairment of intestinal absorption seems to occur.

Peterson et al. (1984) conducted behavior experiments and suggested a model for the TCDD-induced wasting syndrome that is based on the hypothesis, advocated by Keesey and Powley (1975, 1986), that body weight in rats is regulated to an internal standard or hypothalamically programmed set-point. According to this hypothesis, the body weight at a given age is constantly being compared to this set-point value and, if differences occur, feed consumption is adjusted. When TCDD lowers this set-point, reduction in food consumption results as the rat attempts to reduce its weight to a new lower level. This hypothesis has been tested in several experiments under carefully controlled feeding conditions. Repeated studies have demonstrated that reduction of feed intake due to increased food spillage is not sufficient to account for the loss of body weight in TCDD-treated SD rats. Additionally, TCDD-treated rats maintain and defend their reduced weight level with the same precision that ad libitum-fed control rats defend their normal weight level (Seefeld and Peterson, 1983, 1984; Seefeld et al., 1984a,b). The percentage of the daily feed intake that is absorbed by the gastrointestinal tract of TCDD-treated and control rats is similar (Potter et al., 1986; Seefeld and Peterson, 1984).

Reduced appetite as a result of inhibition of tryptophan-2,3,-dioxygenase causes gradual development of eventual lethal hypoglycemia in TCDD-induced wasting syndrome in rats (Weber et al., 1994). No reduced appetite associated with gradual body weight loss and no tryptophan effects are observed in TCDD-exposed mice, although appetite and body weight loss are observed in mice at the terminal stage of wasting syndrome. Hypophagia was the major cause of adipose and lean tissue loss in male Fischer 344 rats, C57Bl/6 mice, and albino guinea pigs when exposed to a calculated LD_{50} dose of TCDD. Body weight loss followed a similar time-course in TCDD-treated and pair-fed control animals of all three species (Kelling et al., 1985).

Body weight loss appears to contribute to lethality in a species- and strain-dependent fashion, but weight loss appears to play a greater role in causing death in SD rats and guinea pigs than it does in Fischer 344 rats and C57Bl/6 mice. Loss of body weight and loss of appetite are also prominent signs of thyroid dysfunction. However, some data indicate that the effect of TCDD on thyroid hormones cannot explain the TCDD-induced decrease in body weight gain.

Reduced gluconeogenesis due to inhibition of phosphoenol pyruvate carboxykinase (PEPCK) by TCDD has been suggested as one of the primary contributing factors to a gradual development of an eventual lethal hypoglycemia in wasting syndrome in rats (Stall et al., 1993) and mice (Weber et al., 1995).

TCDD-induced wasting is associated with reduction of adipose tissue mass, hypertriglyceridemia, redistribution of fatty acids (Gasiewicz and Neal, 1979; Chapman and Schiller, 1985; Brewster and Matsumura, 1988), and diabetic-like symptoms (Brewster and Matsumura, 1988). Carbohydrate and lipid metabolism are severely impaired in the liver and adipose tissue by TCDD. Glucose transport systems play vital roles in controlling the rate of energy utilization in adipose tissues. TCDD also affects lipoprotein lipase (LPL) activity. The rate of fat storage is determined by LPL, which controls the serum level of triglycerides. Brewster and Matsumura (1984) found that LPL activity was decreased in guinea pigs to 20% of the value of ad libitum-fed controls after 1 day, and that this effect persisted throughout the study (10 days). The authors suggest that TCDD irreversibly reduces adipose LPL activity, thus making the animals less capable of adapting to nutritional changes and needs. In the pancreas, LPL regulates the production and release of insulin, and in the liver it controls glucose metabolism and fatty acid synthesis. From their observations on the significant reduction of glucose-transporting activity in adipose tissue and pancreas in guinea pigs by TCDD at a very low dose (single IP injection of 0.03 µg/kg), Enan et al. (1992a,b) concluded that the reduction in glucose transporters is one of the major causes of TCDD-induced wasting syndrome in this species. Downregulation of the cellular glucose uptake in NIH 3T3 L1 preadipocyte cell line in culture by TCDD has also been observed (Olsen et al., 1994). Pretreatment of these cells with

4,7,-phenanthroline, an Ah receptor blocker, prevents the effect of TCDD on glucose uptake, suggesting that TCDD-induced downregulation of functional glucose transporter proteins is mediated through the Ah receptor.

The insulin-recruitable form of glucose transporter Type 4 (GLUT4) provides energy to the cell by supplying glucose to the muscle and tissue tissues. Impairment of GLUT4 in adipose tissue, liver, and pancreas (Enan et al., 1992a,b), and reduction of PEPCK in liver (Viluksela et al., 1995), could play important roles in the pathogenesis of TCDD-induced diabetes.

In a series of studies on Wistar rats, Lakshman et al. (1988, 1989, 1991) demonstrated that single intraperitoneal injections of TCDD (from 1 µg/kg) caused a dose-dependent inhibition of fatty acid synthesis in the liver and adipose tissue. Adipose tissue was found to be more sensitive than the liver. They also found an increased mobilization of depot fat into the plasma compartment, accompanied by an increase in plasma free fatty acid concentrations.

In vitro studies of isolated heart mitochondria have indicated that a TCDD concentration of 1.5 nmol/mg in mitochondrial protein affects oxygen activation associated with cell respiration. Superoxide radicals and H_2O_2 were indicated to be involved in the development of the observed effects (Nohl et al., 1989).

Loss of muscle tissue, accompanied by a decreased glucocorticoid receptor-binding capacity and an increased glutamine synthetase activity, has been observed in male Fischer 344N rats given a single oral TCDD dose of 100 µg/kg (Max and Silbergeld, 1987).

Another biochemical effect associated with TCDD-induced wasting syndrome is the decrease in hepatic vitamin A storage in TCDD-exposed animals (Thunberg et al., 1979; Håkansson et al., 1989a, 1991). Vitamin A is necessary for growth; vitamin A deficiency will result in depressed body weight gain and reduced food intake. However, in contrast to TCDD-treated animals, the vitamin A-deficient animals continue to eat and grow, though body weight gain is less than normal (Hayes, 1971).

The hypothesis that decreased feed intake could be a result of a direct TCDD effect on the brain was initially indicated by Pohjanvirta et al. (1989), although contradictory information has been provided by other studies (Stall and Rozman, 1990). The intraperitoneal administration of TCDD at 50 µg/kg to male SD rats (~LD_{50} level) caused a significant decrease in the serum concentration of prolactin, detectable after 4 hours, compared with pair-fed vehicle controls and noninjected controls (Jones et al., 1987). Further studies have demonstrated that the effect of TCDD was reversed by pimozide, a dopamine receptor antagonist, and [that the rate constant of dopamine depletion after α-methyl-p-tyrosine and the turnover rate were significantly elevated.] This suggests a hypothalamic site of TCDD action in their experiments (Russell et al., 1988), a finding supported by additional data on changes to central thermoregulation by dioxin in golden hamsters (Gordon et al., 1996) and rats (Gordon and Miller, 1998).

Changes in intermediary metabolism have been demonstrated in TCDD-treated experimental animals. Conflicting data on how TCDD affects serum glucose and hepatic glycogen levels have been reported earlier (WHO/IPCS, 1989). Several studies have suggested that the ultimate cause of death in some mammalian species may be a progressive hypoglycemia (Ebner et al., 1988; Gorski and Rozman, 1987; Gorski et al., 1990). Serum glucose levels in the guinea pig, however, were not affected by treatment of the animals with TCDD (Gasiewicz and Neal, 1979). Slight reductions in serum glucose levels were noted in both L-E and H/W rats (Pohjanvirta et al., 1989). Rozman et al. (1990) have suggested that the subchronic and chronic toxicities of TCDD are related to the inhibition of key enzymes of gluconeogenesis. They demonstrated that the induction of appetite suppression was preceded by the inhibition of PEPCK, which caused a reduction in gluconeogenesis. This was followed by a progressive increase in plasma tryptophan levels that was suggested to cause a serotonin-mediated reduction of the feed intake. In SD rats, TCDD in doses of 25 and 125 µg caused a rapid decrease (50%) in PEPCK activity 2 days after dosing, followed by a dose-dependent decrease in glucose-6-phosphatase activity 4 to 8 days after exposure. Both appetite suppression and reduced PEPCK activity occurred in the same dose range (Weber et al., 1991). TCDD-induced impairments of carbohydrate synthesis have also been suggested by studies in chick embryos (Lentnek et al., 1991).

Numerous studies have measured serum levels of free fatty acids, cholesterol, and triglycerides in various species after TCDD treatment (WHO/IPCS, 1989), but no pronounced qualitative differences have been observed between species or strains of mice.

The wasting syndrome seems to be a generalized effect, elicited in all species and strains, but at various dosages (single or repeated administration). Specific studies have not been performed to elucidate the extent to which this syndrome is elicited through the interaction of TCDD with the Ah receptor, although the binding affinities of various CDDs and CDFs to the Ah receptor, as well as those of related PCBs, have been shown to strongly correlate with their potency to induce the wasting syndrome in both rats and guinea pigs (Safe, 1990).

3.5.2. Hepatotoxicity

Even at sublethal doses, TCDD induces hyperplasia and hypertrophy of parenchymal cells and, thus, hepatomegaly in all species investigated. There is, however, considerable variation in the extent and severity of this lesion among the species tested. Other liver lesions are more species-specific. Lethality following the administration of TCDD cannot be explained by these liver lesions alone, although they may be a contributing factor in the rat and rabbit. The morphological changes in the liver are accompanied by impaired liver function characterized by liver enzyme leakage, increased microsomal monooxygenase activities, porphyria, impaired

plasma membrane function, hyperlipidemia, and increased regenerative DNA synthesis (U.S. EPA, 1984, 1985; WHO/IPCS, 1989).

Hepatotoxic reaction in various strains of rats given lethal doses of TCDD is characterized by degenerative and necrotic changes including the appearance of mononuclear cell infiltration, multinucleated giant hepatocytes, increased numbers of mitotic figures and pleomorphism of cord cells, an increase in the hepatic smooth endoplasmic reticulum, and parenchymal cell necrosis. The histological findings are accompanied by hyperbilirubinemia, hypercholesterolemia, hyperproteinemia, and increased serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) activities, which further indicate damaged liver function (WHO/IPCS, 1989). These lesions may be severe enough to be a contributing factor in death. The lesions observed after sublethal doses are qualitatively almost identical to those observed after lethal doses.

Early studies in mice found similar effects. More recently, Shen et al. (1991) reported a comparative study on the hepatotoxicity of TCDD in Ah-responsive and Ah-nonresponsive mice (C57BL/6J and DBA/2J, respectively). The C57BL/6J mice given a single dose of 3 µg/kg TCDD developed mild to moderate hepatic lipid accumulation but no inflammation or necrosis. Severe fatty change, mild inflammation, and necrosis occurred at 150 µg/kg. The DBA/2J mice given 30 µg/kg developed hepatocellular necrosis and inflammation but no fatty change. Lipid accumulation was only slight after 600 µg/kg. The authors concluded that the Ah locus may be involved in determining the steatotic effects of TCDD. This is consistent with the findings of Birnbaum et al. (1990) on the differential toxicity of TCDD in C57BL/6J mice congenic at the Ah locus. In this study, wild type mice were 8- to 24-fold more sensitive than congenic mice deficient at the Ah locus for a spectrum of effects, including increased liver weight, hepatocellular cytomegaly, fatty change, bile duct hyperplasia, and serum liver enzyme changes.

The guinea pig shows less severe morphological alteration in the liver than other species, although ultrastructural changes of the liver are found. Likewise, the hamster exhibits little or no liver damage even after a fatal dose, but liver lesions have been observed after prolonged periods following the administration of nonlethal doses.

Several parameters relating to disturbed hepatic plasma membrane function have been studied (U.S. EPA, 1984, 1985; WHO/IPCS, 1989). Adenosine triphosphatase (ATPase) activities were depressed and protein kinase C activity was increased in rats, but not in guinea pigs, treated with TCDD (Bombick et al., 1985). TCDD also induced a decrease in the binding of EGF. The relative doses of TCDD needed to suppress EGF binding to 50% of the control level were 1, 14, and 32 µg/kg for the guinea pig, the SD rat, and the Syrian Golden hamster, respectively (Madhukar et al., 1984). A single intraperitoneal dose of 115 µg TCDD/kg bw

decreased the EGF binding by 93.1%, 97.8%, and 46.0% in C57Bl/6, CBA, and AKR mice, respectively, 10 days after treatment (Madhukar et al., 1984).

Further studies on the interaction of TCDD with the EGF receptor have been performed in congenic mice of the strain C57BL/6J (Lin et al., 1991a,b). The ED_{50} for the TCDD-induced decrease in maximum binding capacity of the EGF receptor was 10 times higher in the Ah-nonresponsive mice than the Ah-responsive animals. This study supports the hypothesis that the effects of TCDD on EGF receptor ligand binding are mediated by the Ah receptor.

The effects of TCDD on biliary excretion of various compounds have also been studied. Of special interest are studies on the excretion of ouabain, a model compound for neutral nonmetabolized substrates such as estradiol, progesterone, and cortisol, which was depressed in a dose-related manner by a single oral dose of TCDD in rats (Yang et al., 1977, 1983b). The available data suggest that the hepatic membrane transport of ouabain may be selectively impaired by TCDD. Peterson et al. (1979a,b) have indicated that changes in ATPase activities are not responsible for reduced ouabain excretion.

TCDD administration stimulates the accumulation of porphyrins in the liver and an increase in urinary porphyrin excretion (Goldstein et al., 1973, 1976, 1982). Indeed, during manifest porphyria, accumulation of porphyrins occurs not only in the liver but also in the kidney and spleen of rats (Goldstein et al., 1982).

Contradictory results on species variations have been published. It seems clear that porphyria can be produced in both mice and rats, but the condition is always the result of subchronic or chronic administration. Exposure to single doses has not been demonstrated to produce porphyria. The mechanism underlying the induction of porphyria has not been elucidated. Cantoni et al. (1981) exposed rats orally to 0.01, 0.1, and 1 µg TCDD/kg bw/week for 45 weeks. Increased coproporphyrin levels were observed at all dose levels. A marked porphyric state appeared only at the highest dose tested, after 8 months of exposure.

Induction of aminolevulinic acid (ALA)-synthetase, the initial and rate-limiting enzyme involved in heme synthesis, does not seem to be a necessary event in TCDD-induced porphyria. Despite porphyria being evident, mice exposed to 25 µg TCDD/kg bw/week for 11 weeks were not found to have any increased ALA activity (Jones and Sweeney, 1980). A more likely suggestion is that decreased hepatic porphyrinogen decarboxylase is the primary event in porphyria induced by halogenated aromatics (Elder et al., 1976, 1978). TCDD depresses this enzyme activity in vivo in the liver of mice (Cantoni et al., 1984a,b; Elder and Sheppard, 1982; Jones and Sweeney, 1980), but not in vitro (Cantoni et al., 1984b). Of interest, too, are the results reported in van Birgelen et al. (1996a), where the porphyrinogenic effects of TCDD were correlated with CYPIA2 induction, and demonstrated a strong synergistic relationship with coadministered PCBs.

A comparative study of TCDD-induced porphyria has not been conducted in responsive and nonresponsive mice. In a study on Ah-responsive (Ah^b) and Ah-nonresponsive (Ah^d) C57BL/6J female mice, however, the urinary excretion of porphyrins was examined after treatment of the animals with hexachlorobenzene for 17 weeks (Hahn et al., 1988). After 15 weeks of treatment with 200 ppm hexachlorobenzene in the diet, the excretion of porphyrins was 200 times higher in the Ah^b mice than the controls. In contrast, the Ah^d mice only showed a sixfold increase. Induction of P-450c(1A1) was observed only in Ah^b mice, while induction of P-450d(lA2) was observed in both strains, but to a lesser degree in the Ah^d mice.

3.5.3. Epidermal Effects

Chloracne and associated dermatological changes are common responses to high exposures to TCDD in humans. However, this type of toxicity is expressed only in a limited number of animal species (e.g., rabbits, monkeys, cows, and hairless mice).

In a rabbit ear bioassay, a total dose of 80 ng TCDD gave a chloracnegenic response, while no response was obtained when the total dose applied to the ear was 8 ng (Jones and Krizek, 1962; Schwetz et al., 1973). The application of TCDD in various vehicles has been demonstrated to markedly decrease this response (Poiger and Schlatter, 1980). The hairless mouse is a less sensitive model for chloracnegenic response than the rabbit ear bioassay (Knutson and Poland, 1982; Puhvel et al., 1982). Following repeated applications of ~0.1 µg TCDD over several weeks, however, an acnegenic response was noted in the hairless mouse strains, SkH:HR1 and HRS/J. An acnegenic response was also caused by repeated applications of 2 mg of 3,4,3′,4′-TCB (Puhvel et al., 1982). Female HRS/J hairless mice have also been used to test the dermal toxicity and skin tumor-promoting activity of 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and 1,2,3,4,7,8-HxCDF (Hebert et al., 1990b). All of the tested compounds induced coarse, thickened skin with occasional desquamation. These effects were more severe after the application of PeCDF and HxCDF.

Keratinocytes, the principal cell type in the epidermis, have been utilized as an in vitro model for studies of TCDD-induced hyperkeratosis both in human- and animal-derived cell cultures. The response to TCDD is analogous to the hyperkeratinization observed in vivo.

A TCDD-induced keratinization response in vitro was first demonstrated in a keratinocyte cell line derived from a mouse teratoma (XB cells). The keratinization was doserelated (Knutson and Poland, 1980b). Late-passage XB cells (termed XBF cells) lost their ability to respond by keratinization after TCDD treatment. Both XB cells (keratinization assay) and XBF cells (flat-cell assay) have proven to be useful in in vitro bioassays to determine the dioxin-like activities of both environmental samples and pure isomers (Gierthy and Crane, 1985a,b; Gierthy et al., 1984).

Several continuous lines of human keratinocytes, derived from neonatal foreskin or squamous cell carcinomas, have been shown to respond to TCDD in nM concentrations, with a variety of signs indicating alterations in the normal differentiation process (WHO/IPCS, 1989). The responses include decreased DNA synthesis, decreased number of proliferating basal cells, decreased binding of EGF, and an increase in the state of differentiation (Osborne and Greenlee, 1985; Hudson et al., 1986). The responses were also obtained with TCDF, but not with 2,4-diCDD (Osborne and Greenlee, 1985). TCDD has also been shown to inhibit high-density growth arrest in human squamous carcinoma cell lines. Indeed, the minimum concentration for increases in cell proliferation was 0.1 nM in the most sensitive cell line (SCC-15G). This effect is not due to modulation of the transforming growth factor-β binding (Hebert et al., 1990b,c).

3.5.4. Enzyme Induction

TCDD has repeatedly been found to increase the activities of various enzymes. While observations of enzyme inhibition have also been made, enzyme induction has been one of the most extensively studied biochemical responses produced by TCDD. The mixed-function oxidase (MFO) system is the most thoroughly investigated, and AHH and EROD (as markers for CYPlA1 induction) are the most frequently assayed enzyme activities. The induction of MFO activities might potentiate the toxicity of other foreign compounds that require metabolic transformation by the MFO system before they can exert their toxic effects. Furthermore, increased MFO activities might adversely affect important metabolic conversions of endogenous compounds. TCDD also affects a variety of other enzymes (e.g., uridine diphosphate-glucoronosyltransferase [UDPGT] and glutathione-s-transferase [GST]) that are components of multifunctional enzyme systems involved in the conjugation, biotransformation, and detoxification of a wide variety of endogenous and exogenous compounds.

Several investigators have studied the relative potency of various halogenated dioxins, dibenzofurans, and biphenyls to induce AHH or EROD activities (Safe, 1990). An apparent structure-activity relationship was found between the location of the halogen atoms on the dibenzo-p-dioxin molecule and the ability to induce AHH activity both in vivo and in vitro. Isomers with halogens at the four lateral ring positions produced a greater biological response than those with halogens at three lateral ring positions. Two lateral halogen atoms seemed to be insufficient to produce a biological response. Numerous studies have indicated that there is very strong agreement between the Ah-binding affinity of various CDDs, CDFs, and related PCBs and their potency to induce AHH, both in vivo and in vitro (Safe, 1990). Structure-activity studies have also demonstrated a clear correlation between the toxicity and induction potency of a series of CDDs, CDFs, and coplanar PCBs (Poland and Glover, 1973; Safe, 1990). This is discussed in Chapter 2 of this report.

On a molecular basis, TCDD is the most potent MFO-inducing compound known, and MFO induction seems to be the most sensitive biochemical response produced. Measurements of the induction of AHH or EROD (mediated through CYPlA1) are considered to be very sensitive markers of TCDD-induced enzyme induction. According to Kitchin and Woods (1979), induction in the rat takes place at doses as low as 0.002 µg TCDD/kg bw. The NOAEL for a single administration to rats seems to be 1 ng/kg, while a single dose of 3 ng/kg causes a detectable induction of AHH or EROD (Kitchin and Woods, 1979; Abraham et al., 1988). For more detailed dose-response information, see Chapter 8 of this report. Enzyme induction has also been observed in the offspring of various species after prenatal and postnatal (milk) exposure to TCDD (Lucier et al., 1975; Korte et al., 1990; Wærn et al., 1991b).

The effect of TCDD on enzyme activities has been most frequently investigated in the rat (WHO/IPCS, 1989). TCDD has been shown to increase both the contents of cytochrome P-450lA1 and cytochrome P-450lA2 in the liver, as well as other microsomal enzyme activities involved in the oxidative transformation and conjugation of xenobiotics (e.g., aniline hydroxylase, AHH, biphenyl hydroxylase, 7-ethoxycoumarin-O-deethylase [ECOD], EROD, and UDPGT) (U.S. EPA, 1984, 1985; WHO/IPCS, 1989).

TCDD also affects some other hepatic enzymes not related to the MFO system, including aldehyde dehydrogenase, δ-ALA synthetase DT-diaphorase, transglutaminase, ornithine decarboxylase, transaminases (L-alanine aminotransferase [ALT] and L-aspartate aminotransferase [AST]), plasma membrane ATPases, porphyrinogen carboxylase, prostaglandin synthetase, enzymes involved in testosterone metabolism, and RNA polymerase (U.S. EPA, 1984, 1985; WHO/IPCS, 1989).

Studies of different species have also revealed that enzyme induction due to TCDD exposure varies with both species and strain. Pohjanvirta et al. (1988) studied enzyme induction in the L-E and H/W (Kuopio) rat strains (LD_{50} ~10 and >3,000 µg/kg, respectively). Differences in the inducibility of EROD, ECOD, or ethylmorphine N-demethylase were not found, nor were there any differences with regard to the amount of available Ah receptor or the amount of cytochrome P-450 in the hepatic microsomal fractions. Similarly, differences regarding possible induction of UDPGT were absent (Pohjanvirta et al., 1990).

Enzyme induction studies on mice have been performed mainly with strains that are genetically different at the Ah locus, thus making them responsive or nonresponsive to the induction of hepatic cytochrome P-4501A1-related enzyme activities. Qualitatively, and in general, the same responses can be obtained in both strains, but there may be more than one order of magnitude difference with regard to the doses required to elicit a response. TCDD is thus 10-fold more potent in inducing hepatic cytochrome P-450lA1 and the related AHH activity in C57BL/6J mice (Ah-responsive) than in DBA/2 mice (Ah-nonresponsive) (Poland and

Knutson, 1982; Nebert, 1989) and C57BL/6L mice congenic at the Ah locus (Birnbaum et al., 1990).

Although the guinea pig is the most sensitive species to the toxic effects of TCDD, it does not respond to the administration of TCDD with liver toxicity or extensive enzyme induction. Indeed, even at lethal doses, the induction of MFO, as measured by AHH activity, is only very slight (Beatty and Neal, 1977; Håkansson et al., 1994). The data on enzyme induction in rabbits are rather limited and somewhat conflicting with regard to increases in the amount of cytochrome P-450 (Hook et al., 1975; Liem et al., 1980). Similarly, hepatic enzyme induction has been only partially studied in Syrian Golden hamsters. When hamsters were given a lethal dose of TCDD, increased hepatic GST and glutathione reductase activities were found. The ED_{50} values for the induction of hepatic ECOD and reduced NADP:menadione oxidoreductase activities and cytochrome P-450 content in male Syrian Golden hamsters were 1.0, 2.0, and 0.5 µg TCDD/kg bw, respectively (extremely low doses, compared with doses that produce tissue damage and lethality in this species) (Gasiewicz et al., 1986).

In a comparative study of EROD induction in guinea pigs, rats, C57BL/6 and DBA/2 mice, and Syrian Golden hamsters, the animals were given single doses that were intended to be equitoxic (i.e., 1, 40, 100, 400, and 400 µg TCDD/kg, respectively) compared with the acute toxicity for the respective species and strain. EROD induction was noted in all species except for the hamster. During the observation period (112 days), the EROD induction dropped to more or less normal values in all rats and mice, while the induction (albeit low compared with the other species) was sustained for the whole period in the guinea pig (Håkansson et al., 1994). This might be due to higher half-life of TCDD in guinea pigs than rats or mice.

The N-demethylation of caffeine has been applied as a noninvasive method for studying enzyme induction in vivo. Studies on the marmoset monkey (Callithrix jacchus), utilizing ^{14}C-labeled caffeine and measuring $^{14}CO_2$ exhalation by a breath test, has indicated a NOAEL of 1 ng/kg and a LOEL of 3 ng/kg (Kruger et al., 1990). Studies by Butler et al. (1989) and others indicate that this reaction is dependent on cytochrome P-450lA2.

In the chick embryo, both AHH and δ-ALA synthetase have been reported to be extremely sensitive to the inductive effects of TCDD and related compounds (Poland and Glover, 1973; Brunström and Andersson, 1988; Brunström, 1990).

Although TCDD is relatively nontoxic in cell cultures, it is a very potent inducer of AHH or EROD activities in in vitro systems, including lymphocytes and primary hepatocytes, as well as established and transformed cell lines.

The ED_{50} values for AHH induction by TCDD have been determined in 11 established cell lines and in fetal primary cultures from 5 animal species and cultured human lymphocytes. The values ranged from 0.04 ng/mL medium in C57BL/6 mouse fetal cultures and 0.08 ng/mL in

the rat hepatoma H-4-II-E cell line to >66 ng/mL in the HTC rat hepatoma cell line (Niwa et al., 1975). Several cultured human cells or cell lines have been shown to be inducible for AHH activity by TCDD including lymphocytes (Atlas et al., 1976), squamous cell carcinoma lines (Hudson et al., 1983; Hebert et al., 1990a), breast carcinoma cell lines (Jaiswal et al., 1985), and lymphoblastoid cells (Nagayama et al., 1985).

TCDD was demonstrated to be the most potent AHH inducer of 24 chlorinated dibenzo-p-dioxin analogues (Bradlaw et al., 1980) in a rat hepatoma cell culture (H-4-II-E) that is extremely sensitive to AHH induction. The EC_{50} values for AHH and EROD induction in the same cell system varied over 7 orders of magnitude for 14 different CDDs, the most potent being TCDD and the least potent being 2,3,6-triCDD (Mason et al., 1986). Additional details on these and other enzyme induction dose-response characteristics and modeling are included in Chapter 8 of this report.

3.5.4.1. Appraisal

Based on data from Kitchin and Woods (1979), Abraham et al. (1988), Kruger et al. (1990), and Neubert (1991), a NOAEL value of 1 ng/kg bw can be calculated for enzyme induction for both rats and marmoset monkeys. At this dose, the tissue concentrations for both species were found to be 4 ppt for adipose tissue and 3 ppt for the liver. It is interesting to note that the wide range of sensitivities toward the acute toxicity of TCDD is also reflected in the wide range of sensitivities for enzyme induction both in vivo and in vitro, although the two groups of effects are not necessarily parallel. Finally, it is evident that the structure-activity relationships revealed from in vitro testing correlate fairly well with in vivo studies within a given species or strain.

3.5.5. Endocrine Effects

In many respects, TCDD toxicity mimics endocrine imbalance. Alterations in endocrine regulation have been suggested from human exposure to TCDD that resulted in hirsutism and chloracne. Chronic exposure to TCDD causes impaired reproduction in experimental animals, possibly by interfering with the estrus cycle in combination with some steroid-like activities of TCDD. This has prompted studies on the interaction of TCDD with steroid hormones and their receptors.

Evidence has been provided suggesting that chronic or subchronic exposures to TCDD impair thyroid functions. Dose-dependent reductions of plasma thyroid hormone levels have been observed in TCDD- and PCB-exposed animals (van der Kolk et al., 1992; van Birgelen et al., 1995a,b).

In a subchronic 13-week TCDD feeding study with female Sprague-Dawley (S-D) rats, a decrease in thyroid hormone (T_4) levels occurred, associated with elevation of microsomal UDPGT activity when thyroxine was used as substrate for thyroxine glucuronosyltransferase (T_4UGT) (van Birgelen et al., 1995b). In addition, involvement of CYP1A1 and UGT1A1 by TCDD indicates that the TCDD-induced thyroid functional abnormalities are mediated though the AhR (van Birgelen et al., 1995b). 2,3,3',4,4',5-hexachlorobiphenyl (PCB 156) has also been shown to reduce plasma total T_4 levels, and induces UDPGT by using thyroxine as substrate for T_4UGT (van Birgelen, 1995a). Similar results have also been observed in a 30-week chronic study with female S-D rats suggesting that TCDD-induced thyroid hormone function is caused by chronic perturbation of the liver-pituitary-thyroid axis (Sewell et al., 1995).

van Birgelen et al. (1995a,b) demonstrated the effects of TCDD and coplanar PCB126 (3,3,4,4',5-PCB) on thyroid hormone metabolism in female SD-rats. Oral exposure to 0.2, 0.4, 0.7, 5, and 20 µg/kg diet of TCDD and 7 to 180 µg/kg diet of PCB 126 significantly decreased the plasma total thyroxine (TT_4) levels. An intake of 0.047 µg/kg/day was estimated to be the LOAEL for decrease in plasma thyroid hormone levels.

A dose-dependent decrease in serum T_4 levels has also been observed in male and female SD rats as a result of high-dose subchronic exposures to 1,2,3,7,8-pentaCDD (PeCDD) or 1,2,3,4,7,8-hexaCDD (HxCDD) and low-dose subchronic exposures to TCDD/kg. Serum T_4 levels in PeCDD or HxCDD-exposed males returned to close to normal levels by the end of the off-dose period (Viluksela et al., 1998).

van Birgelen et al. (1995b), in a 13-week TCDD feeding study using 7-week-old female S-D rats, found that the LOAEL for decrease in plasma T_4 was 47 ng/kg bw/day. Dose-response relationships for CYP1A1 and CYP1A2 were determined by nonlinear curve fitting. The critical values for the 95% confidence limits for CYP1A1 and CYP1A2 inductions ranged from 0.7 and 4 ngTCDD/kg bw/day.

Janz and Bellward (1997) reported that a single intraperitoneal dose of 20 µg/kg bw of TCDD to adult great blue heron, Ardea heidias, increased plasma T_4 levels (control: 39 ± 4 ng/mL; exposed: 55 ± 5 ng/mL; $p<0.05$), but no effect occurred on plasma total T_3 levels or on the plasma T_3 to T_4 ratio.

Increased systemic levels of glucocorticoids may mimic some of the symptoms of TCDD toxicity (e.g., involution of lymphoid tissues, edema, and mobilization of fatty acids from adipose tissues). Thus, it has been suggested that TCDD increases glucocorticoid activity through indirect effects on glucocorticoid receptors. Poland et al. (1976) demonstrated that cortisol and synthetic glucocorticoids do not bind to the TCDD receptor.

Conflicting data have been reported on TCDD-induced levels of glucocorticoids. However, significant changes to the liver cytosolic glucocorticoid receptor were induced by

TCDD at doses 10,000-fold lower in adrenalectomized SD rats than in control rats (Sunahara et al., 1989). The data further indicate that the binding capacity of hepatic glucocorticoid receptor was altered, but not the apparent equilibrium dissociation constant (Kd). Studies in congenic strains of Ah-responsive and Ah-nonresponsive C57BL/6J female mice (Goldstein et al., 1990; Lin et al., 1991a,b) have also demonstrated that TCDD decreased the maximum binding capacity of the hepatic glucocorticoid receptor in both strains of mice by ~30%.

Steroids are endogenous substrates for the hepatic MFO system. TCDD influences the activity of this enzyme system and may alter steroid metabolism in vivo and the magnitude of steroid-mediated functions.

Early studies reported contradictory data on changes in steroid levels. Umbreit and Gallo (1988) suggest that estrogen receptor modulation, and the animal's physiological response to this modulation, can explain some of the toxicity observed in TCDD-treated animals. The susceptibility of different species to TCDD correlates, to some extent, with their steroid glucuronidation capacity. For example, hamsters have low steroid UDPGT activity while guinea pigs have a corresponding high activity. Another example is given by comparing the SD and Gunn rat, the latter being defective in producing some UDPGTs. The homozygous Gunn rat is 3-10 times more resistant to the effects of TCDD than is the SD rat (Thunberg, 1984; Thunberg and Håkansson, 1983). The results of TCDD exposure in various species and strains are complex. The ability of the strain to counteract TCDD-induced modulation of the estrogen receptor depends on its ability to synthesize and excrete estrogens. Interactions of TCDD and related compounds with estrogen have been reviewed by Safe et al. (1991).

The importance of estrogens as modulators of TCDD-induced toxicity has also been demonstrated by Lucier et al. (1991), who found that the tumor-promoting effects of TCDD could be effectively prevented by removing the ovaries from female rats before exposure to TCDD. This finding agrees with the results obtained from long-term bioassays that demonstrated liver tumors only in female rats (Kociba et al., 1978; NTP, 1982).

Studies on congenic strains of Ah-responsive and Ah-nonresponsive C57BL/6J female mice found a statistically significant difference in the responsiveness of the hepatic estrogen receptor. This indicates that the Ah receptor regulates the effects of TCDD on the hepatic estrogen receptor (Goldstein et al., 1990; Lin et al., 1991a, b).

TCDD-induced changes in levels or activities of testosterone or its metabolites have been reported from several studies (Keys et al., 1985; Mittler et al., 1984; Moore and Peterson, 1985; Neal et al., 1979). A single oral dose of 50 µg TCDD/kg bw increased the plasma corticosterone level in SD rats 7 and 14 days postexposure (Neal et al., 1979). It has also been shown, however, that a single oral dose of 25 µg TCDD/kg bw decreases the plasma corticosterone in

SD rats 14 and 21 days postexposure. It is important to note that Neal et al. (1979) also observed a slight decrease in serum corticosterone during days 1-4 posttreatment.

Mittler et al. (1984) demonstrated a decreased activity of testicular 16-α-testosterone hydroxylase, 6-ß-hydroxytestosterone, and 7-α-hydroxytestosterone in young SD rats 90 hours postexposure to single intraperitoneal doses of 0.2, 1, or 5 µg TCDD/kg bw.

A single dose of 0.06 µmol TCDD/kg bw decreased levels of 3α-, 6α-, and 16ß-hydroxytestosterone and an increase of 7α-hydroxytestosterone has also been observed in young male Wistar rats (Keys et al., 1985). Moore et al. (1985) noted decreases in serum testosterone and dihydrotestosterone levels in 15 µg TCDD/kg bw-dosed male SD rats. The data do not, however, allow for any conclusions with regard to the possible relationship to receptor-mediated toxicity. TCDD induces several enzymes related to testosterone metabolism, which suggests that the changes observed may be secondary to the induction of various enzymes. Serum testosterone and dihydrotestosterone were found to be dose-dependently depressed by TCDD treatment in male SD rats, when compared with pair-fed and ad libitum-fed controls. The ED_{50} for this effect was ~15 µg/kg (Moore et al., 1985). It was further shown that testosterone synthesis was decreased in the animals due to depressed production of pregnenolone by the testis (Kleeman et al., 1990). In the same strain of rats, a single 100 µg/kg oral dose of TCDD was found to cause a 55 percent decrease in testicular cytochrome $P\text{-}450_{scc}$ activity and to inhibit the mobilization of cholesterol to cytochrome $P\text{-}450_{scc}$. The authors concluded that the latter effect probably was responsible for the inhibition of testicular steroidogenesis (Moore et al., 1991). Maternal exposure to TCDD has been shown to affect the male reproductive system at low doses; the lowest dose tested was 64 ng/kg (Mably et al., 1991, 1992a,b,c). This is discussed in Chapter 5.

In ovo exposure of white Leghorn chickens to TCDD, in the dose range of 1-10,000 pmol/egg, increased the cardiac release of prostaglandins (Quilley and Rifkind, 1986). Studies on chick embryos have indicated that the induction of cytochrome P-450 by TCDD results in a major increase in the NADPH-dependent metabolism of arachidonic acid (Rifkind et al., 1990). These effects are clearly related to receptor-mediated enzyme induction.

3.5.6. Vitamin A Storage

Decreased hepatic vitamin A storage has been reported in animals exposed to various chlorinated aromatic compounds. Because only minute quantities are needed to produce ill effects, and because of its persistence in nature, TCDD is unique in its capacity to reduce the vitamin A content of the liver. A single oral dose of 10 µg TCDD/kg bw decreased both the total amount and the concentration of vitamin A in the liver of adult male SD rats (Thunberg et al., 1979). The decrease was evident 4 days after dosing and progressed with time. After 8 weeks, the treated animals had a total liver vitamin A content corresponding to 33% of that of controls.

Decreased dietary intake of vitamin A could not account for this difference. A significant increase in the UDPGT activity was observed, suggesting an increased excretion of glucuronide-conjugated vitamin A. No correlation between the UDPGT activity and the hepatic vitamin A reduction was seen, however, when homozygous Gunn rats lacking inducible UDPGT (Aitio et al., 1979) and heterozygous Gunn rats with inducible UDPGT were treated with a single oral dose of 10 µg TCDD/kg bw (Thunberg and Håkansson, 1983).

A study combining pair-feed restriction and a single TCDD treatment found that decreases in liver reserves of vitamin A were not related to a decreased intake of vitamin A via the diet (Håkansson et al., 1989b).

Puhvel et al. (1991) reported a comparative study in which congenic haired (+/+) and hairless (hr/hr) HRS/J mice were fed a vitamin A-deficient diet and treated topically with TCDD. The sensitivity to TCDD-induced cutaneous changes was essentially 100 times higher in hairless mice than in haired mice (0.01 and 1.0 µg 3 times/week for 3 and 2 weeks, respectively). In the haired phenotype, the effects of vitamin A depletion by itself were not seen by cutaneous histology, nor were any changes observed in cutaneous morphology attributable to TCDD. In the hairless mice, however, vitamin A deficiency increased the keratinization of dermal epithelial cysts and increased the sensitivity of these cysts to TCDD-induced keratinization. Analysis of vitamin A demonstrated that TCDD exposure did not affect cutaneous levels of the vitamin but did significantly lower levels of vitamin A in the liver. TCDD-induced body weight loss and atrophy of the thymus glands were not affected by the vitamin A status in either strain.

In a study on tumor promotion by TCDD, in which enzyme-altered hepatic foci were induced in the livers of female SD rats, Flodström et al. (1991) found that vitamin A deficiency by itself enhanced foci development. The effects of TCDD treatment were also markedly enhanced, including TCDD-induced thymus atrophy.

Several studies have been performed to elucidate the mechanism of TCDD-vitamin A interaction. Håkansson et al. (1989c) and Håkansson and Hanberg (1989) have demonstrated that TCDD specifically inhibits the storage of vitamin A in liver stellate cells. Brouwer et al. (1989) demonstrated that a single dose of TCDD (10 µg/kg) to female SD rats reduced vitamin A in the liver, lungs, intestines, and adrenal glands, while increasing its concentration in serum, kidneys, and urine. They also found a 150% increase in the free fraction of serum retinol binding protein. Taken together, all of these data in the rat indicate that TCDD induces an increased mobilization of vitamin A from hepatic and extrahepatic storage sites into the serum, accompanied by an enhanced elimination of the vitamin via the kidney into the urine.

In a comparative study of TCDD toxicity in male SD rats and Hartley guinea pigs (Håkansson et al., 1989a), the animals were given single intraperitoneal doses of 40 and 0.5 µg/kg bw, respectively (i.e., comparable fractions of their respective LD_{50}). Similar

reductions in hepatic vitamin A were observed for both species, while serum and renal vitamin A concentrations were increased in the rat but unaffected in the guinea pig. Hepatic EROD activity was markedly increased in the rat but unchanged in the guinea pig. Furthermore, rats seemed to recover from the wasting, thymic atrophy, and liver enlargement and resumed their ability to store vitamin A in the liver at 4-8 weeks after exposure. No such trends for wasting and vitamin A storage were observed in guinea pigs, even 16 weeks after exposure. A complementary study also included C57BL/6 mice, DBA/2 mice, and Syrian Golden hamsters (Håkansson et al., 1991). The effects on TCDD-induced decrease of vitamin A in the liver and lung correlated reasonably well with other toxic symptoms observed in the animals. On the other hand, studies of two strains of rats, L-E and H/W (the H/W being >300 times more resistant to TCDD toxicity), could not demonstrate significant differences in the TCDD-induced changes in vitamin A in the liver, kidney, testicles, or serum after a sublethal dose of 4 µg/kg (Pohjanvirta et al., 1990). These findings show that the correlation between TCDD-induced lethality and changes in vitamin A status found among other species also apply to these strains of rats.

The interaction of 3,4,3′,4′-TCB with vitamin A has been studied by Brouwer and van den Berg (1983, 1984, 1986), Brouwer et al. (1985, 1986), and Brouwer (1987). The effects of TCB on vitamin A differ in many respects from those of TCDD. TCB is rapidly converted in vivo into a polar 5-OH-TCB metabolite, which binds with a relatively high affinity to transthyretin (TTR). As a consequence of this interaction, the physiological functions of TTR in retinoid and thyroid hormone transport are severely affected in TCB-exposed animals. The model proposed by Brouwer (1987) may explain some of the characteristic toxicological lesions related to exposure to this PCB. This mechanism of action seems to be clearly separated from the Ah receptor-mediated toxicity of CDDs and CDFs. Hydroxylated metabolites of TCDD have also been demonstrated to bind in a similar manner to TTR (Lans et al., 1993). Due to the very slow metabolism of TCDD (or other 2,3,7,8-substituted CDDs/CDFs), however, this mechanism probably plays a very minor role in toxicity.

Taken together, these data indicate that TCDD interferes with the metabolism and storage mechanisms for vitamin A (Kelley et al., 1998). Because supplementation of dietary vitamin A seems unable to counteract all of the observed toxic effects, this would imply either that the effect on vitamin A storage is secondary to TCDD toxicity or that the cellular utilization of vitamin A is affected by TCDD.

3.5.7. Lipid Peroxidation

Lipid peroxidation and oxidative stress have been indicated as factors that affect the acute toxicity of TCDD (WHO/IPCS, 1989; Wahba et al., 1989a,b, 1990a,b; Pohjanvirta et al., 1989; Alsharif et al., 1990; Stohs et al., 1990). Among the effects noted have been membrane

lipid peroxidation, decreased membrane fluidity, and increased incidence of single-strand breaks in DNA. No studies relating these observations to the Ah receptor have been performed. When considering the available data on TCDD and lipid peroxidation, it is not possible to define a relationship between lipid peroxidation and TCDD-induced lethality. However, oxidative stress is observed only at high doses of TCDD following acute exposure. Acute TCDD exposure at high doses has been shown to produce reactive oxygen species (Alsharif et al., 1994 a,b), lipid peroxidation (Alsharif et al., 1994b), and decreased membrane fluidity (Alsharif et al., 1990) in the mouse and rat.

Oxidative stress has been proposed as one of the reasons for increased susceptibility of female mice to TCDD-induced toxicity. In female C57BL/6J mice, intraperitoneal exposure to 5 µg/kg of TCDD for 3 consecutive days results in a long-term increase in hepatic oxidized glutathione and 8-hydroxydeoxyguanosine levels. Levels of 8-hydroxydeoxyguanosine, a product of DNA base oxidation and subsequent excision repair, remain elevated about 20-fold 8 weeks after treatment. This suggests a sustained TCDD-induced oxidative stress resulting in potentially promutagenic DNA base damage (Shertzer et al., 1998). Induction of CYP1A1 by TCDD has also been suggested to cause an increased excretion rate of 8-oxoguanine, a biomarker of oxidative DNA damage (Park et al., 1996).

Oxidative brain tissue damage may play a role in TCDD-induced central nervous system abnormalities. Hassoun et al. (1998) reported that subchronic oral exposure of B6C3F1 mice to TCDD for 13 weeks can result in a dose-dependent increase in superoxide anions (indicated by reduction in cytochrome c), lipid production, and DNA single-strand breaks in brain tissues. The authors posited involvement of the cytochrome P-450 system in TCDD-induced oxidative stress. Slezak et al. (1999), using CYP1A2 knockout ($CYP1A2^{-/-}$) mice, demonstrated that TCDD-induced oxidative stress (indicated by production of thiobarbituric acid-reactive substances as a measure of lipid peroxidation, production of reactive oxygen species via in vitro reduction of CYC, and changes in glutathione) is not mediated through the cytochrome P-450 type 1A2 isozyme (CYP1A2). Hassoun et al. (1997) also posited that TCDD-induced fetal death and fetal and placental weight reductions in C57BL/6J mice may be caused by oxidative damage induced by TCDD. Ellagic acid at 6 mg/kg/day on days 10, 11, and 12 of gestation and 3 mg/kg on day 13 protected against TCDD administration on day 12 at 30 µg/kg bw. Vitamin E succinate administered at 100 mg/kg/day through gestation days 10, 11, and 12 and at 40 mg/kg on day 13, instead of ellagic acid, was a less effective protective agent.

Iron administered before TCDD administration (75 µg/kg bw) to AhR-responsive AhRb-1 C57BL/6J mice potentiated hepatic porphyria, hepatocellular damage, and plasma hepatic enzyme markers (Smith et al., 1998). The mechanism was oxidative because hydroxylated and peroxylated derivatives of the uroporphyrins formed from uroporphyrinogen,

and μ-glutathione transferase were also induced. Iron overcame the weak porphyria and toxicity responses of TCDD in AhRb-2 BALB/c and AhRd SWR mice, but not in DBA/2 mice, which remained TCDD resistant. Thus, metabolic factors may play a part in the responses of some mice strains to TCDD through an oxidative process that disturbs iron regulatory protein capacity.

Increased accumulation of lipofuscin pigments, which are by-products of lipid peroxidation, in heart muscles of TCDD-exposed rats (Albro et al., 1978) and iron deficiency in animals resulting in in vitro inhibition of lipid peroxidation and reduced TCDD-induced hepatotoxicity (Sweeney et al., 1979) suggested that oxidative stress may play a role in TCDD-induced acute toxicity. Subsequently, Stohs et al. (1983) demonstrated that lipid peroxidation is increased in isolated liver microsomes from TCDD-exposed rats. Further observations suggest a possible role of reactive oxygen species in TCDD acute toxicity. Alsharif et al. (1994a,b) observed that a maximum increase in superoxide anion production occurs on day 1 of posttreatment in female SD rats treated with 50 and 125 μg/kg bw of TCDD, and that TCDD-induced oxidative stress is mediated through the Ah receptor in mice. TCDD-induced superoxide anion production by peritoneal lavage primary macrophages and its mediation through the Ah receptor suggests involvement of reactive oxygen species in a broad spectrum of TCDD-induced toxicity. Bagchi et al. (1993) found that products from altered lipid peroxidation and increased oxidative stress result in elevated serum and urinary levels of certain lipid metabolic products, such as malondialdehyde, formaldehyde, acetaldehyde, and acetone, following a single oral exposure to 50 μg/kg bw of TCDD in female SD rats. Vos et al. (1978) suggested that endotoxin shock may be the cause of TCDD-induced lethality, and that the tumor necrosis factor-α (TNF-α) may be a contributing factor, even though it has not been detected in the serum of TCDD-treated mice without exposure to endotoxin. Alsharif et al. (1994c) demonstrated that anti-TNF-α antibody can decrease phagocytic cell activity following TCDD treatment. This suggests that TNF-α release, a possible activator of TCDD-induced oxidative stress, may have some role in TCDD-induced activation of phagocytic cells.

3.5.8. Neurotoxicity

Exposure to dioxin-like coplanar PCBs may result in neurotoxicity. Eriksson et al. (1991) suggested that dioxin-like coplanar PCBs have neurologic activities that affect the cholinergic receptors in the hippocampus. Seegal (1996) provided evidence that perinatal exposure to coplanar 3,3',4,4'-PCB (PCB 77) results in significant elevation of dopamine in the frontal cortex. Dopamine is an important neurotransmitter, dependent on tyrosine, that is associated with initiation and control of motor behavior, learning, and memory functions. The neurons and astroglia of rat hippocampal neural cells are responsive to relatively low levels of TCDD through mechanisms that are probably not associated with altered gene transcription and

that may involve other cellular targets (Hanneman et al., 1996). TCDD induces phosphorylation and other responses within minutes of treatment, probably through a nonnuclear role of the Ah receptor.

Eriksson and Fredriksson (1998) demonstrated that a single oral exposure of NMRI mice to either 0.51 or 51 mg/kg bw of 3,3',4,4',5,5'-hexachlorobiphenyl (PCB 169) on postnatal day 10 can result in derangement of spontaneous motor behavior. In addition, permanent impairment of learning and working memory was revealed when these animals reached adulthood. This study suggests that exposure to PCB 169 during the neonatal period, at a time when there is incomplete development of the infant's blood-brain barrier and during rapid brain development, can result in vulnerability of the brain to neurologic effects, which in many cases can only be manifested during adulthood. In utero and lactational exposure to TCDD (100 ng/kg/d) or coplanar PCBs resulted in reduction of errors on a radial arm maze working memory task in grown up S-D rats exposed through their mothers (Seo et al., 1999). The effect was more pronounced in males than females. There was no difference in performance of the Morris water maze task or the spatial discrimination-reversal learning task for exposed males and females or unexposed rats. Both adult male and female S-D rats exposed maternally to TCDD showed a deficit in learning a visual discrimination-reversal learning task, a finding also observed in monkeys.

Postnatal oral exposure of primates to PCBs can result in long-term behavioral dysfunctions. In monkeys, oral exposure from birth to 20 weeks of age to 7.5 µg/kg/day of a PCB mixture, representative of the PCB residues generally found in human breast milk samples, also results in significant impairment in discrimination-reversal learning activities (Rice, 1997).

3.6. MECHANISMS OF TOXICITY

The most reliable and consistent symptom of TCDD toxicity among all experimental animals is weight loss. The cause of the body weight loss seems to be reduced food intake, apparently occurring secondarily to a physiological adjustment that reduces the body weight to a maintenance level that is lower than normal. The physiological trigger for this body weight set-point might be a target for TCDD.

Delayed expression of TCDD-induced toxic responses, including lethality, suggests that these toxic responses may not be the result of a direct insult by the parent compound (Mukerjee, 1998; Rozman, 1999). Progressive hypoglycemia from feed refusal and reduced gluconeogenesis seems to be the ultimate cause of TCDD-induced lethality (Gorski et al., 1990). In the L-E strain rat, reduced gluconeogenesis, indicated by decreased PEPCK activity, has been suggested to contribute to the acute toxicity of TCDD (Fan and Rozman, 1994; Viluksela et al., 1999). One of the major causes of TCDD-induced lethality also is dose-dependent reduction of tryptophan 2,3-dioxygenase (TdO) activity (Fan and Rozman, 1994; Stall et al., 1993), indicating

that subtle differences in the regulation of intermediary metabolism may be responsible for strain differences in the susceptibility of rats to TCDD (Fan and Rozman, 1994).

There have been significant advances in understanding the cause of TCDD-induced voluntary feed refusal. The neurotransmitter 5-hydroxytryptamine (5-HT), or serotonin, controlled by the availability of the amino acid tryptophan (Carlsson and Lindquist, 1978), suppresses feed intake behavior (Leibowitz, 1993). TCDD increases the plasma level of free tryptophan in L-E rats but not H/W rats (Unkila et al., 1994a). Increase in brain tryptophan levels (Rozman et al., 1991; Unkila et al., 1994b) and 5-HT turnover are closely connected with changes in plasma tryptophan (Unkila et al., 1994b). In L-E and H/W rats, the potencies of dioxin congeners highly correlate with their ability to disrupt tryptophan homeostasis. The order of potency is: TCDD > 1,2,3,7,8-PeCDD > 1,2,3,4,7,8-HxCDD > 1,2,3,4,6,7,8-HpCD (Unkila et al., 1998). TCDD lethal dose exposure results in increased brain 5-HT synthesis in L-E rats (Unkila et al., 1993), whereas in resistant H/W rats no such increase of 5-HT occurs. The dose-related changes in plasma free tryptophan are closely associated with the severity of the wasting syndrome observed in L-E rats (Unkila et al., 1994b). Increased circulating tryptophan and rapid turnovers of tryptophan and 5-HT in the brain are associated with TCDD-induced reduced feed intake, wasting, and lethality (Rozman et al., 1991; Unkila et al., 1994b). However, tryptophan metabolism or carbohydrate homeostasis does not explain the wide interspecies differences in susceptibility to acute lethality encountered between guinea pigs (the most acutely susceptible species) and hamsters (the most resistant species) (Unkila et al., 1995).

Despite extensive research to elucidate the ultimate events underlying the toxic action of TCDD, definitive answers are not yet available. The toxicity of TCDD apparently depends on the fact that the four lateral positions of the molecule are occupied by chlorine, resulting in high-affinity binding to the AhR. Mechanisms of toxicity are discussed in detail in Chapter 2. TCDD toxicity involves many different types of symptoms, which vary from species to species and from tissue to tissue, both quantitatively and qualitatively. Age- and sex-related differences in sensitivity have also been reported. Another characteristic of TCDD toxicity is the delay before all the endpoints of toxicity are manifested (from 2 weeks to 2 months), which is seen in all species.

Polymorphism in the Ah locus, which has been shown to be the structural gene for the cytosolic receptor, seems to determine the sensitivity of genetically different strains of mice to TCDD and congeners. Ah-responsive strains of mice (e.g., C57BL/6) are characterized by high hepatic levels of a high-affinity TCDD-receptor protein, highly elevated levels of hepatic cytochrome P-4501A1 and associated enzyme activities in response to treatment with 3-MC (3-methylcholanthrene), and sensitivity to the ulcerative action of DMBA (7,12-

dimethylbenz[a]anthracene) on the skin. Ah-nonresponsive mice (e.g., DBA/2) lack these characteristics.

Based on these findings, several genetic studies have been performed to elucidate the role of the receptor in TCDD toxicity. In contrast to 3-MC, TCDD induces AHH activity and several toxic effects both in Ah-responsive and Ah-nonresponsive strains of mice. The dose required to produce the effect in an Ah-nonresponsive strain, however, is approximately 10-fold greater than that needed in an Ah-responsive strain. This indicates that the Ah-nonresponsive strain also contains the TCDD receptor, but the receptor is defective (Okey and Vella, 1982). Data from studies of DBA/2 mice given either single or multiple doses of TCDD (Jones and Sweeney, 1980; Smith et al., 1981) suggest that the LD_{50} in this strain of mice is at least fivefold greater than the values recorded for the C57BL/6 and C57BL/10 strains (Jones and Greig, 1975; Smith et al., 1981; Vos et al., 1974). TCDD-induced hepatic porphyria has also been shown to segregate with the Ah locus in mice (Jones and Sweeney, 1980). The correlative differences between the C57Bl/6 and DBA/2 strains of mice, in terms of altered specific binding of TCDD and sensitivity to this compound, may not be applicable to other species (Gasiewicz and Rucci, 1984).

In a genetic-crossing experiment between L-E and H/W rats (Pohjanvirta, 1990), it was demonstrated that the F_1 offspring were as resistant to TCDD toxicity as the H/W rats (LD_{50}, >3,000 μg/kg). Further studies on the F_2 generation indicated that the distribution of resistant and susceptible phenotypes was consistent with inheritance regulated by 2 (possibly 3) autosomal genes displaying complete dominance, independent segregation, and an additive coeffect.

Despite enormous variability in the recorded LD_{50} values for the guinea pig, rat, mouse, rabbit, and hamster, the amount and physical properties of the hepatic and extrahepatic receptors are comparable in these species (Gasiewicz and Rucci, 1984; Poland and Knutson, 1982). Furthermore, although the recorded LD_{50} values for TCDD vary >100 times among the chick embryo, the C3H/HeN mouse, and the SD rat, the ED_{50} doses for AHH induction in these species are comparable (Poland and Glover, 1974). Even between strains of rats with a difference of >300 times in LD_{50}, no differences in enzyme induction could be demonstrated (Pohjanvirta et al., 1988). In the guinea pig, the most TCDD-susceptible species, AHH induction is not a prominent symptom, even at lethal doses of TCDD. A number of cell types, including primary cultures and established and transformed cell lines from several species and tissues, are inducible for AHH activity, indicating the presence of the receptor. Yet toxicity is not expressed in these systems (Knutson and Poland, 1980a). The available data thus suggest that the receptor for TCDD may be a prerequisite but is not sufficient in itself for the mediation of toxicity.

Recent observations suggest that some of the TCDD-induced toxicity in mice require other modes of action, beyond AhR-mediated DNA transcription. For example, wasting syndrome, thymus involution, and loss of adipose tissue in c-src$^{+/+}$ mice are correlated to c-src kinase activation, which is physically linked to AhR. These TCDD-induced toxic effects are not induced in src$^{-/-}$ mice and are marginal in c-src$^{-/+}$ mice (Matsumura et al., 1997a,b). These toxic effects can also be prevented in c-src$^{+/+}$ mice pretreated with geldanamycin, a c-src kinase inhibitor (Enan et al., 1998a; Dunlap et al., 1999). Based on c-src deficiency not affecting TCDD induction of the cytochrome P-450 type 1A1 isozyme (CYP1A1), the gene activation pathway of TCDD's action through the AhR nuclear translocator (ARNT) gene appears to be independent of the phosphorylation pathway of TCDD toxic activities modulated through the c-src gene. Involvement of c-src kinase activation in TCDD-induced toxicity has also been observed in the guinea pig. Enan et al. (1998b) showed that male guinea pigs pretreated with the src-kinase inhibitor geldanamycin did not suffer TCDD wasting. These investigators obtained similar results with src-deficient mice. Treatment with estradiol also protected male guinea pigs from TCDD-induced wasting. Furthermore, a nuclear AhR complex is not required for one of the signal transduction pathways associated with TCDD-induced early response of the c-fos and junB genes (Puga et al., 1992; Hoffer et al., 1996).

A strong correlation between lack of AhR affinity and lack of acute TCDD toxicity has been demonstrated in the knockout AhR$^{-/-}$ mouse. No significant difference in short-term toxicity was observed between the vehicle control group and knockout homozygous AhR$^{-/-}$ mice receiving TCDD at 2,000 µg/kg bw. Postexposure effects at day 28 were limited to vascularities of the lung and scattered necrosis of hepatocytes in AhR$^{-/-}$ resistant mice. In contrast, lipid accumulation and inflammatory cell infiltration of the liver were seen in heterozygous AhR$^{+/-}$-susceptible mice at the much lower dose of 200 µg/kg TCDD (Fernandez-Salguero et al., 1996). Although some of the TCDD-induced toxicity of the liver and thymus are mediated by the AhR, the mechanism for vascularities of the lung and the scattered necrosis of the lung and liver in AhR knockout mice may involve alternative pathways. As proposed by Matsumura et al. (1997a, b), these toxicity pathways still require the AhR and associated cytosolic proteins (Enan and Matsumura, 1996), but not nuclear AhR and DNA transcription.

Mutation of the p53 tumor suppresser gene associated with certain cancers confers resistance to TCDD-induced acute toxicity. The DBA/2 mouse has a complex mutation in the promoter region of the Tryp53 locus (the p53 region of the mouse). Both homozygous and heterozygous Tryp53 knockout mouse types have a high spontaneous incidence of cancer (Harvey et al., 1993). Inhibition of hepatocellular proliferation due to acute TCDD exposure also increases expression of the hepatic tumor suppressor p53 gene associated with the cell cycle inhibitory protein in the Balb/c mouse (Rininger et al., 1997). Results from these studies support

the hypothesis, proposed by Blagosklonny (1997), that high levels of the tumor suppressor p53 protein that confer protection against cancer may also increase sensitivity to the acute toxicity of TCDD.

3.7. SUMMARY

Most of the toxicity data available for TCDD are from oral experiments in animals. Very few percutaneous and no inhalation exposure toxicity data are available in the literature. Animal data following oral exposure indicate that TCDD is one of the most toxic compounds known and that it produces a wide spectrum of toxic effects.

There is a wide range of differences in sensitivity to TCDD lethality. The male guinea pig is the most sensitive, with an oral LD_{50} value of 0.6 µg/kg (Schwetz et al., 1973), and the male hamster the least sensitive, with an LD_{50} value of 5,051 µg/kg (Henck et al., 1981). This difference in sensitivity is more than 8,000-fold. The mink seems to be the second most sensitive to lethality, with an oral LD_{50} dose of 4.2 µg/kg for the male (Hochstein et al., 1988) and an LC_{50} value of 0.26 µg/kg for the female (Hochstein et al., 1998). The oral LD_{50} value for the male rat is 22 µg/kg (Schwetz et al., 1973). The rabbit LD_{50} value is 115 µg/kg (Schwetz et al., 1973). Unlike most toxic chemicals, the lethality of TCDD is delayed, with time to death being species and strain specific. Single lethal dose exposure results in death within 7-50 days and is generally associated with a wasting syndrome involving progressive loss of up to 50% body weight and eventual death without any clear or identifiable lethal pathological lesions. The characteristic signs and symptoms of lethal toxicity by TCDD are severe weight loss and thymic atrophy.

At least for acute exposure, the TCDD-induced toxicity appears to depend on the total dose administered over a given time, either through a single treatment or a limited number of multiple treatments. One of the consistent signs of TCDD toxicity in most species is thymic atrophy. Other toxic effects include hyperplasia or atrophy of the spleen, testes, or ovaries, bone marrow depletion, and systemic hemorrhage. Severe chloracne is one of the signs of TCDD exposure in people (Crow, 1978). Similar lesions or precursor lesions can be induced by TCDD in cattle (McConnell et al., 1980), rhesus monkeys (Norback and Allen, 1973; McConnell et al., 1978b), rabbits (Schwetz et al., 1973), and hairless mice (Knutson and Poland, 1982; Puhvel et al., 1982). The liver is extremely sensitive to TCDD toxicity in all animals, regardless of duration of exposure. The degree of severity of liver toxicity seems to be species-specific. Morphological alterations in liver toxicity are less severe in the guinea pig, the most sensitive species to lethality, than other species. The hamster, the most resistant species for lethality, shows liver lesions after a prolonged period of chronic exposure to nonlethal doses. Toxic effects include liver weight changes, fatty liver, impaired liver function characterized by increased microsomal monooxygenase, SGOT and SGPT activities, porphyrin accumulation,

impaired membrane function, hyperbilirubinemia, hypercholesterolemia, and hyperproteinemia. Severe episodes of toxic hepatitis have been observed in rats and mice. Various physiological equilibrium processes, such as vitamin A storage, plasma membrane functions, and the formation of keratin and cell differentiation, are affected by TCDD exposure. Pericardial and peritoneal edema resulting in death occur in chickens (Firestone, 1973). Systemic edema has also been observed in monkeys (Norback and Allen, 1973) and mice (Vos et al., 1974).

Sensitivity to TCDD toxicity segregates with the Ah locus. The potency of other congeners to induce lethality correlates with their ability to bind to the Ah receptor. Other congeners are less toxic than 2,3,7,8-TCDD. The lateral 2,3,7, and 8 position of the dioxin molecule must be chlorinated (or halogenated) to induce the greatest toxicity. The addition of chlorine atoms reduces toxicity. Increased microsomal AHH and EROD activities are markers for CYP1A1 (discussed in Chapter 2) and are associated — not necessarily causally — with the systemic toxicity of PCDDs, PCDFs, and coplaner PCBs.

Except for 2,3,7,8-TCDD and a mixture of 1,2,3,6,7,8- and 1,2,3,7,8,9-HxCDD, there are no long-term chronic bioassay data for PCDD/PCDF congeners that can be used for assessing the chronic risk. In the absence of any long term chronic toxicity bioassay data, enzymatic activity and other short-term in vivo and in vitro data are used in developing a toxicity ranking scheme (see Chapter 9).

One of the possible mechanisms by which TCDD and related compounds interfere with normal endocrine function is the ability to disrupt natural hormones. Hirsutism and diminished libido caused by TCDD seems to be due to its endocrine disruptive activities. A single oral dose of 20 µg/kg to rats can reduce serum testosterone levels (Nienstedt et al., 1979). Catabolism of exogenous estrone in TCDD-pretreated, ovariectomized rats is decreased (Shiverick and Muther, 1983). Alterations in hormonal levels by TCDD and its antiestrogenic action are discussed in Chapter 5. TCDD tumor promotion activity in liver carcinogenesis can be prevented in ovariectomized rats, indicating that estrogen status influences TCDD toxicity (Lucier et al., 1991). Animals exposed to TCDD and related compounds in utero or as infants exhibit varying degrees of behavioral disorders. These disorders resemble those seen in infants exposed to agents resulting in thyroid hormone deficiencies in utero or in infancy. Thyroidectomy of animals resulted in partial protection from TCDD-induced wasting syndrome and immunotoxicity, suggesting possible involvement of thyroid function in the manifestation of pathological conditions (Bastomsky, 1977; Rozman et al., 1984; Pazdernik and Rozman, 1985). Monkeys exposed for 4 years to TCDD at low ppt levels and studied for an additional 7-10 years have been reported to develop endometriosis (Rier et al., 1993). Estrogen, glucocorticoid, prolactin, insulin, gastrin, melatonin, and other hormones are affected by TCDD either by its

activity on the hormone or receptor. Further studies are needed to elucidate the mechanism of TCDD-induced endocrine disruptive activities.

The subchronic NOAEL for porphyria in female SD rats is estimated to be 0.01 µg/kg/week (= 0.001 µg/kg/day = 1 ng/kg/day) (Goldstein et al., 1982). A chronic NOAEL of 1 ng/kg/day for hepatotoxicity is estimated for SD rats from a 2-year chronic study (Kociba et al., 1978). In addition to liver toxicity, chronic exposure has been found to be associated with amyloidosis and dermatitis in Swiss mice (Toth et al., 1979). From this study, a LOAEL of 1 ng/kg/day for amyloidosis and dermatitis has been estimated for mice. Chronic exposure to 1.5 ng/kg/day in diet results in hair loss, edema, and pancytopenia in monkeys (Allen et al., 1977; Schantz et al., 1979). The lowest doses that have been demonstrated to elicit various biological responses in certain animals are compiled in Table 3-4.

Single-dose acute exposures to CDDs yield a large area under the curve (AUC) because of their long half-life and thus may be viewed as subchronic exposures. Subchronic/chronic exposures yield similar toxicity profiles to an acute exposure when similar total cumulative doses are administered. When corrected for excretion, depending on half-life, the corrected cumulative subchronic/chronic exposure doses seem to be analogous to the acute exposure doses. Similar data are available for 2,3,7,8-TCDF (Ioannou et al., 1983).

It is evident, from the complex picture evolving from the data outlined above, that TCDD elicits a variety of toxic responses following both short-term and long-term exposure. It is also clearly evident that there are very large differences in the sensitivity to specific TCDD-induced toxicities among various species and strains. This conclusion is valid for the severity of effects of almost all the responses studied. Qualitatively, however, there seems to be fairly good agreement among the types of responses that can be observed. For example, almost all responses can be produced in every species and strain if the right dose is chosen. Tissues or cell lines from humans and animals seem to respond to dioxin at similar exposure levels and in identical ways in regard to CYP1A1 activity, cytotoxicity, and inhibition of cell proliferation (DeVito et al., 1995). In highly sensitive species (e.g., the guinea pig), lethality may prevent some responses from occurring. Our present knowledge rules out enzyme induction as such, as the proximate cause of toxicity and death. Although the toxicokinetics of TCDD vary between species, these differences are not sufficient to explain the variabilities in sensitivity to TCDD lethality. The available data indicate an involvement of TCDD in processes regulating cellular differentiation and proliferation, as well as those controlling endocrine homeostasis. Alterations in the regulation of such processes, which are not equally active in all cells throughout the organism, would be expected to result in effects that vary among tissues and species. The overwhelming number of toxic responses to TCDD, including lethality, typically show a delay in their appearance. This supports the assumption that these responses are not the result of a direct insult

from the compound. A lethal dose of TCDD in rats increases the neurotransmitter 5HT, controlled by increased levels of tryptophan in plasma and brain, suppresses voluntary feed consumption resulting in wasting syndrome, and leads eventually to mortality a few weeks postexposure. The induction of hepatic cytochrome P-450-dependent monooxygenases (such as CYP1A1) is one of the hallmarks of TCDD exposure. This effect has been demonstrated to be mediated through interaction with a specific protein called the Ah receptor. This process involves the binding of TCDD to the receptor, followed by the binding of the receptor-ligand complex to DNA recognition sites. This leads to the expression of specific genes and translation of their protein products, which then mediate their biological effects. As discussed in detail in Chapter 2, the mechanisms of action for enzyme induction are understood mainly at the molecular level, where the Ah receptor and its genetic regulation is clearly an important mechanistic step. Very little, however, is known about the mechanisms of the middle and high dose responses at the molecular level.

Studies in congenic mice that are relatively Ah-responsive or Ah-nonresponsive have demonstrated that the majority of TCDD-induced toxic responses segregate with the Ah locus. However, the number and affinity of Ah receptor expressed in most laboratory species and strains are rather comparable. The Ah receptor is thus unlikely to be the only determinant of TCDD-induced toxicity. Rather, it has to be assumed that species and strain differences are confined to the latter parts of the receptor-mediated chain of events (e.g., binding of the receptor-ligand complex to DNA and the subsequent expression of specific genes). In some cases, the binding affinity of the Ah receptor is different or defective. Some of the responses may be secondary in the sense that they are caused by the altered homeostasis of endogenous compounds, caused by TCDD-induced increased activities of various enzymes. An additional AhR-related pathway involving c-src kinase in the cytoplasm has been implicated in wasting syndrome, thymus atrophy, and loss of adipose tissue in mice.

Table 3-1. Acute lethality of TCDD to various species and substrains

Species/strain (sex)	Route	LD_{50} (µg/kg)	Time of Death (days postexposure)	Follow-up (days)	Body weight loss[a] (%)	References
Guinea pig/Hartley (male)	*per os*	0.6-2.1	5-34	NR 30	50	McConnell et al., 1978a; Schwetz et al., 1973
Mink/NR (male)	*per os*	4.2	7-17	28	31	Hochstein et al., 1988
Chicken/NR (NR)	*per os*	<25	12-21	NR	NR	Greig et al., 1973
Monkey/rhesus (female)	*per os*	~70	14-34	42-47	13-38	McConnell et al., 1978b
Rat/L-E (male)	intraperitoneal	~10	15-23	48-49	39	Tuomisto and Pohjanvirta, 1987
Rat/Sherman, Spartan (male) (female)	*per os*	 22 13-43	9-27	NR	NR	Schwetz et al., 1973
Rat/Sprague-Dawley (male) (female) (weanling male)	intraperitoneal	 60 25 25	NR	20	NR	Beatty et al., 1978
Rat/Fischer Harlan (male)	*per os*	340	28[b]	30	43	Walden and Schiller, 1985
Rat/H/W (male)	intraperitoneal	>3,000	23-34	39-48	40-53	Pohjanvirta and Tuomisto, 1987; Pohjanvirta et al., 1988
Mouse/B6 (male) D2A/2J (male) B6D2F1 (male)	*per os*	182 2,570 296	24[b] 21[b] 25[b]	30	25 33 34	Chapman and Schiller, 1985
Mouse/B6 D2 B6D2F1	intraperitoneal	132 620 300	NR	NR	NR	Neal et al., 1982
Rabbit/New Zealand White (male and female)	*per os* dermal	115 275	6-39 12-22	NR 22	NR NR	Schwetz et al., 1973

Table 3-1. Acute lethality of TCDD to various species and substrains (continued)

Species/strain (sex)	Route	LD_{50} (µg/kg)	Time of death (days post-exposure)	Follow-up (days)	Body weight loss[a] (%)	References
Rabbit/New Zealand White (male and female)	intraperitoneal	~50	7-10	10-20	11	Brewster et al., 1988
Hamster/Golden Syrian (male and female)	per os	1,157-5,051	2-47	50	NR	Henck et al., 1981
Hamster/Golden Syrian (male and female)	intraperitoneal	>3,000	14-32	55	1[c]	Olson et al., 1980

[a]Of succumbed animals.
[b]Mean time to death.
[c]Data from five animals.
NR = Not reported.

Table 3-2. Toxic response following exposure to 2,3,7,8-TCDD: species differences[a]

Response	Monkey	Guinea pig	Cow[b]	Rat	Mouse	Rabbit[b]	Chicken[b]	Hamster
Hyperplasia or metaplasia								
Gastric mucosa	++	0	+	0	0			0
Intestinal mucosa	+							++
Urinary tract	++	++	++	0	0			
Bile duct or gall bladder	++	0	+		++			0
Lung: focal alveolar				++				
Skin	++	0	+[c]	0	0	++		0
Hypoplasia, atrophy, or necrosis								
Thymus	+	+	+	+	+		+	+
Bone marrow	+	+			±		+	
Testicle	+	+		+	+			
Other responses								
Liver lesions	+	±	++	+	++	+	+	±
Porphyria	0	0		+	++		+	0
Edema	+	0		0	+		++	+

[a]Sources: Allen and Lalich, 1962; Allen et al., 1977; Henck et al., 1981; Kimmig and Schultz, 1957; Kociba et al., 1978, 1979; McConnell, 1980; McConnell et al., 1978a,b; Moore et al., 1979; Norback and Allen, 1973; Olson et al., 1980; Schwetz et al., 1973; Turner and Collins, 1983; Vos et al., 1973; Vos and Beems, 1971; Vos and Koeman, 1970.

[b]Responses followed exposure to 2,3,7,8-TCDD or stucturally related chlorinated hydrocarbons.

[c]Skin lesions in cattle have been observed, but they differ from the skin lesions observed in other species.

0 = lesion not observed, + = lesion observed (number of "+" denotes severity), ± = lesion observed to a very limited extent, blank = no evidence reported in literature.

Table 3-3. Studies on chronic exposure (except for studies on cancer) to TCDD in laboratory animals

Species/strain	Sex and no. per group	Doses tested	Treatment schedule	Parameters monitored	References
Rats/Sprague-Dawley	M/10	0, 1, 5, 50, 500, 1,000, 5,000, 50,000, 500,000, 1,000,000 ng/kg	Continuous in diet for 65 weeks	Survival	van Miller et al., 1977
Rats/Sprague-Dawley	M, F/10	0.001, 0.01, 0.1 µg/kg/day	Continuous in diet for 2 years	Extensive histopathology, hematology, and clinical chemistry	Kociba et al., 1978, 1979
Mice/Swiss	M/38-44	0, 0.007, 0.7, 7.0 µg/kg/week	Gavage weekly for 1 year	Histopathology	Toth et al., 1979
Mice/B6C3F1	M/50, F/50 M/75, F/75	0.01, 0.05, 0.5 µg/kg/week (males) 0.04, 0.2, 2.0 µg/kg/week (females) 0.0	Gavage biweekly for 2 years	Extensive histopathology	NTP, 1982
Monkey/Macaca mulatta	F/8	500 ng/kg	Continuous in the diet for 9 months	Extensive histopathology, hematology, and clinical chemistry	Allen et al., 1977

Table 3-4. Lowest effect levels for biological responses of 2,3,7,8-TCDD in experimental animals

Species	Dose or concentration and duration	Effect	Reference
Guinea pigs	0.6 μg/kg, single oral dose	Lethality (single dose LD_{50})	Schwetz et al., 1973
Rhesus monkey	1.0 μg/kg, single oral dose	Acute (systemic) toxicity	McNulty, 1977
Sprague-Dawley rat	2.0 ng/kg, single oral dose[a]	Induction of AHH (CYP1A1)	Kitchin and Woods, 1979
Marmoset monkey	3.0 ng/kg, single oral dose	Induction of N-demethylation (CYP1A2)	Kruger et al., 1990
Guinea pig	1 ng/kg-day for 8 weeks	Immunosuppression (decreased response to tetanus toxin)	Zinkl et al., 1973
Swiss mouse	1 ng/kg-day for 1 year	Amyloidosis and dermatitis	Toth et al., 1979
Rhesus monkey	500 ppt in diet for 9 months (12 ng/kg-day); 2 ppb in diet for 61 days (50 ng/kg-day)	Chronic lethality	Allen et al., 1977; McNulty, 1977
Rhesus monkey	50 ppt in diet for 20 months (1.5 ng/kg-day)	Chronic toxicity (hair loss)	Schantz et al., 1979
Sprague-Dawley rat	10 ng/kg-day for 2 years in feed	Porphyrin metabolism	Kociba et al., 1978

[a]0.6 ng/kg = no effect level.

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4. IMMUNOTOXICITY

4.1. INTRODUCTION

Concern over the potential toxic effects of chemicals on the immune system arises from the critical role of the immune system in maintaining health. It is well recognized that suppressed immunological function can result in increased incidence and severity of infectious diseases as well as some types of cancer. Conversely, inappropriate enhancement of immune function or the generation of misdirected immune responses can precipitate or exacerbate development of allergic and autoimmune diseases. Thus, both suppression and enhancement of immune function are considered to represent potential immunotoxic effects of chemicals.

The immune system consists of a complex network of cells and soluble mediators that interact in a highly regulated manner to generate immune responses of appropriate magnitude and duration. Consequently, comprehensive evaluation of immunotoxicity must include specific assessments of multiple functional parameters on a kinetic basis. In addition, because an immune response develops in a time-dependent manner relative to antigen exposure, the immunotoxicity of a chemical can be profoundly influenced by the timing of chemical exposure relative to antigen challenge. Consideration of these levels of complexity involved in immunotoxicology assessment is critical for interpreting the effects of chemical exposure on immune function (Kerkvliet, 1994).

Extensive evidence has accumulated to demonstrate that the immune system is a target for toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and structurally related polyhalogenated aromatic hydrocarbons (PHAHs), including the polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), and polybrominated biphenyls (PBBs). This evidence was derived primarily from numerous studies in various animal species, mainly rodents, but also guinea pigs, rabbits, monkeys, marmosets, and cattle. Epidemiological studies also provide some evidence that PHAHs alter immune parameters in humans. In animals, relatively high doses of PHAHs produce lymphoid tissue depletion, except in the thymus, where lower doses cause cellular depletion. Alterations in specific immune effector functions and increased susceptibility to infectious disease have been identified at doses of TCDD well below those that cause significant lymphoid tissue depletion. Both cell-mediated and humoral immune responses are suppressed following TCDD exposure, which suggests that multiple cellular targets within the immune system are altered by TCDD. Evidence also suggests that the immune system is indirectly targeted by TCDD-induced changes in nonlymphoid tissues. In addition, in parallel with increased understanding of the cellular and molecular mechanisms involved in immunity, studies on TCDD are beginning to establish

biochemical and molecular mechanisms of TCDD immunotoxicity. These advances are highlighted in this document.

There is an enormous literature based on descriptive studies of the immunotoxic effects of TCDD and related PHAHs in laboratory animals. Unfortunately, widely differing experimental designs, exposure protocols, and immunologic assays used, have made it difficult to define a "TCDD-induced immunotoxic syndrome" in a single species, let alone across species. Before 1994, only one report directly compared the effects of TCDD on the immune system of rats, mice, and guinea pigs, and even then, different immunologic parameters were assessed, and different antigens were used in the different species (Vos et al., 1973). In that study, the delayed-type hypersensitivity (DTH) response to tuberculin was evaluated in guinea pigs and rats for assessment of cell-mediated immunity, and the graft versus host (GVH) response was measured in mice. A decreased DTH response to tuberculin was observed in guinea pigs following 8 weekly doses of 40 ng/kg TCDD (total dose, 320 ng/kg), whereas in rats the DTH response to tuberculin was unaffected by 6 weekly doses of 5 μg/kg TCDD (total dose, 30,000 ng/kg). The GVH response in mice was suppressed by 4 weekly doses of 5 μg/kg TCDD (total dose, 20,000 ng/kg). The greater sensitivity of guinea pigs compared with rats and mice to the immunosuppressive effects of TCDD is consistent with their greater sensitivity to other toxic effects of TCDD (McConnell et al., 1978; Poland and Knutson, 1982).

Although the results of Vos et al. (1973) appear to suggest that cell-mediated immunity in mice is more sensitive to TCDD than in rats, no studies have directly compared cell-mediated immunity in rats and mice using the same antigens and endpoints. However, a 1994 study made a direct comparison of the effects of TCDD on humoral immunity in rats and mice (Smialowicz et al., 1994). In this study, the primary plaque-forming cell (PFC) response to sheep red blood cells (SRBCs) was suppressed in B6C3F$_1$ mice (ED_{50} of 0.68 μg/kg TCDD), but the anti-SRBC response was either unaffected or enhanced in Long Evans and Fischer 344 rats, respectively, at a dose as high as 30 μg/kg TCDD. This response of rats was corroborated by Fan et al. (1996), who observed that TCDD at 20 and 40 μg/kg did not alter serum IgM levels to SRBC, whereas IgG levels were enhanced. In contrast, the primary PFC and serum antibody response to the T cell–independent (TI) antigen trinitrophenyl lipopolysaccharide (TNP-LPS) was reported to be suppressed in both mice and rats following exposure to TCDD at 10 and 30 μg/kg, respectively (Smialowicz et al., 1996).

In a study in mice (Clark et al., 1981), the DTH response to oxazolone was suppressed by 4 weekly doses of 4 μg/kg TCDD (total dose, 16,000 ng/kg), whereas the DTH response to SRBC was unaffected by a 10-fold higher dose of TCDD, which illustrates that DTH responses to different antigens are not equally sensitive to TCDD-induced suppression, even in the same species. When PCB and PBB studies are considered, variable effects on DTH and other immune

reactions are also apparent (Vos and van Driel-Grootenhuis, 1972; Thomas and Hinsdill, 1978; Fraker, 1980; Luster et al., 1980a). Because the exact basis for the interstudy variability is not known, it would serve no useful purpose in terms of risk assessment to catalog all of the reported effects of TCDD and other PHAHs on the immune system. Several comprehensive reviews have been published on the immunotoxic effects of PHAHs in general (Kerkvliet, 1984; Vos and Luster, 1989; Kerkvliet and Burleson, 1994; Holsapple, 1995) and TCDD in particular (Holsapple et al., 1991a, b). The reader is also referred to the previous EPA TCDD risk assessment document (Sonawane et al., 1988) for another perspective on TCDD immunotoxicity. The present document does not address this extensive literature, but rather emphasizes more recent developments in the field of PHAH immunotoxicity that may assist in the risk assessment process. Gaps in our knowledge that require further research are also identified.

4.2. ROLE OF THE AH LOCUS IN PHAH IMMUNOTOXICITY

One of the most important advances in the study of PHAH toxicity in recent years has been the elucidation of a genetic basis for sensitivity to the toxicity of these chemicals, which may ultimately provide a logical explanation for many of the controversial data in the literature on PHAH toxicity in different species and in different tissues of the same species. In this regard, many biochemical and toxic effects of PHAHs appear to be mediated via binding to an intracellular protein known as the aryl hydrocarbon (Ah) or TCDD receptor in a process similar to steroid hormone receptor-mediated responses (Poland and Knutson, 1982; Cuthill et al., 1988). Ah receptor (AhR) activation follows stereospecific ligand binding; interaction of the receptor-ligand complex with dioxin-response elements (DREs) in the genome induces transcription of the structural genes encoding mRNA for CYP1A1 enzyme activity (i.e., cytochrome P4501A1) as well as expression of additional unidentified genes, the products of which are hypothesized to mediate PHAH toxicity (Whitlock, 1990). Differences in toxic potency between various PHAH congeners generally correlate with differences in AhR-binding affinities. The most toxic PHAH congeners are approximate stereoisomers of 2,3,7,8-TCDD and are halogen substituted in at least three of the four lateral positions in the aromatic ring system.

In mice, allelic variation at the Ah locus has been described (Poland et al., 1987; Poland and Glover, 1990). The different alleles code for AhRs that differ in their ability to bind TCDD and thus help to explain the different sensitivities of various inbred mouse strains to TCDD toxicity. Ah^{bb}-C57Bl/6 (B6) mice represent the prototype "responsive" strain and are the most sensitive to TCDD toxicity, whereas Ah^{dd}-DBA/2 (D2) mice represent the prototypic "nonresponsive" strain and require higher doses of TCDD to produce the same toxic effect. Congenic Ah^{dd} mice on a B6 background have been derived that differ from conventional B6 mice primarily at the Ah locus. The spectrum of biochemical and toxic responses to TCDD

exposure was similar in both strains, but the doses needed to bring about the responses were significantly higher in congenic mice homozygous for the Ah^d allele compared with mice carrying two Ah^b alleles (Birnbaum et al., 1990; Kerkvliet et al., 1990a).

Two lines of evidence have been used to investigate AhR dependence of acute immunotoxicity of TCDD and related PHAHs: (1) comparative studies using PCDD, PCDF, and PCB congeners that differ in their binding affinity for the AhR and (2) studies using mice of different genetic background known to differ at the Ah locus.

A comparison of the relative potency of PHAHs that differ in their binding affinity for the AhR is presented in Tables 4-1 and 4-2. These data are based on single-dose exposure (oral or intraperitoneal) of B6 mice to the various PHAHs for suppression of the anti-SRBC response and the cytotoxic T lymphocyte (CTL) response, respectively. As shown in Table 4-1, the potency of TCDD to suppress the primary antibody response to SRBCs has been reported by several laboratories, with remarkable agreement in the ID_{50} value of 0.7 μg/kg in B6 mice. The ID_{50} of $B6C3F_1$ mice has been reported to be lower (<0.1 μg/kg) (Narasimhan et al., 1994), similar (<1 μg/kg) House et al., 1990; Smialowicz et al., 1994), or slightly higher (1.2 μg/kg) (Holsapple et al., 1986a) in comparison with B6 mice. It should be noted that 4 weekly i.p. doses of 10 but not 1 or 0.1 μg/kg TCDD significantly suppressed the anti-SRBC response in B6 mice (Clark et al., 1981). This sub-chronic dosing protocol (Clark et al., 1981) does not readily explain this decreased potency because Vecchi et al. (l983) reported that 5 weekly doses of 2 μg/kg or 8 weekly doses of 0.5 μg/kg TCDD significantly suppressed the anti-SRBC response. The basis for the discrepancies between the data of Clark et al. (1981) and other laboratories regarding the potency of TCDD to suppress the anti-SRBC response is unknown.

In contrast to the reproducible data on TCDD, relative potency for other PHAH congeners shown in Table 4-1 is difficult to evaluate because few congeners have been examined in more than one study. In the few cases where the same congener has been evaluated independently, discrepancies in the data exist. For example, both Davis and Safe (1990) and Silkworth et al. (1984) evaluated the potency of the 2,3,4,5,3′,4′-HxCB congener (PCB 156) in the anti-SRBC response. The ID_{50}s from these two data sets differ by almost two orders of magnitude (0.7 mg/kg vs. 31 mg/kg, respectively). When the same congener was compared with TCDD for suppression of the CTL response, the ID_{50} was 70 mg/kg (Table 4-2). Although the basis for these discrepancies between laboratories and immune function endpoints is unknown, it is apparent that the immunotoxicity database should be expanded so that these differences can be resolved.

Vecchi et al. (1983) were the first to report that antibody response to SRBCs was differentially suppressed by TCDD in B6 mice compared with D2 mice, such that D2 mice required a dose approximately 10 times higher to produce the same degree of suppression.

Immunosuppression in F1 and backcross mice supported the role of the Ah locus in expression of TCDD immunotoxicity. 2,3,7,8-TCDF was significantly less potent than TCDD and showed a similar differential immunosuppressive effect in B6 and D2 mice. At the same time, Silkworth and Grabstein (1982) reported a B6 versus D2 strain-dependent difference in sensitivity to suppression of the anti-SRBC response by 3,4,3′,4′-tetrachlorobiphenyl (PCB 77), a ligand for the AhR. In comparison, the 2,5,2′,5′-tetrachlorobiphenyl (PCB 52) isomer, which lacks affinity for the AhR, was not immunosuppressive in either B6 or D2 mice. Structure-activity relationships were extended by Kerkvliet et al. (1985) in studies that compared the immunosuppressive potency of chlorinated dioxin and furan isomers that contaminate technical-grade pentachlorophenol. The 1,2,3,6,7,8-hexachlorinated dibenzo-*p*-dioxin (HxCDD), 1,2,3,4,6,7,8-heptachlorinated dibenzo-*p*-dioxin (HpCDD), and 1,2,3,4,6,7,8-heptachlorinated dibenzofuran (HpCDF) isomers, which bind the receptor, were all significantly immunosuppressive. The dose of each isomer that produced 50% suppression of the anti-SRBC response (ID_{50}) was 7.1, 85, and 208 μg/kg for HxCDD, HpCDD, and HpCDF, respectively (Figure 4-1). The ID_{50} for TCDD was 0.65 μg/kg based on the data of Vecchi et al. (1980). More extensive structure-dependent immunosuppressive activities of technical grade PCB mixtures (Davis and Safe, 1990), PCB congeners (Davis and Safe, 1989), and PCDF congeners (Davis and Safe, 1988) have also been reported. Results of these studies using different PHAH congeners are summarized in Table 4-1.

The role of the AhR in suppression of the anti-SRBC response was verified in studies using B6 mice congenic at the Ah locus (Kerkvliet et al., 1990a). As expected, congenic Ah^{dd}-B6 mice were significantly less sensitive to TCDD-induced immune suppression as compared with wild-type Ah^{bb}-B6 mice. Unexpectedly, however, the dose response in congenic Ah^{dd}-B6 mice appeared to be bimodal, with a portion of the response sensitive to suppression by low doses of TCDD. Because of the bimodal response, the data did not permit extrapolation of an ID_{50} dose in the congenic mice. The results were interpreted to suggest potential non-AhR-mediated immunosuppressive effects. It should be noted, however, that studies by Silkworth et al. (1993) using rederived congenic Ah^{dd}-B6 mice did not corroborate a bimodal dose response. Their data, which indicated an ID_{50} of 7.5 μg/kg in congenic Ah^{dd}-B6 mice compared with an ID_{50} of 0.54 μg/kg in Ah^{bb}-B6 mice, are consistent with an AhR-dependent mechanism of immune suppression.

AhR dependency of PHAH immunotoxicity has also been demonstrated in mice using other immunologic responses. For example, Kerkvliet et al. (1990a) reported that the ID_{50} for suppression of the antibody response to TNP-LPS in Ah^{bb}-B6 mice was 7.0 μg/kg compared with a significantly higher ID_{50} of 30 μg/kg in congenic Ah^{dd}-B6 mice. Because the antibody response to TNP-LPS shows little requirement for macrophages or T helper cells (Jelinek and Lipsky,

1987), these results suggest an AhR-dependent B cell response. In terms of cytotoxic T cells, Clark et al. (1983) were first to report data suggesting that TCDD and PCB isomers suppressed in vitro CTL responses of B6 and D2 mice through an AhR-dependent mechanism. Subsequently, Kerkvliet et al. (1990b) reported that B6 mice congenic at the Ah locus showed Ah-dependent sensitivity to suppression of the CTL response following exposure to either TCDD or 3,4,5,3′,4′,5′-hexachlorobiphenyl (HxCB) (PCB 169). Furthermore, the potency of TCDD and of three HxCB congeners to suppress the CTL response of mice directly correlated with their relative binding affinities for the AhR (Table 4-2, from Kerkvliet et al., 1990b). The ID_{50} of TCDD for suppression of the CTL response in B6 mice was 7.0 μg/kg.

It should be noted that the dose of TCDD required to suppress the CTL response reported by Kerkvliet et al. (l990b) is significantly greater than that reported by Clark et al. (1981), who reported CTL suppression following 4 weekly doses of 0.1 μg/kg TCDD. Clark et al. (1983) also reported that doses of TCDD as low as 4 ng/kg to B6 mice suppressed in vitro generation of CTL and that the suppression was Ah dependent. The potency of TCDD described in Clark's studies has not been corroborated by other laboratories (Holsapple et al., 1991b; Hanson and Smialowicz, 1994). For example, the in vivo and in vitro CTL response in B6 mice was not affected at doses ranging from 0.01 to 3.0 μg/kg given at weekly intervals for 4 weeks (Hanson and Smialowicz, 1994).

If immunotoxicity of TCDD and structurally related PHAHs depends on AhR-mediated mechanisms, then co-exposure to subsaturating levels of more than one Ah agonist should produce additive effects. An additive interaction has been demonstrated in mice coexposed to 1,2,3,6,7,8-HxCDD and 1,2,3,4,6,7,8-HpCDD, two relatively strong AhR ligands (Kerkvliet et al., 1985). On the other hand, coexposure of mice to an immunotoxic dose of TCDD and a subimmunotoxic dose of different commercial Aroclors or certain PCB congeners resulted in partial antagonism of TCDD suppression of the anti-SRBC response (Bannister et al., 1987; Davis and Safe 1988, 1989). An apparently similar antagonism was observed following coexposure to 2,3,7,8-TCDF (10 μg/kg) and TCDD (1.2 μg/kg) (Rizzardini et al., 1983). The mechanism for this antagonism has not been fully elucidated, but the effects are consistent with competition for binding at the AhR because the weaker agonist was administered in excess compared with TCDD. In other studies, Silkworth et al. (1988, 1993) have shown that immunotoxicity of TCDD can be modified by coexposure to other PHAHs present as cocontaminants of actual environmental samples from Love Canal, New York. Smialowicz et al. (1997) examined the anti-SRBC response in mice cotreated with TCDD and 2, 2', 4, 4', 5, 5'-hexachlorobiphenyl (PCB153). PCB153 alone enhanced this response such that when given with an immunosuppressive dose of TCDD (1 μg/kg) the anti-SRBC response was not suppressed.

These results indicate that PCB153 acts as a functional rather than an AhR or dispositional antagonist of TCDD-induced immunosuppression.

Recent work by Sulentic et al. (1998) provides evidence for the critical role of the AhR in TCDD-induced suppression of IgM secretion. B cell lines, which differ in their expression of the AhR (i.e., CH12.LX cells express AhR and BCL-1 cells do not), were used in this study. TCDD treatment resulted in marked induction of AhR expression as well as suppression of LPS-induced IgM secretion in CH12.LX but not BCL-1 cells. Furthermore, TCDD induced CYP1AI induction in CH12.LX but not BCL-1 cells. These results implicate the AhR as a critical factor in TCDD-induced inhibition of IgM secretion.

The data indicate that suppression of the antibody response to T cell–dependent and –independent antigens and the CTL response by PHAHs are primarily AhR-dependent. However, the underlying mechanism(s) for these effects remain to be elucidated. It should also be emphasized that the data supporting an AhR dependency have been obtained from studies in inbred mice using an acute or subacute exposure regimen. Except for thymic atrophy, structure-immunotoxicity relationships in other species, including rats, have not been established, and inbred strains of other species with defined Ah genotype are not currently available. Nevertheless, it is important to note that thymic cortical atrophy does not occur in AhR deficient ($AhR^{-/-}$) mice despite having received a 10-fold higher TCDD dose than mice expressing a functional AhR ($AhR^{+/-}$), which experience significant reduction in the size and cellularity of thymic cortical areas (Fernandez-Salguero et al., 1996).

Results from other studies suggest that non-Ah-dependent effects may also occur. For example, mice exposed for 14 days to 2,7-dichlorodibenzo-*p*-dioxin (2,7-DCDD), a dioxin congener with very weak affinity for the AhR, had suppressed antibody responses to SRBC (Holsapple et al., 1986b). This suppression was observed in the absence of any change in thymus weight or in AHH activity. More recently, Morris et al. (1992) reported that sensitivity of D2 mice to TCDD-induced suppression of the anti-SRBC response increased significantly when TCDD was administered daily over 2 weeks rather than as an acute single dose. Unfortunately, in these studies, the lowest dose of TCDD produced near-maximum suppression of the anti-SRBC response of $B6C3F_1$ mice in the acute exposure model, precluding detection of any similar increase in sensitivity of the $B6C3F_1$ mice to chronic dosing. In contrast to these findings, Vecchi et al. (1983) reported that multiple exposures to TCDD (2 μg/kg for 5 weeks or 0.5 μg/kg for 8 weeks) did not increase the sensitivity of D2 mice to suppression of the anti-SRBC response. Thus, the basis for any change in potency resulting from multiple treatment or chronic exposure to TCDD and the role of AhR-mediated events in the phenomenon remain to be elucidated.

Some in vitro studies also suggest that suppression of the in vitro antibody response may occur independent of the AhR. Tucker et al. (1986) and Holsapple et al. (1986a) reported that direct addition of TCDD in vitro suppressed the antibody response to SRBCs. However, based on the response of cells from congenic mice as well as a limited structure-activity study, the data of Tucker et al. (1986) supported an AhR-dependent suppression, whereas the data of Holsapple et al. (1986a) did not. In the latter study, the magnitude of suppression was comparable using cells from responsive B6C3F_1 or congenic heterozygous (Ah^{bd}-B6) mice compared with nonresponsive D2 or homozygous Ah^{dd}-B6 mice. In addition, Holsapple et al. (1986a) reported that 2,7-DCDD, which lacks affinity for the AhR, was equipotent with TCDD in suppressing the in vitro response.

Davis and Safe (1991) directly compared the in vitro structure-immunotoxicity relationships for a series of PHAH congeners that show >14,900-fold difference in in vivo immunotoxic potency. Results of these studies indicated that all of the congeners were equipotent in vitro and produced a similar concentration-dependent suppression of the in vitro anti-SRBC response using cells from either B6 or D2 mice. Coexposure to the AhR antagonist α-napthoflavone antagonized the immunosuppression induced by either TCDD or 1,3,6,8-TCDF (a weak AhR agonist). Collectively, these results suggested a mechanism of suppression in vitro that was independent of the AhR.

Morris et al. (1991) demonstrated that suppression of the in vitro antibody response to SRBC by TCDD was critically dependent on the type and concentration of the serum used in the in vitro culture. When splenocytes were cultured in the presence of normal mouse serum (NMS), the profile of activity was dependent on the genotype (i.e., Ah^{bb} or Ah^{dd}) of the lymphocytes rather than the source of NMS (Morris et al., 1994). These results are important, because they may help to explain the variable effects observed by different laboratories performing in vitro TCDD-antibody response assays.

The majority of evidence indicates that immunotoxicity of PHAHs is AhR mediated. This evidence comes primarily from the in vivo mouse data described above. Recent studies also indicate that murine T lymphocytes and leukocytes express the Ah receptor (Lawrence et al., 1996; Williams et al., 1996). A complete understanding of the role of the AhR in murine leukocytes and PHAH-mediated immunotoxicity, however, requires further study. Although other data suggest that non-AhR mechanisms may have some role in TCDD-induced immunotoxicity, further studies are required to provide definitive evidence for this mechanism. Studies employing novel approaches -such as the development and use of variant lymphoma cells that express variable levels of the AhR (e.g., hepatoma cells [Miller et al., 1983; Karenlampi et al., 1988]), the use of AhR knockout mice (Fernandez-Salguero et al., 1995; Gonzalez et al.,

1995), or the use of pure binding antagonists (Lu et al., 1995, 1996), would help to provide such evidence.

4.3. SENSITIVE TARGETS FOR PHAH IMMUNOTOXICITY

Despite considerable investigation, the cells that are most sensitive to alteration by PHAH exposure leading to suppressed immune function have not been unequivocally identified. The in vivo immunotoxicity of TCDD, expressed in terms of suppression of the anti-SRBC response of B6 or B6C3F_1 mice, is highly reproducible between laboratories. Because the magnitude of the anti-SRBC response depends on the concerted interactions of antigen-presenting cells (APCs), regulatory T cells (helper and suppressor), and B cells, this response has been used most widely to evaluate target cell sensitivity to PHAHs. In addition, the CTL response has served as a model for evaluating PHAH-induced suppression of T cell function. These immune responses can be modulated by nonimmunological factors, including hormonal and nutritional variables, and PHAHs are known to affect endocrine and metabolic functions. These indirect effects will be apparent only in in vivo studies, whereas direct effects on APC and lymphocyte functions would be evident following in vitro exposure to PHAHs.

One potentially important indirect mechanism is through effects on the endocrine system, because the activity of several endocrine hormones (e.g., glucocorticoids, sex steroids, thyroxine, growth hormone, and prolactin) that regulate immune responses have been shown to be altered by TCDD and other PHAHs (see Chapter 3, Acute, Subchronic and Chronic Toxicity and Chapter 5, Developmental and Reproductive Toxicity). Consequently, studies have been performed to examine the possible role of PHAH-induced indirect effects on the immune systems of rodents.

Kerkvliet et al. (1990b) reported that exposure of mice to 3,4,5,3′,4′,5′-HxCB (PCB169)followed by injection of P815 allogeneic tumor cells induced a dose-dependent elevation of serum corticosterone concentrations that correlated with the dose-dependent suppression of the anti-P815 CTL response. However, because adrenalectomy or treatment with the glucocorticoid receptor antagonist RU38486 failed to protect mice from the immunosuppressive effect of PCB169 (DeKrey et al., 1993), a role for the elevated CS in the suppression of the CTL response seems unlikely. Adrenalectomy and hypophysectomy also failed to prevent TCDD-induced thymic atrophy in rats (van Logten et al., 1980).

In other studies using the P815 allogeneic tumor model, Kerkvliet and Baecher-Steppan (1988a) reported that male mice were more sensitive than female mice to suppression of the CTL response by PCB169. Castration of male mice partially ameliorated the immunosuppressive effects of HxCB (DeKrey et al., 1993), suggesting a role for testosterone in suppression of this response. Male mice were found to be more sensitive than female mice to PCB169-induced

reductions in serum prolactin levels (DeKrey et al., 1994). However, it was concluded that PCB169-induced hypoprolactinemia was not responsible for CTL suppression in mice, because bromocryptine, which severely suppressed serum prolactin levels, failed to alter CTL activity.

Pazdernik and Rozman (1985) suggested that thyroid hormones may play a role in TCDD immunotoxicity based on the finding that radiothyroidectomy prevented the suppression of the anti-SRBC response in rats treated with TCDD. However, because thyroidectomy alone suppressed immune function, the significance of the findings requires further study. Taken together, the current data do not provide convincing evidence supporting a role for hormones in PHAH-induced indirect mechanisms of immunosuppression.

Kerkvliet and Brauner (1987) compared the sensitivity of antibody responses to antigens that differ in their requirements for APC and T cells as an in vivo approach to evaluate the cellular targets of 1,2,3,4,6,7,8-HpCDD humoral immunotoxicity. The TI antigens, DNP-Ficoll and TNP-LPS, were used in these studies. These TI antigens differ from each other in their requirement for APC (higher for DNP-Ficoll) and their sensitivity to regulatory (amplifier and suppressor) T cell influence (DNP-Ficoll is sensitive, TNP-LPS is not) (Braley-Mullen, 1982). Obviously, all antibody responses require B cell differentiation into antibody-secreting plasma cells. Although HpCDD produced dose-dependent suppression of the antibody response to all three antigens, sensitivity to suppression directly correlated with the sensitivity of the response to T cell regulation. The ID_{50}s were 53, 127, and 516 µg/kg for SRBC, DNP-Ficoll, and TNP-LPS, respectively. These results were interpreted as follows: If one assumes that B cell function is targeted in the TNP-LPS response, then regulatory T cells and/or APC may represent the more sensitive target in the SRBC and DNP-Ficoll responses. The difference in sensitivity between the SRBC and DNP-Ficoll responses suggests that the T helper cell may be a particularly sensitive target. The differential sensitivity of the antibody responses to TNP-LPS versus SRBC has been corroborated in TCDD-treated mice (House et al., 1990; Kerkvliet et al., 1990a). Thus, the in vivo sensitivity of the antibody response to SRBC, described in these studies, appears to depend on the T cell and/or APC components of the response rather than the B cell, unless the B cells that respond to SRBC are different from the B cells that respond to TNP-LPS. Currently, evidence for such a difference is lacking.

These in vivo results differ from the ex vivo data of Dooley and Holsapple (1988). Using in vitro immunization with SRBC, DNP-Ficoll or LPS of separated and reconstituted splenic T cells, B cells, and adherent cells from vehicle- and TCDD-treated mice, they reported that B cells from TCDD-treated mice were functionally compromised in in vitro antibody responses but T cells and macrophages were not. These ex vivo results corroborated an earlier study in which TCDD suppressed the in vitro antibody response to these same antigens in a dose-related manner and at comparable concentrations (Holsapple et al., 1986a). Taken together, these ex vivo data

suggested that the B cell is the primary target for the direct effects of TCDD, because the antigens employed differ in their dependence on T cells and accessory cells (Holsapple, 1995).

The basis for the different responses to TI antigens in these studies has not been established. However, it has been suggested for the ex vivo work that the effects of TCDD on T cells may be indirectly induced following antigen exposure such that removal of the cells from the TCDD environment of the host prior to antigen challenge would preclude detection of T cell dysfunction (Kerkvliet and Burleson, 1994). This interpretation is supported by the findings of Tomar and Kerkvliet (1991) that spleen cells taken from TCDD-treated mice were not compromised in their ability to reconstitute the antibody response of lethally irradiated mice, and the reported lack of direct effects of TCDD and other PHAHs on T cells in vitro (Clark et al., 1981; Kerkvliet and Baecher-Steppan, 1988a, b).

Although the direct effects of TCDD on T cells in vitro have not been demonstrated, it is clear that functional T cell responses generated in vivo are compromised following in vivo exposure. Nude mice that are congenitally T cell deficient were significantly less sensitive to HpCDD-induced immunotoxicity when compared with their T cell–competent littermates (Kerkvliet and Brauner, 1987). Likewise, exposure to TCDD or PCB169 suppressed the development of CTL activity following alloantigen challenge (Kerkvliet et al., 1990b). The influence of TCDD exposure on regulatory T cell functions has been addressed in several studies. Clark et al. (1981) first proposed that T suppressor cells were induced by TCDD in the thymus that were responsible for the suppressed CTL response. However, increased suppressor cell activity in peripheral lymphoid tissue was not observed in mice exposed to TCDD (Dooley et al., 1990) or PCB169 (Kerkvliet and Baecher-Steppan, 1988b). In terms of T helper cell activity, Tomar and Kerkvliet (1991) reported that a dose of 5 μg/kg TCDD suppressed the in vivo generation of carrier-specific T helper cells. Lundberg et al. (1990) reported that thymocytes from B6 mice treated with TCDD (50 μg/kg) were less capable of providing help for an in vitro anti-SRBC response. However, Clark et al. (1983) reported in ex vivo studies that T cells from TCDD-treated mice produced normal levels of interleukin-2 (IL-2). A study using the P815 tumor allograft model suggests that TCDD alters early $CD4^+$ T cell activation events, which lead to premature termination of cytokine production by $CD8^+$ T cells, suppression of CTL activity, and suppression of alloantibγody production by B cells (Kerkvliet et al., 1996). Tumor necrosis factor (TNF), IL-2, and interferon γ (IFNγ) were suppressed in P815-injected mice exposed to TCDD. In contrast, TNF and IL-2 were not affected and IFNγ was reduced in anti-CD3 injected mice exposed to TCDD (Prell et al., 1995). These results suggest that the effects of TCDD on cytokine production may be determined by the inducing stimulus.

The influence of TCDD exposure on B cell function has been addressed primarily in in vitro studies, but direct effects of PHAHs on macrophages and T cells in vitro have not been

described. The issue of TCDD effects on B cells is difficult to address in vivo given that most B cell responses (except perhaps anti-LPS responses) depend on interactions with T cells and macrophages. In vitro studies have described the direct effects of TCDD on activation and differentiation of purified B cells (Holsapple et al., 1986a; Luster et al., 1988; Morris et al., 1991; Karras and Holsapple, 1994a, b; Karras et al., 1995). These studies suggest that TCDD inhibits terminal differentiation of B cells via alteration of an early activation event (Luster et al., 1988; Karras and Holsapple, 1994b). Increased phosphorylation and tyrosine kinase activity in TCDD-treated B cells may underlie this B cell dysfunction (Kramer et al., 1987; Clark et al., 1991a). Also, Karras and Holsapple (1994a) suggest that the antiproliferative effect of TCDD on B cells is due to inhibition of calcium-dependent activation; this inhibition results in suppression of B cell surface Ig-induced antibody production (Karras et al., 1996).

Macrophage functions have also been examined following TCDD exposure and generally found to be resistant to suppression by TCDD when assessed ex vivo. Macrophage-mediated phagocytosis, macrophage-mediated tumor cell cytolysis or cytostasis, oxidative reactions of neutrophils and macrophages, and spontaneous natural killer (NK) cell activity were not suppressed following TCDD exposure, with doses as high as 30 μg/kg failing to suppress NK and macrophage functions (Vos et al., 1978; Mantovani et al., 1980). More recent studies, however, indicate that virus-augmented pulmonary NK activity, but not spontaneous pulmonary NK activity, is suppressed by TCDD (Yang et al., 1994). Phorbol ester–activated antitumor cytolytic and cytostatic activity of neutrophils is also selectively inhibited by TCDD (Ackermann et al., 1989).

On the other hand, it is interesting to note that the pathology associated with TCDD toxicity often includes neutrophilia and an inflammatory response in liver and skin characterized by activated macrophage and neutrophil accumulation (Vos et al., 1973; Weissberg and Zinkl, 1973; Vos et al., 1974; Puhvel and Sakamoto, 1988; Herbert et al., 1990). Although these observations may reflect a normal inflammatory response to tissue injury, some experimental evidence suggests that inflammatory cells may be activated by TCDD exposure. For example, Alsharif et al. (1994) reported that TCDD increased superoxide anion production in rat peritoneal macrophages. In addition, it has been shown that TCDD exposure results in an enhanced inflammatory response following SRBC challenge (Kerkvliet and Oughton, 1993). This effect of TCDD was characterized by a twofold to fourfold increase in the number of neutrophils and macrophages locally infiltrating the intraperitoneal site of SRBC injection. However, the kinetics of the cellular influx were not altered by TCDD. Likewise, the expression of macrophage activation markers (I-A and F4/80) and the antigen-presenting function of the peritoneal exudate cells were unaltered by TCDD. Using specific inhibitors of the proinflammatory cytokines TNF and IL-1 (Moos et al., 1994) found that the TCDD-induced

hyperinflammatory response was mediated by TNF . However, although exogenous TNF suppressed the antibody response to SRBC, the increased inflammatory response and suppression of the response to SRBC were not apparently linked, because coincident treatment with the soluble TNF receptor rhuTNFR:Fc, which blocks TNF activity, further suppressed rather than normalized the immunosuppression by TCDD alone (Moos and Kerkvliet, 1995). Thus, the relationship, if any, between the inflammatory and immune effects of TCDD remains to be elucidated.

Evidence also suggests that the long-recognized hypersusceptibility of TCDD- and PCB-treated animals to endotoxin (LPS) (Thomas and Hinsdill, 1978, 1979; Vos et al., 1978; Loose et al., 1979) may be related to an increased production of proinflammatory factors. TNF production may be responsible for endotoxin hypersensitivity in TCDD-treated mice and that the Ah locus mediates this response (Clark et al., 1991b; Taylor et al., 1992). The ability of methylprednisolone to reverse the mortality associated with TCDD/LPS treatment is also consistent with an inflammatory response (Rosenthal et al., 1989). Similarly, increased inflammatory mediator production may underlie the enhanced rat paw edema response to carrageenan and dextran in TCDD-treated rats (Theobald et al., 1983; Katz et al., 1984). Whereas serum complement activity has been reported to be suppressed in dioxin-treated mice (White et al., 1986), enhanced activity was reported at the lowest exposure level when 1,2,3,6,7,8-HxCDD was tested. Work by Sutter et al. (1991) indicates that IL-1β gene expression, as well as plasminogen activator inhibitor-2, in keratinocytes is elevated by TCDD. On the other hand, House et al. (1990) reported that inflammatory macrophages obtained from TCDD-treated mice produced control levels of IL-1 when examined ex vivo. Thus, the effect of TCDD on inflammatory mediator production may be a "priming effect" and require coexposure to antigen or LPS. The influence of TCDD on inflammatory mediator production and action is an important area for further study.

Since the rapid influx of phagocytic cells to the site of pathogen invasion is an important factor in host resistance to infection, the ability of TCDD to augment the production of inflammatory chemoattractive mediators would imply that TCDD exposure could result in enhanced host resistance. However, because TCDD exposure is, at the same time, immunosuppressive, which results in decreased specific immune responses generated by T and B lymphocytes, the overall impact of TCDD exposure on disease susceptibility will likely vary depending on the nature of the pathogen and the major mode of host response to the specific infectious agent. Such effects may in fact help explain the disparate effects of TCDD in different host resistance models that are described below.

Taken together, it is obvious that multiple targets exist for PHAH-induced immunosuppression, including both T and B lymphocytes. Lymphocyte precursor cells as well

as lymphoid-associated tissue such as thymus epithelium and bone marrow stromal elements are also affected by dioxins (discussed later in the chapter). The class or subclass of T or B lymphocytes that is the proximate target for PHAH-induced immunosuppression remains to be determined, as do the mechanisms by which immunosuppression by these chemicals is achieved.

4.4. INFLUENCE OF TCDD ON HOST RESISTANCE TO DISEASE

The ability of an animal to resist and/or control viral, bacterial, parasitic, and neoplastic diseases is determined by both nonspecific and specific immunological functions. Decreased functional activity in any immunological compartment may result in increased susceptibility to infectious and neoplastic diseases. Animal host resistance models that mimic human disease are available and have been used to assess the effect of TCDD on altered host resistance.

TCDD exposure increases susceptibility to challenge with the gram-negative bacterium *Salmonella*. TCDD was given per os at 0.5 to 20 μg/kg once a week for 4 weeks to male 4-week-old C57Bl/6Jfh (J67) mice and challenged 2 days after the fourth dose (when mice were 8 weeks old) with either *Salmonella bern* or *Herpesvirus suis* (also known as pseudorabies virus). Results with *S. bern* indicated increased mortality at 1 μg TCDD/kg (total dose of 4 μg/kg) and reduced time to death after bacterial challenge with 5 μg TCDD/kg (total dose of 20 μg/kg). In contrast, the same doses of TCDD did not alter the time to death or the incidence of mortality following *Herpesvirus suis* infection (Thigpen et al., 1975). A TCDD feeding study by Hinsdill et al. (1980) also demonstrated increased susceptibility of 7-week-old Swiss Webster outbred female mice to *S. typhimurium* var. *copenhagen*. Mice were fed control feed or feed containing 10, 50, or 100 ppb TCDD for 8 weeks, after which they were injected intravenously with $10^{3.5}$ *S. typhimurium* var. *copenhagen*. Results indicated that 50 and 100 ppb TCDD increased mortality from *Salmonella* and shortened the time to death, whereas 10 ppb caused an increased bacteremia.

Vos et al. (1978) reported that TCDD resulted in increased sensitivity to endotoxin (*E. coli* O 127:B 8 lipopolysaccharide) and suggested that the increased susceptibility to *Salmonella* caused by TCDD might be caused by the endotoxin of this gram-negative bacterium. Vos et al. demonstrated reduced resistance to endotoxin with a single oral dose of 100 μg TCDD/kg using 3- to 4-week-old outbred female mice and challenged with endotoxin 5 days later. Vos et al. also reported enhanced mortality from intravenous injection of endotoxin 2 days after the final oral dose of TCDD (1.5, 5, 15, or 50 μg/kg, once a week for 4 weeks) in 3- to 4-week-old male outbred Swiss mice. These studies indicate a reduced resistance to endotoxin after single or multiple doses of TCDD. Thomas and Hinsdill (1979), using *S. typhimurium* lipopolysaccharide, demonstrated a reduced resistance to endotoxin in the offspring of female Swiss Webster mice fed TCDD prior to mating, during gestation, and between parturition and weaning. Rosenthal et

al. (1989) used female B6C3F_1, DBA/2, as well as congenic mice to demonstrate that acute doses of 50, 100, or 200 μg/kg TCDD per os increased endotoxin-induced mortality in B6C3F_1 mice, which was associated with hepatotoxicity and decreased clearance of the endotoxin. D2 and Ah^{dd} congenic mice were relatively resistant to this effect, implicating AhR-dependent mechanisms in endotoxin hypersensitivity.

White et al. (1986) reported that *Streptococcus pneumoniae*, a gram-positive bacterium that does not contain endotoxin, caused increased mortality in 5- to 6-week-old female B6C3F_1 mice after subchronic oral administration of TCDD (1 μg/kg for 14 days) and challenged with *S. pneumoniae* intraperitoneally 1 day after the last treatment. The 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (HCDD) isomer also resulted in a dose-dependent increase in susceptibility to *S. pneumoniae*.

Enhanced susceptibility to viral disease has also been reported after TCDD administration. Clark et al. (1983) injected TCDD intraperitoneally once a week for 4 weeks and challenged mice 7 to 22 days later with *Herpes simplex* type II strain 33 virus. Mice receiving TCDD at 0.04, 0.4, or 4.0 μg/kg weekly (total dose of 160, 1,600, and 16,000 ng/kg) all had significantly enhanced mortality to Herpesvirus type II infection. House et al. (1990) also reported an enhanced susceptibility to viral infection following low-level singledose TCDD administration intraperitoneally. B6C3F_1 female mice, 6 to 8 weeks of age, were challenged with influenza A/Taiwan/1/64 (H2N2) virus 7 to 10 days following TCDD. TCDD administration at 10, 1.0, or 0.1 μg/kg decreased resistance to virus. The lowest observable effect level was 0.1 μg/kg, making this one of the most sensitive endpoints for TCDD immunotoxicity. However, the only immune parameter suppressed by TCDD, which is related to host resistance to this virus, was the serum hemagglutination antibody titers to influenza. Unfortunately, only mice dosed at 10 μg/kg TCDD were evaluated for these virus-specific antibodies. No alterations in macrophage function, NK cell activity, or interferon levels were observed in TCDD-exposed mice (House et al., 1990).

Recently, the sensitivity of TCDD-exposed mice to influenza virus challenge was corroborated by Burleson et al. (1996), who observed enhanced mortality to influenza A/Hong Kong/8/68 (H3N2) virus following a single exposure to 0.1, 0.05, or 0.01 μg/kg TCDD. Increased mortality at 0.01 μg/kg TCDD was the lowest observable effect level and as such represents the most sensitive adverse effect level yet reported for TCDD (Burleson et al., 1996). However, the role of TCDD in altering immune-mediated mechanisms important in resistance to this virus remains to be elucidated. Furthermore, because increased mortality was not correlated with increased virus titers in the lungs of mice, and TCDD did not alter the expected virus-enhanced increase in lung:body weight ratio nor the virus-induced decrease in thymus weight, other nonimmune virus-mediated physiological changes may be involved in this increased

mortality. Further studies are warranted to confirm this very low level, TCDD-induced effect and to delineate the underlying mechanisms responsible for this altered host resistance.

Rats exposed to TCDD daily for 14 days at a total dose of 10 μg/kg had significantly augmented rat-adapted influenza virus replication in the lungs (Yang et al., 1994). The increased virus replication was correlated with a significant suppression of virus-augmented but not spontaneous pulmonary NK cell activity, suggesting that reduced NK activity may be at least in part related to enhanced susceptibility of rats to influenza virus (Yang et al., 1994).

TCDD exposure has also been shown to result in more severe infections from parasites. Tucker et al. (1986) studied the effects of TCDD administration on *Plasmodium yoelii* 17 XNL, a nonlethal strain of malaria, in 6- to 8-week-old $B6C3F_1$ female mice. A single dose of TCDD at 5 μg/kg or 10 μg/kg per os resulted in increased susceptibility to *P. yoelii*. The peak parasitemia was greater and of longer duration in TCDD-treated animals than in controls, the difference being significant at 5 μg/kg on day 10 and at 10 μg/kg on days 12 and 14. A single dose of TCDD at 10 or 30 μg/kg intraperitoneally 7 days prior to infection of $B6C3F_1$ mice with *Trichinella spiralis* resulted in delayed onset of adult parasite elimination, and at 1.0 μg/kg TCDD suppressed the proliferative response of splenocyte and mesenteric lymph node cells stimulated with *T. spiralis* antigen (Luebke et al., 1994). Tissue levels of TCDD were also higher in infected versus noninfected mice in this study. In a separate study, TCDD at 1, 10, or 30 μg/kg administered intraperitoneally 7 days prior to infection of Fischer 344 rats with *T. spiralis* did not affect adult parasite elimination or the numbers of encysted larvae in muscle. Furthermore, proliferative responses of lymphocytes from rats dosed at 30 μg/kg and stimulated with parasite antigen were enhanced in contrast to the suppression observed in $B6C3F_1$ mice (Luebke et al., 1995). The different responses observed in mice versus rats for this host resistance model are similar to those reported by Smialowicz et al. (1994) for the antibody response to SRBCs, in that the latter response was suppressed in mice and enhanced in rats. In a recent study, aged (76-week-old) rats exposed to TCDD and infected with *T. spiralis*, were less able to limit the burden of encysted larvae, compared to young (10-week-old) rats (Luebke et al. 1999). These results suggest that TCDD may exacerbate the age-related decreased resistance to this parasite.

Luster et al. (1980a) demonstrated enhanced growth of transplanted tumors in mice treated with TCDD at doses of 1.0 or 5.0 μg/kg in $B6C3F_1$ mice. Dams were given TCDD by gavage at day 14 of gestation and again on days 1, 7, and 14 following birth; host resistance studies were performed 6 to 8 weeks after weaning. This exposure protocol resulted in an increased incidence of PYB6 tumors in pups from dams receiving repeated doses of 1.0, but not 5.0, μg TCDD/kg.

Although it is clear that TCDD adversely affects numerous host resistance models detailed above, the effects of TCDD on susceptibility to *Listeria monocytogenes* infections are ambiguous. The disparate results may reflect different study designs, including dose, route, single versus multiple administrations, mouse strain, age, or sex. However, it is clear that TCDD, under certain conditions, results in increased susceptibility to *Listeria*. Hinsdill et al. (1980) reported the increased susceptibility of 7-week-old Swiss Webster outbred female mice to *Listeria*. Mice were fed control feed or feed containing 10 or 50 ppb TCDD for 8 weeks, after which they were injected intravenously with 10^5 *Listeria*. Results indicated that the 50 ppb diet increased bacteremia and mortality. Luster et al. (1980b) used doses of 1.0 or 5.0 μg TCDD/kg in $B6C3F_1$ mice. Dams were given TCDD by gavage at day 14 of gestation and again on days 1, 7, and 14 following birth, and host resistance studies were performed 6 to 8 weeks after weaning. This exposure protocol resulted in an increased susceptibility to *Listeria* in pups from dams receiving repeated doses of 5.0 μg TCDD/kg. However, Vos et al. (1978) reported that oral administration of 50 μg TCDD/kg once a week for 4 weeks to 3- to 4-week-old male Swiss mice followed by intravenous challenge 4 days after the last dose with *Listeria* had no effect on nonspecific phagocytosis and killing of *Listeria*. House et al. (1990) used $B6C3F_1$ female mice, 6 to 8 weeks of age and challenged intravenously with *Listeria* 7 to 10 days following a single dose of TCDD at 10, 1.0, and 0.1 μg/kg. TCDD did not enhance mortality from *Listeria*.

In summary, results from host resistance studies provide evidence that under certain conditions exposure to TCDD results in increased morbidity and mortality for bacterial, viral, parasitic, and neoplastic disease. These effects are observed at relatively low doses and likely result from TCDD-induced suppression of immunological function. However, the specific immunological functions targeted by TCDD in each of the host resistance models remain to be fully defined. Possible nonimmunological mechanisms, which may also contribute to altered host resistance by PHAHs, should also be investigated. Future work should also address the role of the AhR in host resistance.

4.5. ROLE OF THE THYMUS IN PHAH IMMUNOTOXICITY

Thymic involution is one of the hallmarks of exposure to TCDD and related PHAHs in all species examined. In mice, thymic involution occurs by an AhR-dependent mechanism. Poland and Knutson (1982) demonstrated that C57Bl/6 mice were 10-fold more sensitive to TCDD-induced thymic atrophy than DBA/2 mice. Because the thymus has a critical role in the ontogeny of T lymphocytes, thymic involution is often referred to as an immunotoxic effect. However, although an intact thymus is crucial to the developing immune system during the prenatal and early postnatal period of rodents as well as during the prenatal period of humans, the physiological role played by the thymus in adult life has not been established. In animal models,

adult thymectomy has little effect on the quantity or quality of T lymphocytes, which have already matured and populated the secondary lymphoid organs (Benjamini and Leskowitz, 1991). Likewise, in humans, childhood and adult thymectomy produces no clearly identifiable adverse consequences in terms of altered immune function, although some might argue that such studies have not been done. On the basis of this knowledge, it is not surprising that a direct relationship between the effects of TCDD on the thymus and immune suppression has not been established in studies using adult animals. In fact, adult thymectomy prior to PHAH exposure did not modify TCDD- or HpCDD-induced suppression of the anti-SRBC response (Tucker et al., 1986; Kerkvliet and Brauner, 1987). Furthermore, suppression of immune responses occurs at dose levels of PHAH significantly lower than those required to induce thymic atrophy (Vos et al., 1978; Silkworth and Antrim, 1985; Holsapple et al., 1986b; Tucker et al., 1986; Kerkvliet and Brauner, 1990). Thus, thymic involution does not represent a surrogate marker for TCDD immunotoxicity in adult animals. On the other hand, it is possible that chronic exposure to TCDD resulting in chronic thymic atrophy may produce more delayed, subtle effects on immune function not yet identified (Clarke and MacLennan, 1986).

In contrast to adult animals, congenital thymic aplasia or neonatal thymectomy results in severe reduction in the number and function of T lymphocytes and produces a potentially lethal wasting disease (Benjamini and Leskowitz, 1991). Similarly, there is evidence from studies that rodents exposed to TCDD or PCBs during the prenatal or neonatal period are more sensitive to immune suppression compared with rodents exposed as adults and that the prenatal effects are more selective for cell-mediated immunity (Vos and Moore, 1974; Faith and Moore, 1977; Luster et al., 1980b). Perinatal exposure of mice and rats to TCDD alters thymocyte differentiation and maturation in vivo (Holladay et al., 1991; Blaylock et al., 1992; Gehrs and Smialowicz, 1997, 1999; Gehrs et al., 1997).

TCDD has also been shown to alter thymocyte maturation in vitro by inducing terminal differentiation of thymic epithelial cells (Greenlee et al., 1985; Cook et al., 1987). Addition of TCDD to fetal thymic organ cultures (FTOCs) also alters thymocyte maturation (Dencker et al., 1985; d'Argy et al., 1989). 3,3',4,4'-Tetrachlorobiphenyl (PCB77) has also been found to alter the normal developmental pathways of fetal thymocytes in vitro (Esser and Welzel, 1993; Kremer et al., 1994). In mouse FTOCs the addition of TCDD or PCB77 resulted in an overall reduction in thymocytes but a significant increase in mature $CD4^{-}CD8^{+}$ thymocytes which were $CD3^{+}$,$\alpha\beta TCR^{+}$,$CD69^{+}$,HSA^{-},$IL\text{-}2R^{-}$ (Esser and Welzel, 1993; Kremer et al., 1995). These mature $CD8^{+}$ thymocytes were functionally competent, in that they responded to stimulation by Con A or anti-CD3 and possessed cytotoxic activity when cultured with H-2 allogeneic spleen cells (Lai, et al., 1995). Data from experiments using FTOC recultivation techniques, in which intact thymic lobes and thymocyte-depleted (i.e., stroma) lobes were employed, suggested that TCDD drives

thymocytes into differentiation faster than the precursor pool can be replenished by self-renewal (Kremer et al., 1994). Because TCDD affected thymic stroma but did not directly affect thymocytes, the findings of Kremer et al. (1994) suggest that the nonlymphoid compartment (i.e. stroma) rather than the thymocytes themselves may be the target of these PHAHs.

Work by Silverstone et al. (1994a) indicates that TCDD-induced thymic atrophy can be mediated, at least in part, by damage to prethymic T cell precursor stem cells in both bone marrow and liver. Perinatal exposure of mice to TCDD resulted in alteration in the lymphocyte stem cell population, as indicated by a significant reduction in the lymphocyte stem cell–specific enzyme terminal deoxynucleotidyl transferase (TdT) in fetal liver and neonatal bone marrow lymphoid cells (Fine et al., 1989). In contrast, thymic TdT synthesis was relatively unaffected on a per cell basis by perinatal TCDD exposure. TCDD also inhibited the ability of pre-T stem cells (prothymocytes), from both fetal livers and neonatal bone marrow, to repopulate the thymus of irradiated syngeneic mice (Fine et al., 1990). TCDD-induced thymic atrophy did not involve apoptotic mechanisms in thymocytes affected by the bcl-2 proto-oncogene, and this atrophy appears to be mediated through the AhR and not through effects on the estrogen receptor (Silverstone et al., 1994a, b; Frazier et al., 1994).

Thymic alterations in adult mice exposed to TCDD appear to depend on AhR activation in hemopoietic cells. Using chimeric mice with TCDD-responsive (AhR[+/+]) stromal components and TCDD-unresponsive (AhR[-/-]) hematopoietic components, or the reverse, Staples et al. (1998a) demonstrated that the hemopoietic compartment is the target of TCDD-induced thymic atrophy and thymic phenotype alterations. The mechanisms underlying these alterations are not clear, although TCDD-induced apoptosis of thymocytes, via Fas-Fas ligand interactions, has been reported (Kamath et al., 1997, 1999). However, other evidence indicates that apoptosis is not a key mechanism of TCDD-induced thymic atrophy (Staples et al. 1998b)

Taken together, the data indicate that PHAHs induce alterations of T cell maturation in the thymus. These are mediated in part by effects on accessory cells and on extra-thymic precursor cells. In addition, TCDD also influences B cell development in the bursa of chick embryos (Nikolaidis et al., 1990), as well as lymphocyte stem cells in the fetal liver and bone marrow of mice (Fine et al., 1989, 1990). Such alterations may have an important role in the observed suppression of immune function by PHAHs in perinatally exposed animals.

4.6. IMMUNOTOXICITY FOLLOWING PRENATAL/NEONATAL EXPOSURE TO PHAHS

The reported increase in susceptibility of very young animals to PHAH immunotoxicity necessitates close examination of the available literature on prenatal or neonatal immunotoxic effects. Several studies have examined immune function in mice, rats, and guinea pigs following

exposure to TCDD or PCB during fetal development (Vos et al., 1973; Vos and Moore, 1974; Thomas and Hinsdill, 1979; Luster et al., 1980b).

Results of work in which exposure of the progeny occurred via placental transfer and lactation are summarized in Table 4-3. Study 1 presents results of two studies, one using B6 (Vos and Moore, 1974) and the other $B6C3F_1$ mice (Luster et al., 1980a); study 2 presents results of outbred Swiss mice (Thomas and Hinsdill,1979); and study 3 presents results from two studies of rats (Vos and Moore, 1974; Faith and Moore, 1977). The most sensitive indicator of TCDD immunotoxicity in these studies was an increase in the growth of transplanted tumor cells in the offspring of $B6C3F_1$ mice (Ah responsive strain) treated with 1 μg/kg TCDD at 4 weekly intervals. (Total TCDD dose to dam was 4 μg/kg; dose to offspring was not determined.) The offspring of Swiss mice fed a diet containing 1 ppb TCDD for 7 weeks showed enhanced mortality following endotoxin challenge, while the plaque-forming cell response to SRBCs and delayed hypersensitivity response were suppressed in offspring of mice fed 5.0-ppb TCDD diets. (Estimated daily dose to 20 g dam consuming 5 g of 5-ppb TCDD diet is equivalent to 1.25 μg/kg TCDD/day.) Rats appeared to be relatively more resistant to the immunotoxic effects of prenatal or neonatal exposure to TCDD than mice based on the finding that 5, but not 1, μg/kg TCDD given four times at weekly intervals produced immunotoxicity in the offspring. Immunotoxic end points that were unaffected by the highest exposure levels in these studies included blastogenesis induced by LPS and serum antibody titers to bovine gamma globulin (BGG). However, a significant finding of this study was that suppression of the DTH response to oxazalone was relatively long lived in that suppression of this response was evident in 145-day-old rats. Taken together, these studies suggest that cell-mediated rather than humoral immunity is more sensitive to perinatal TCDD exposure.

Two later studies examined immune function in offspring of female mice, in the first study exposed to TCDD (Holladay et al., 1991) and in the second study to PCBs (Kanechlor 500) (Takagi et al., 1987), with the offspring cross-fostered to unexposed lactating mice at birth. Thus, exposure was limited to placental exposure. B6 mice exposed to 3.0 μg/kg TCDD on gestational days 6 to 14 gave birth to offspring that had significant thymic atrophy and hypoplasia measured on gestational day 18 or on day 6 postnatally. The thymic effects were no longer apparent by day 14. At 7 to 8 weeks postnatally, mitogen responses and antibody plaque-forming cell response to SRBCs were unaltered, but the CTL response was significantly suppressed compared with controls (Holladay et al., 1991). These results suggest a selectivity of prenatal TCDD on the CTL and not the T helper cells involved in the antibody response to SRBCs. In contrast to these results, Takagi et al. (1987) exposed female C3H mice per os to 50 mg/kg Kanechlor 500 twice per week for 4 weeks, at which time steady-state tissue levels were noted. The offspring derived from mating to unexposed males had an unaltered antibody response to the

T-independent antigen DNP-dextran. On the other hand, carrier-primed T helper cell activity assessed by adoptive transfer was significantly suppressed by PCB exposure when assessed 4 and 7 weeks after birth but fully recovered by 11 weeks. Together, these studies confirm prior studies to indicate that T cell function is selectively altered by PHAH when exposure is prenatal. Although both T helper cells and CTL show altered function, T helper cell activity may recover faster than CTL function.

Fine et al. (1990) reported on TCDD levels in mouse offspring following maternal treatment with TCDD (10 μg/kg) on gestational day 14. The fetal liver had the highest concentration on gestational day 18 (235 fg/mg), which declined slightly by postnatal day 6 to around 100 fg/mg. Concentration of TCDD in the thymus on gestational day 18 was 140 fg/mg, which declined to 20 fg/mg on day 6 after birth. (These thymic TCDD concentrations are equivalent to 60 to 425 pM, assuming 1 kg of tissue is equivalent to 1 L of water.) TCDD concentrations in the spleen remained constant at about 40 fg/mg during the same timeframe, whereas bone marrow concentrations were very low (about 3 fg/mg). These concentrations of TCDD were associated with thymic atrophy (Fine et al., 1989) and significant reduction in the ability of prothymocytes in liver and bone marrow to repopulate an irradiated thymus (Fine et al., 1990).

Recent studies in rats indicate that perinatal exposure to TCDD results in relatively long-lived and persistent suppression of immune responses. Lactating female Leeds rats were exposed to TCDD in their feed, starting on postnatal day 1 through 18, at 0.1, 0.5, or 2.5 μg TCDD/kg, with an estimated total TCDD consumption of 0.2, 1.0, or 5.0 μg/kg/body weight, respectively (Badesha et al., 1995). Both T cell–dependent (i.e., SRBC) and T cell–independent (i.e., DNP-Ficoll, TNP-LPS, and LPS) antibody responses were suppressed in a dose-related manner in 130-day-old offspring.

In another group of studies, a single oral exposure of pregnant Fischer 344 dams on GD-14 to 0.1, 0.3, 1.0, or 3.0 μg TCDD/kg resulted in suppression of the DTH response to BSA (Gehrs et al., 1997; Gehrs and Smialowicz, 1999). Depressed DTH responses persisted for up to 19 months in the male offspring of dams exposed to 3.0 μg TCDD/kg. While both male and female offspring exposed to TCDD on GD-14 displayed reduced DTH responses, the DTH response of males appears to be more affected than that of females. A cross-fostering study indicated that both gestational and lactation exposure of the offspring are required for suppression of the DTH response following gestational day 14 exposure of the dams (Gehrs et al., 1997). A single low dose (0.1 μg/kg) of TCDD given to dams on gestational day 14 resulted in suppression of the DTH response that persists in the offspring for up to age 14 months (Gehrs and Smialowicz, 1999). These results suggest that perinatal exposure to TCDD may lead to a permanent defect in the immune defenses associated with the DTH response, which are critical

for protection against certain intracellular bacterial and parasitic infections as well as certain viruses. If so, then the fetus and neonate may be more at risk for TCDD-induced immune perturbation, which may manifest, early or later in life, as susceptibility to certain infectious diseases.

4.7. IMMUNOTOXICITY OF PHAHS IN NONHUMAN PRIMATES

Studies using nonhuman primates as surrogate models for humans have been conducted to assess PHAH immunotoxicity. Immunological effects were described in rhesus monkeys and their offspring chronically exposed to TCDD at levels of 5 or 25 ppt for 4 years (Hong et al., 1989). In the mothers, the total number of T cells increased in monkeys fed 25 ppt TCDD, with a selective increase in $CD8^+$ cells and a decrease in $CD4^+$ cells. However, no significant effect on T cell function was established when assessed as proliferation response to mitogens, alloantigens, or xenoantigens. NK cell activity and production of antibodies to tetanus immunization were normal. In the offspring of TCDD-exposed dams examined 4 years after exposure, a significantly increased antibody response to tetanus toxoid (TT) immunization was observed that correlated with TCDD tissue levels. Body burden of TCDD in the offspring ranged from a low of 290 ppt to a high of 1,400 ppt. Interestingly, there was no strict correlation between exposure levels and resulting body burden. Immunoenhancement of the antibody response to TT in the offspring of the monkeys exposed to TCDD is in contrast to immunosuppression observed in rodents exposed perinatally. However, other studies in nonhuman primates cited below indicate that humoral immunity is suppressed in nonhuman primates by other PHAHs.

In other TCDD studies, a single injection of TCDD in marmosets (*Callithrix jacchus*) resulted in a delayed decrease in the percentage of $CD4^+$ T cells and $CD20^+$ B cells in the blood and an increase in the percentage of $CD8^+$ cells (Neubert et al., 1990). The total number of T cells was not significantly altered by TCDD exposure. The $CD4^+$ subset most affected was the $CDw29^+$ "helper-inducer" or "memory" subset, with significant effects observed after a TCDD dose of 10 ng/kg. The no-observed-effect level for this effect was 3 ng/kg TCDD. Concomitant with suppression of the CDw29 subset in TCDD treated animals, the percentage of $CD4^+CD45RA^+$ cells increased. This subset has been classified as "suppressor-inducer" or "naive" cells. The changes in the T cell subsets were intensified following in vitro culture of the cells with mitogen (Neubert et al., 1991).

Interestingly, however, another study from the same laboratory reported that chronic exposure of young marmosets to very low levels of TCDD (0.3 ng/kg/week for 24 weeks) produced the opposite effect on the $CD4^+CDw29^+$ subset, resulting in a significant increase in this population (Neubert et al., 1992). Concomitantly, the $CD4^+CD45RA^+$ subset decreased.

Upon transfer of the animals to a higher dose of TCDD (1.5 ng/kg/week) for 3 weeks, the enhancement effect was reversed and suppression of the $CD4^+CDw29^+$ subset was observed, with maximum suppression after 6 weeks of exposure to the higher dose. In addition, the $CD8^+CD56^+$ T cytotoxic T cell subset was transiently increased but normalized even though TCDD dosing continued. After discontinuation of dosing, the reduction in the percentage and absolute number of $CD4^+CDw29^+$ cells persisted for 5 weeks, reaching normal range 7 weeks later. These results led the authors to conclude that extrapolation of the results obtained at higher doses to very low exposures is not justified with respect to the effects induced by TCDD on the immune system of marmosets (Neubert et al., 1992).

Neubert et al. (1995b) performed a study to determine if a functional deficiency could be detected in marmosets that displayed altered peripheral blood T and B subsets following exposure to TCDD (Neubert et al., 1990). No reduction was observed in the in vitro lymphoproliferative response to TT by peripheral blood lymphocytes from marmosets vaccinated with tetanus and exposed to a single dose of 100 ng/kg TCDD at the time of the second booster vaccination (Neubert et al., 1995b). These results are interesting because no association was established between this functional endpoint and the earlier observed TCDD-induced peripheral blood lymphocyte subset changes in mature marmosets given a single injection of TCDD (Neubert et al., 1990).

Immunomodulatory effects of chronic low-level PCB exposure in monkeys have also been investigated. In early studies, Thomas and Hinsdill (1978) reported that rhesus monkeys fed diets containing 2.5 or 5 mg/kg of Aroclor 1248 had significantly suppressed antibody responses to SRBCs but not to TT. These monkeys also had chloracne, alopecia, and facial edema. Similarly, exposure of cynomolgus monkeys to Aroclor 1254 (100 or 400 μg/kg/day) for 3 months suppressed antibody responses to SRBCs but not TT (Truelove et al., 1982). Suppressive effects on anti-SRBC responses were more severe in cynomolgus monkeys when the PCB mixture contained PCDFs (Hori et al., 1982). Tryphonas et al. (1989; 1991a, b) reported results of studies in rhesus monkeys exposed chronically to Aroclor 1254 (5 to 80 μg/kg/day) for 23 or 55 months. These exposures resulted in steady-state blood PCB levels that ranged from a mean low of 0.01 ± 0.001 ppm in the 5 μg/kg group to a mean high of 0.11 ± 0.01 ppm in the 80 μg/kg group. The only consistently altered immune parameter was the primary and anamnestic antibody responses to SRBCs, which were suppressed in a dose-dependent manner. In contrast, the antibody response to pneumococcus vaccine antigen measured at 55 months of exposure was not significantly altered. At 23 months, the percentage of T helper cells in the blood was significantly decreased in the 80 μg/kg group, and the percentage and absolute number of T suppressor cells were increased; however, these effects were not apparent at 55 months of exposure (Tryphonas et al., 1991b). Lymphoproliferative responses to PHA and Con A were not

significantly altered at 23 months but were dose- dependently suppressed at 55 months. Proliferation to alloantigens was not significantly altered. Likewise, serum immunoglobulin and hydrocortisone levels did not differ between treatment groups. After 55 months, chemiluminescent response (time to peak) of monocytes from PCB-exposed monkeys was slower than that from controls. Also noted at 55 months were a significant elevation in serum hemolytic complement levels, a dose-related increase in NK cell activity, and a dose-related increase in thymosin alpha-1 levels but not thymosin beta-4 levels (Tryphonas et al., 1991a). Effects on interferon levels were inconsistent, and TNF production was not altered.

The studies in nonhuman primates are important from the standpoint that the antibody response to SRBCs emerges as the only immunological parameter consistently suppressed by PHAH in several different animal species. Notable exceptions are the reports that TCDD does not suppress antibody response to SRBCs in rats (Smialowicz et al., 1994; Fan et al., 1996). At the present time, it is not clear why the antibody response to SRBCs is most consistently altered by PHAH exposure in different species. Sensitivity of the anti-SRBC response does not appear to be caused solely by T cell dependency of the response because antibody responses to other T-dependent antigens (e.g., TT, BGG) are not suppressed and may be enhanced following PHAH exposure. It is possible that the particulate nature of the SRBC antigens is an important factor even though a mechanistic basis for this is not readily apparent. The sensitivity of the technique used to quantify the antibody response may also contribute to apparent increased sensitivity of the SRBC model, which is most often measured as the PFC response rather than serum antibody titers which are usually more variable. Nonetheless, the finding that the SRBC response is also suppressed in nonhuman primates exposed to PCBs lends support to the use of the anti-SRBC database for risk assessment of PHAHs.

4.8. IMMUNOTOXICITY OF PHAHS IN HUMANS: IN VIVO EXPOSURE

Immunotoxicity of TCDD and related PHAHs in humans has been the subject of several studies derived from accidental, occupational, or environmental exposure to PCDDs, PCDFs, and/or PCBs(see Chapter 7, Human Effects). Perhaps the most important human case studies involve two incidents in which large numbers of individuals were exposed to PCB-contaminated rice oil containing PCDFs and other PHAHs. The first occurred in Japan in 1968 and the second in Taiwan in 1979, and the resulting symptoms associated with exposure were called "Yusho" and "Yu-Cheng" which mean "oil disease" in Japanese and Chinese, respectively (Tsukamoto, 1969; Chang et al., 1980a). The most common clinical symptoms included acne-form eruptions and follicular accentuation, pigmentation of the skin and nails, swelling of the eyelids and increased discharge, nausea, headaches, and numbness of the limbs (Chang et al., 1980b).

Clinical studies revealed decreased serum concentration of γ-globulin and decreased DTH responses in Yu-Cheng patients (Chang et al., 1980b).

Patients also presented with increased frequency of various kinds of infection, especially of the respiratory tract and skin (Shigematsu et al., 1978; Nakanishi et al., 1985; Lu and Wu, 1985). Immunologic effects, in studies that compared a group of 30 Yu-Cheng patients and 23 normal controls, included decreased serum IgA and IgM, but not IgG, and decreased percentage of total T cells (E rosettes), active T cells (active E rosettes), and T helper (Tμ) cells in peripheral blood (Chang et al., 1981). Monocytes and polymorphonuclear cells from these exposed patients also had reduced numbers of Fc receptors compared with controls (Chang et al., 1982a). In a subsequent study, the DTH response to streptokinase and streptodornase in 30 exposed patients was significantly reduced compared with 50 controls (Chang et al., 1982b). The percentage of anergic patients increased, and the degree of induration decreased with increased PCB concentration in the blood. In contrast, lymphoproliferative responses of peripheral blood lymphocytes (PBLs) to PHA, pokeweed mitogen (PWM), and tuberculin PPD, but not Con A, were significantly augmented in PCB-exposed patients (Lu and Wu, 1985). PCB concentrations in the blood ranged from 3 to 1,156 ppb, with a mean of 89 ± 6.9 ppb. The oil was contaminated at PCB concentrations of 4.8 to 204.9 ppm, with a mean of 52 ± 39 ppm (Ko et al., 1981a, b). Followup studies 3 years later indicated that the DTH to PPD was reduced, that the percentage of total T cells had recovered but the percentage of helper T cells was reduced and of suppressor T cells increased, and that lymphoproliferative responses were enhanced in exposed patients compared with controls (Wu et al., 1984; Lu and Wu, 1985).

The patterns of immune function alterations in the Yu-Cheng patients described above were relatively consistent between the original and 4-year followup studies. These observations would suggest a rather robust and persistent alteration in the immune parameters examined. Unfortunately, it is not clear how many, if any, of the same patients were tested in each of these different studies to allow a direct assessment of the persistence of these effects.

Mothers of Yu-Cheng children reported increased incidence of pneumonia and bronchitis in their children during the first 6 months of life (Rogan et al. 1988). In a followup study, school-age children prenatally exposed to PCBs and PCDFs (n=103), were compared with nonexposed control children (n=96) for middle-ear disease (Chao et al., 1997). The exposed children had a higher prevalence of otitis media compared with their matched controls. Furthermore, exposed children with ear disease had higher serum levels of 2,3,4,7,8-pentachloro- and 1,2,3,4,7,8-hexachloro-dibenzofurans than did children with no middle-ear disease. In the summer of 1995, 105 Yu-Cheng children and 101 control children were given physical exams (Yu et al., 1998). The frequency of influenza, but not otitis media, asthma, or enteronitis attacks, during the 6 months prior to examination, as reported by the parents of the Yu-Cheng children,

was higher than for the controls. Blood samples were obtained from 29 Yu-Cheng and 22 control children for evaluation of total serum IgM, IgG, and IgA levels, as well as percentages of circulating T cells, B cells, and NK cells. There were no differences between Yu-Cheng and control children for any of these immune parameters (Yu et al., 1998).

Tests of altered immune function were also described in Michigan dairy farmers exposed to PBBs through contaminated dairy products and meat in 1973 (Bekesi et al., 1979). As in the PCB-exposed patients, the percentage and absolute numbers of T cells in peripheral blood of PBB-exposed farmers were significantly reduced compared with a control group. However, in contrast to PCB-exposed individuals (Lu and Wu, 1985), lymphoproliferation responses to PHA, PWM, and allogeneic leukocytes were significantly decreased in PBB-exposed persons. Also in contrast to PCB exposure, skin testing using standard recall antigens indicated that PBB-exposed farmers had significantly increased responses, particularly to candida and Varidase. Tissue levels of PBBs in the subjects were not determined in this study.

In contrast, another study of Michigan residents exposed to PBBs revealed no significant differences in lymphocyte number or function compared with nonexposed individuals (Landrigan et al., 1979; Silva et al., 1979). The exposed cohort in this study was drawn from individuals who lived on PBB-quarantined farms, who received food directly from such farms, or who worked or were related to workers engaged in PBB manufacture. No differences in the total leukocyte counts, the absolute numbers of T or B peripheral blood lymphocytes, or the in vitro responses to PHA, Con A, and PWM were observed between this high-exposure group (mean serum PBB level of 787 ppb [range of 188 to 2560], n=32) and a low- exposure group (mean serum PBB level of 2.8 ppb [range of <1 to 11], n=51).

Several studies have also examined the effects of occupational or environmental exposure to TCDD in human populations. Webb et al. (1989) reported the findings from immunologic assessment of 41 persons from Missouri with documented adipose tissue levels of TCDD resulting from occupational, recreational, or residential exposure. Of the participants, 16 had tissue TCDD levels less than 20 ppt, 13 had levels between 20 and 60 ppt, and 12 had levels greater than 60 ppt. The highest level was 750 ppt. Data were analyzed by multiple regression based on adipose tissue level and the clinical dependent variable. Increased TCDD levels were correlated with an increased percentage and total number of $OKT8^+$ ($CD8^+$) cells and increased percentages of $OKT11^+$ (i.e., $CD2^+$) and $OKT3^+$ (i.e., $CD3^+$) T lymphocytes. However, the percentage and total number of $OKT4^+$ cells were not altered. Lymphoproliferative responses to Con A, PHA, PWM, or TT were unaltered, as was the cytotoxic T cell response. Serum IgA, but not IgG, was increased. No adverse clinical disease was associated with TCDD levels in these subjects. Only 2 of the 41 subjects reported a history of chloracne.

The above findings differ from those reported for the Quail Run Mobile Home Park resident cohort study using 152 exposed and 151 unexposed individuals (tissue levels unknown) in which decreased T cell percentages and suppressed cell-mediated immunity were reported (Hoffman et al., 1986). The exposed group was reported to have decreased percentages of PBL $OKT3^+$, $OKT4^+$, and $OKT11^+$ T cells. Using seven standardized recall antigens (i.e., tetanus, diphtheria, *Streptococcus*, tuberculin, *Candida*, *Proteus*, and *Trichophyton*), the researchers observed a significant decrease in the DTH response of TCDD-exposed individuals compared with unexposed controls. The exposed group had an increased frequency of anergy (11.8% vs. 1.1%) and relative anergy (35.3% vs. 11.8%) compared with unexposed controls. However, it is important to note that there were significant technical problems with the interpretation of the skin test responses in this study. Nearly 50% of the skin test data were not used because two of the four skin test readers were inexperienced. Subsequent retesting of these anergic subjects, however, failed to confirm the DTH anergy (Evans et al., 1988). The only T cell measures outside the normal range, which were determined from the initial Quail Run study of Hoffman et al. (1986), were the percentage of $OKT4^+$ cells and the $OKT4^+/OKT8^+$ ratios, which were lower compared with unexposed controls (Evans et al., 1988). On the other hand, when serum from some of these individuals was tested for levels of the thymic peptide, thymosin alpha-1 (Thy_{a-1}), the entire frequency distribution for the TCDD-exposed group shifted toward lower Thy_{a-1} levels (Stehr-Green et al., 1989). The significant difference between the TCDD-exposed persons and controls remained after controlling for age, sex, and socioeconomic status, with a trend of decreasing Thy_{a-1} levels with increasing number of years of residence in the TCDD-contaminated residential area. Thy_{a-1} levels were not correlated with changes in other immune system parameters or with any increased incidence of clinically diagnosed immune suppression. The decrease in Thy_{a-1} levels in humans contrasts with the increase in Thy_{a-1} seen in PCB-treated monkeys (Tryphonas et al., 1991b). Thy_{a-1}, a product of thymic epithelial cells, has a role in modulating the differentiation of prothymocytes to mature thymocytes (Low and Goldstein, 1984).

In July 1976 an explosion in a chemical plant producing trichlorophenol herbicides near Seveso, Italy resulted in the release of TCDD estimated at 1.7 kg (Pocchiari et al., 1979). Several epidemiological evaluations were performed on exposed individuals after the accident. Pocchiari et al. (1979) summarized results of periodic evaluations of immune status of a group of 45 children (21 of whom had chloracne) age 3 to 7 years exposed to TCDD in Zone A, which was the most heavily contaminated area. No abnormalities were reported for the following parameters: serum immunoglobulin concentrations, levels of circulating complement, lymphoproliferative responses to T and B cell mitogens or alloantigens in the MLR, or PBL T and B cell populations. Interestingly, in the summary of a study conducted 6 years after the

explosion, a different cohort of TCDD-exposed children was reported to have exhibited a significant increase in complement protein levels, which reportedly correlated with incidence of chloracne as well as increased numbers of peripheral blood lymphocytes and increased lymphoproliferative responses (Tognoni and Bonaccorsi, 1982; Mocarelli et al., 1986, 1991). However, no specific health problems were correlated with dioxin exposure in these children. Unfortunately, none the studies cited above present any quantitative data. Specific information about the methods and results are not presented. A cursory description of the tests employed and the results obtained are the only information provided for the immune function evaluations. This is extremely unfortunate, because a critical evaluation of these studies and their conclusions cannot be made.

A more thorough study examined possible associations between occupational exposure to the herbicide Agent Orange and its dioxin contaminate and adverse health experienced by Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971 (Roegner et al., 1991) and is summarized by Wolfe et al. (1992). Immunological tests were carried out on a random sample of approximately 40% of the 1,670 participants for whom dioxin measurements in serum were made. Statistical models were used to evaluate associations between test parameters and serum dioxin levels using estimated initial and current serum dioxin levels. The statistical models were implemented using minimal assumptions (only Ranch Hands with current dioxin levels above 10 ppt) and maximal assumptions (all Ranch Hands with current dioxin levels above 5 ppt). The immunological tests included the following: DTH response to the recall antigens *Candida*, mumps, *Trichophyton*, and Staphage-lysate; PBL subsets CD2 (total T cells), CD20 (B cells), CD4 (helper/inducer T cells), CD8 (suppressor/cytotoxic T cells), CD14 (APC monocytes), CD25 (IL-2 receptor positive activated T cells), HLR-DR (B cells, activated T cells and monocytes that present antigen to $CD4^+$ T cells), CD4/CD8 ratio, and TLC (total lymphocytes in circulation); total serum IgM, IgG, and IgA levels; lymphoproliferative response to PHA; NKCI and NKCA activity, which measure NK cell lytic activity with and without IL-2 treatment, respectively; and mixed leukocyte culture (MLC) response (Roegner et al., 1991). This immunological assessment did not find any clinically significant alterations associated with current or initial levels of serum dioxin. A significant association between initial dioxin level and increased IgA levels was found; however, IgM and IgG levels did not indicate the presence of any dioxin-related effects. There was no association between the DTH response and serum dioxin levels. Despite several significant findings for some of the other immunological parameters examined, these data were deemed to be either internally inconsistent or not in a direction expected in an impaired immune system (Roegner et al., 1991; Wolfe et al., 1992).

Results of a followup examination of Air Force personnel involved in Operation Ranch Hand are presented in a report by Grubbs et al. (1995). Many of the immunologic parameters in

the earlier study were examined in this study, with the following exceptions. The PBL subset CD3 (pan T cells) replaced CD2, and CD5 (T cells and B cells) and CD16+CD56 (NK cells) were added to the test screen. The PBL PHA response, NKCI and NKCA activity assays, and MLC response were not performed. However, an autoantibody lupus panel, including tests for antinuclear antibodies; thyroid microsomal antibody; mouse stomach and kidney (MSK) smooth muscle, mitochondrial, and parietal antibodies; and rheumatoid factor, was included in this study. A marginal positive association was found between IgA levels and initial serum dioxin (Grubbs et al., 1995), as reported in the earlier study (Roegner et al., 1991). Also, an inverse relationship was found with dioxin exposure and the presence of autoantibodies to MSK smooth muscle, rheumatoid factor, and the lupus panel summary index. Although Grubbs et al. (1995) recommended that these findings be investigated and clarified in further followups, they concluded that no clinically significant indicators that reflected a consistent relationship between serum dioxin and immune function deficiencies were found in this study.

The most recent followup examination of Air Force personnel involved in Operation Ranch Hand occurred in 1992, and the results and analyses of immune parameters and dioxin body burden were reported by Michalek et al. (1999). A total of 2,233 veterans (Ranch Hand, n=952; Comparison, n=1,281) participated in this physical exam. The immunologic parameters examined in this study were the same as those in the previous followup study (Grubbs et al., 1995). Analysis of the results of the 1992 followup exam revealed only three statistically significant differences. First, an increase was observed in absolute $CD20^+$ (B cells) count in the Background group, whereas the mean absolute count of $CD16^+CD56^+CD3^+$ (T) cells was decreased in the High category. Second, three dioxin-exposed veteran categories (Background, Low, and High) had increased positive thyroid microsomal autoantibody tests; however, only the Low category was significant. Third, there was no significant association between dioxin-exposed veterans and total serum immunoglobulin levels, or in the presence of other autoantibodies. As with the earlier Ranch Hand studies, the authors concluded that there was no consistent relationship between dioxin exposure category and immune system alteration in Ranch Hand veterans (Michalek et al., 1999).

Other human studies involving smaller cohorts, in which exposure to PHAHs was documented, report alterations in certain immunological parameters. Eighteen workers (8 of whom had chloracne) were evaluated for immunological abnormalities 17 years after exposure to TCDD (no tissue levels were reported) in an industrial accident in a plant manufacturing the herbicide 2,4,5 trichlorophenoxyacetic acid (Jennings et al., 1988). Immunological parameters evaluated were the following: serum IgM, IgG, and IgA levels; antinuclear antibodies; immune complexes; T lymphocyte subsets and NK cells; and lymphoproliferative response to PHA. Antinuclear antibodies and immune complexes were detected more frequently in the peripheral

blood of workers exposed to dioxin. No differences were observed in the total number of T or B lymphocytes or in the T4/T8 ratio; however, NK cells identified by the surface marker Leu-7 were higher in the dioxin-exposed workers (Jennings et al, 1988). The significance of these findings is unknown, because only a small cohort was studied and the autoantibody results were opposite to those reported by Grubbs et al. (1995). Also, there are no animal data that indicate increased NK cells associated with TCDD exposure. The NK results also differ from results of a more recent human study by Svensson et al. (1994), who reported that men with high consumption of PHAH-contaminated Baltic Sea fatty fish (n=23) had lower proportions and numbers of PBL NK cells (i.e., $CD56^+$ cells) compared with men with virtually no fish consumption (n=20). NK cells were negatively associated with blood levels of several persistent organochlorine compounds and with estimated intake of fish. Fish consumption, however, was not associated with any alterations in other cell subsets, plasma immunoglobulin levels, or liver enzyme activities. It is important to point out that no attempt was made to determine if the decreased numbers of NK cells were correlated with reduced NK function in this study or with increased NK activity in the study described by Jennings et al. (1988).

A retrospective cohort morbidity study of 158 men accidentally exposed in 1953 to TCDD during the production of trichlorophenol was reported by Zober et al. (1994), in which 73 men had back calculated TCDD values of >1,000 ppt and 85 had values of <1,000 ppt. Increased frequency of upper respiratory tract infections was observed in individuals who had severe chloracne. However, it was indicated that differences in the utilization rates of medical care by the exposed and referent groups could have biased the findings. A clinical study of the 138 men exposed to TCDD in the accident described above attempted to determine if any TCDD dose relationships existed within the exposed population for a number of clinical and immunological parameters (Ott et al., 1994). Increases in serum IgA and IgG and increases in complement C3 and C4 were seen with high current and back-calculated TCDD concentrations and with high current TCDD concentrations, respectively. Marginal decreases in the percentage of lymphocytes, NK cells, T cells, T helper cells, and T suppressor cells were also observed (Ott et al., 1994). However, mean values for all of these parameters were comparable to those of internal referent groups of 42 to 196 individuals (number of referents differed among the parameters examined) who were not part of this clinical study but who participated in routine occupational medical examinations during the same period (Ott et al., 1994).

In another retrospective study, T helper cell function was evaluated in 11 workers, 45 to 63 years of age, who were exposed to high levels of TCDD and other PCDDs between 1966 and 1976 in production and maintenance operations at a German chemical factory producing 2,4,5-trichlorophenol (Tonn et al., 1996). TCDD body burdens were still high (43 to 874 pg/g blood or a mean of 330, which is 10 times higher than in the average German population) 20 years after

exposure. No differences were detected between exposed and control groups for surface marker distribution (e.g., CD3, CD4, CD8, CD19, CD45RO, CD45RA, CD56 or CD57) or mitogen-induced lymphoproliferation responses (e.g., PHA or PWM). However, the exposed group showed reduced lymphoproliferation in response to human lymphocyte antigen-allogeneic lymphocytes (e.g., MLR) and IL-2 stimulation. It was concluded that TCDD has a long-term immunosuppressive effect on T helper cells manifested by reduced function of these cells rather than by reduction in the cell numbers in peripheral blood (Tonn et al., 1996).

Neubert et al. (1993) attempted to determine if workers with moderately increased body burdens of TCDD and related PHAHs (25 to 140 ppt TCDD or 104 to 522 ppt International-Toxicity Equivalencies [I-TE] in blood lipids) displayed altered patterns of PBL subsets similar to those observed in TCDD-exposed marmosets (Neubert et al., 1990, 1991, 1992). A slight trend in increased percentage of $CD4^{+}CD45RO^{+}$ helper-inducer T cells was observed. However, Neubert et al. (1993) concluded that these alterations were of no medical relevance. Furthermore, the data did not support an assumption that moderately increased body burdens of PCDDs/PCDFs in adults result in decreased cellular components of the human immune system. Because adult humans, as well as adult marmosets, are less susceptible to PCDD/PCDF-associated alterations in PBL subsets than are adolescent marmosets, Neubert et al. (1993) suggested that exposure to PHAHs during early development may be the important factor influencing altered lymphocyte subsets.

In a more recent study, Neubert et al. (1995a) evaluated the in vitro lymphoproliferative responses to Con A, PHA, PWM, anti-CD3, and TT of PBL from the same workers described above. No decrease in the lymphoproliferative capacity of lymphocytes from these workers with moderately increased PCDD/PCDF body burdens was observed compared with lymphocyte responses of individuals with PCDD/PCDF body burdens within the reference range (1 to 3 ppt TCDD or 9 to 29 ppt I-TE in blood lipids) for any of these lymphocyte stimulators.

A retrospective examination of possible associations between altered immune parameters and occupational exposure to TCDD of chemical plant workers involved in the manufacture of 2,4,5-trichlorophenate and its derivatives between 1951 and 1972 was reported by Halperin et al. (1998). A total of 259 workers and 243 unexposed referents were included in this study. The workers had had substantial exposure to TCDD as indicated by a lipid adjusted mean serum TCDD concentration of 229 ppt, whereas the controls had a mean TCDD concentration of 6 ppt. Peripheral blood leukocytes and lymphocytes were enumerated, and lymphocytes were evaluated by flow cytometry for a variety of populations including T cells, B cells, and NK cells. In vitro assays for peripheral blood NK cell activity and lymphoproliferative activity of cultured lymphocytes in the presence of the mitogens PHA, ConA, or PWM, or the antigens mumps, Candida, or TT were performed. Total serum concentrations of IgM, IgG, and IgA and

complement factor C3 were also determined. Of the various TCDD categories (based on workers' serum TCDD concentration) except the lowest, there were increased odds of having lower CD26 (activated T cells) counts. In addition, there was a decreased spontaneous proliferation of cultured lymphocytes (i.e., no mitogen or antigen present in the culture); however, lymphocytes from workers in the high TCDD category had increased proliferation in the presence of ConA and PWM. No other immune parameters were affected. It was concluded that the results were unlikely to be of clinical significance (Halperin et al., 1998).

The immunologic effects of pre- and postnatal background exposure to PCBs/dioxins of Dutch infants from birth to 18 months of age were presented in a study by Weisglas-Kuperus et al. (1995). Prenatal PCB exposure was estimated from the sum of PCB congeners 118, 138, 153, and 180 in maternal blood (i.e., 2.25 ± 0.98 μg/L, n=206) and the TEQ level in milk based on 17 PCDDs/PCDFs and 8 dioxin-like PCB congeners (i.e., 66.6 ± 24.4 pg/g fat, n=80). Postnatal exposure was calculated as a product of the total TEQ level in milk multiplied by the weeks of breast-feeding. No relationship was found between pre- and postnatal PCB/dioxin exposure and respiratory tract symptoms (i.e., number of periods with rhinitis, bronchitis, tonsillitis, and otitis) or humoral antibody production at 18 months to vaccination against mumps, measles and rubella at 14 months. Higher prenatal exposure was associated with alterations in T cell subsets, in which increased number of $TCR\gamma\delta^+$ T cells correlated with a total higher TEQ level at birth. Further, higher prenatal exposure was also associated with increased total numbers of T cells, $CD8^+$ cells and $TCR\gamma\delta^+$ T cells at 18 months of age; correlating with higher TEQ levels. A higher TEQ level was also associated with a decreased number of monocytes and granulocytes at 3 months. Despite these statistical associations of cell types with TEQ levels, all values were found to be within normal range. It was indicated that the subtle changes in the number of blood leukocytes do not necessarily mirror alterations in the cell composition of lymphoid and nonlymphoid organs nor do they reflect functional defects (Weisglas-Kuperus et al., 1995).

In a followup study, Weisglas-Kuperus et al. (2000) examined whether changes associated with prenatal exposure to PCBs persist into later childhood. At 42 months of age, antibody levels to measles and mumps were negatively correlated with cord and maternal PCB levels, respectively. A higher prevalence of recurrent middle ear infections and chicken pox, as well as a lower incidence of allergic reactions, were associated with current PCB body burdens. Also, there were significant positive correlations between prenatal PCB exposure and the numbers of peripheral blood lymphocytes and $CD3^+CD8^+$(cytotoxic), $CD4^+CD45RO^+$ (memory), $TcR\alpha\beta^+$, and $CD3^+$HLA-DR^+ (activated) T cells. These values, however, were within the normal range for children at this age. The authors concluded that perinatal background exposure to PCBs and dioxins might be associated with increased susceptibility to infectious diseases.

In summary, no clear pattern of altered immune parameters following exposure to TCDD or related PHAHs has emerged from studies in humans. The basis for the lack of consistent, exposure-related effects is unknown and may depend on several factors. These include the generic difficulties in assessing subclinical immunomodulation using assays with very broad ranges of normal responses, which reduce the sensitivity to detect small changes in a heterogeneous human population. Furthermore, the choice of immune parameters used to evaluate humans exposed to TCDD and related PHAHs has been based to a greater extent on what is clinically feasible than on what has been shown to be sensitive in animal studies. Thus, lack of consistent or significant immunotoxic effects in humans resulting from TCDD exposure may be as much a function of the assays used as of the immune status of the cohort.

An interesting observation, relative to the human data, is that T cells and T cell functions appear to be more frequently affected than other immune cells or functions when PHAH exposure related effects have been reported. This may simply reflect the fact that T cell assays predominate over other assays employed in these studies. Nevertheless, it is interesting that several studies report slight reductions in $CD4^+$ T helper cells (Chang et al., 1981; Wu and Lu, 1984; Lu and Wu, 1985; Hoffman et al., 1986; Evans et al., 1988). Reductions in $CD4^+$ cells and $CD4^+$ subsets have also been reported in non-human primates exposed to PHAHs (Hong et al., 1989; Neubert et al., 1990, 1991, 1992; Tryphonas et al., 1991b). These reductions may not translate into significant immune effects. However, the fact that these cells play a pivotal role in regulating immune responses and that their reduction may presage immunosuppression suggests that these observations are worth further investigation.

4.9. IMMUNOTOXICITY OF PHAHS IN HUMANS: IN VITRO EXPOSURE

Several laboratories have examined the direct effects of TCDD on human lymphocytes in vitro. Neubert et al. (1991) reported decreased PBL subpopulations from humans and nonhuman primates cultured in the presence of TCDD. $CD4^+CD29^+$ helper-inducer/memory T cells and $CD20^+$ B cells were dose-dependently decreased in PWM-stimulated cultures of human PBLs at concentrations as low as 10^{-12} to 10^{-14} M TCDD. However, an attempt to corroborate these findings failed to detect any suppression in human PBL subpopulations, including $CD4^+CD29^+$ helper-inducer/memory T cells and $CD19^+$ B cells, at TCDD concentrations ranging from 10^{-7} to 10^{-14} M (Lang et al., 1994). Furthermore, PWM- or anti-CD3-stimulated lymphocyte proliferation was not altered by TCDD at concentrations of 10^{-7} to 10^{-11} M (Lang et al., 1994).

Similar negative results were obtained by Wood et al. (1992), who reported that exposure of human tonsillar lymphocytes (HTLs) to concentrations of 3×10^{-8} to 3×10^{-10} M TCDD did not affect either PWM-induced proliferation or IgM antibody production. In contrast, 3×10^{-8} to 3×10^{-10} M TCDD suppressed toxic shock syndrome toxin (TSST-1)–induced IgM secretion of

HTL B cells (Wood and Holsapple, 1993). The sensitivity of the HTL B cells to TCDD suppression of TSST-1–induced IgM secretion, however, was found to be highly variable among the different donors. In a separate study, concentrations of 3×10^{-8} to 3×10^{-10} M TCDD suppressed the background proliferation and IgM secretion of low-density HTL B cells (predominately activated cells), but not high-density HTL B cells (predominately resting cells) (Wood et al., 1993). TCDD also suppressed LPS plus T cell replacement factor–stimulated proliferation and IgG secretion of low-density, but not high-density, HTL B cells. These results suggest that TCDD may have a direct effect on HTL low-density B cells and that this lymphocyte subpopulation may be a sensitive target for TCDD.

More recently, Masten and Shiverick (1995) investigated the effect of TCDD on expression of the CD19 gene in the IM-9 human B lymphocyte cell line in an attempt to determine a possible mechanism for TCDD-induced inhibition of human and murine B lymphocyte Ig production. CD19 is a B cell surface signal transducing protein that is expressed from early stages of B cell development, but is lost when B cells differentiate into antibody-producing plasma cells (Tedder et al., 1994). TCDD treatment of IM-9 cells decreased the steady state levels of CD19 mRNA by 67%. A DNA-binding complex in IM-9 nuclear extracts was identified that, based on several criteria, appeared to be the AhR. Furthermore, the AhR complex recognized a DNA binding site for B cell lineage–specific activator protein (BSAP) in the promotor region of the CD19 gene. This BSAP binding site is similar to the consensus AhR DNA binding site. Based on these results, Matsen and Shiverick (1995) suggest that the decrease in CD19 gene expression following TCDD exposure may result from the AhR interfering with BSAP-stimulated CD19 transcription. Further work, however, is required to support this hypothesis. Nevertheless, it is interesting that this work supports the animal in vitro work of Holsapple and coworkers, which indicates that the B cell is a primary cellular target for the direct effects of TCDD (Holsapple, 1995). It also goes beyond the in vitro animal work in that it provides further evidence that the AhR is involved in PHAH-induced immunotoxicity.

4.10. SUMMARY

Cumulative evidence from a number of studies indicates that the immune system of various animal species is a target for toxicity of TCDD and structurally related PHAHs, including other PCDDs, and PCDFs and PCBs. Both cell-mediated and humoral immune responses are suppressed following TCDD exposure, suggesting that multiple cellular targets within the immune system are altered by TCDD. Evidence also suggests that the immune system is indirectly targeted by TCDD-induced changes in nonlymphoid tissues. TCDD exposure of experimental animals results in decreased host resistance following challenge with certain

infectious agents, which likely result from TCDD-induced suppression of immunological functions.

The primary antibody response to the T cell–dependent antigen SRBCs is the most sensitive immunological response that is consistently suppressed in mice exposed to TCDD and related PHAHs. The degree of immunosuppression is related to the potency of the dioxin-like PHAH congeners. There is remarkable agreement among several different laboratories for the potency of a single acute dose of TCDD (suppression at a dose as low as 0.1 μg TCDD/kg with an average ID_{50} value of approximately 0.7 μg TCDD/kg) to suppress this response in Ah-responsive mice. Results of studies that have compared the effects of acute exposure to individual PCDD, PCDF, and PCB congeners, which differ in their binding affinity for the AhR, on this response have provided critical evidence that certain dioxin-like congeners are also immunosuppressive. The degree of immunosuppression has been found to be related to potency of the dioxin-like congeners. Antibody responses to T cell–independent antigens, such as TNP-LPS, and the CTL response are also suppressed by a single acute exposure to TCDD, albeit at higher doses than those that suppress the SRBC response. A limited number of studies reveal that dioxin-like congeners also suppress these responses, with the degree of suppression related to the congeners' AhR binding affinity. Although a thorough and systematic evaluation of the immunotoxicity of TCDD-like congeners in different species and for different immunological endpoints has not been performed, it can be inferred from the available data that dioxin-like congeners are immunosuppressive.

In addition to the TCDD-like congener results, studies using strains of mice that differ in the expression of the AhR have provided critical evidence to support a role for Ah-mediated immune suppression following PHAH exposure. Recent in vitro work also supports a role for Ah-mediated immune suppression. Other in vivo and in vitro data, however, suggest that non-Ah-mediated mechanisms may also function in PHAH-induced immunotoxicity. However, more definitive evidence remains to be developed to support this latter view.

Although in mice the immunosuppressive potency of individual PHAHs is related to their structural similarity to TCDD, this pattern of suppression is observed only after exposure to an individual PHAH. The immunotoxicity of TCDD and related congeners can be modified by co-exposure to PHAHs in simple binary or more complex mixtures resulting in additive or antagonistic interactions. Dose-response data are needed on acute, subchronic, and chronic exposure to the individual PHAHs in a mixture and on the mixture itself in order to fully evaluate potential synergistic, additive, or antagonistic effects of environmentally relevant PHAH mixtures.

Perinatal exposure of experimental animals to TCDD results in suppression of primarily T cell immune functions, with evidence of suppression persisting into adulthood. The effects on

T cell functions appear to be related to the fact that perinatal TCDD exposure of mice alters thymic precursor stem cells in the fetal liver and bone marrow, and thymocyte differentiation in the thymus. These studies suggest that perinatal development is a critical and sensitive period for TCDD-induced immunotoxicity. Efforts should be made to determine the consequences of perinatal exposure to TCDD congeners and PHAH mixtures on immune system integrity.

Animal host resistance models that mimic human disease have been used to assess the effects of TCDD on altered host susceptibility. TCDD exposure increases susceptibility to challenge with bacteria, viruses, parasites, and tumors. Mortality is increased in TCDD-exposed mice challenged with certain bacteria. Increased parasitemia occurs in TCDD-exposed mice and rats challenged with parasitic infections. Low doses of TCDD also alter resistance to virus infections in rodents. Increased susceptibility to infectious agents is an important benchmark of immunosuppression; however, the role of TCDD in altering immune-mediated mechanisms important in murine resistance to infectious agents remains to be elucidated. Also, since little is known about the effects of dioxin-like congeners on host resistance and nothing is known about the relation between the AhR and host resistance, more research is recommended in this area.

Studies in nonhuman primates exposed acutely, subchronically, or chronically to PHAHs have revealed variable alterations in lymphocyte subpopulations, primarily T lymphocyte subsets. On the other hand, in three separate studies in which monkeys were exposed subchronically or chronically to PCBs, the antibody response to SRBC was consistently found to be suppressed. These results in nonhuman primates are important because they corroborate the extensive database of PHAH-induced suppression of the antibody response to SRBC in mice and thereby provide credible evidence for immunosuppression by PHAHs across species. In addition, these data indicate that the primary antibody response to this T cell–dependent antigen is the most consistent and sensitive indicator of PHAH-induced immunosuppression.

The available database derived from well-controlled animal studies on PHAH immunotoxicity can be used for the establishment of no-adverse-effect levels. Because the antibody response to SRBCs has been shown to be dose-dependently suppressed by TCDD and related PHAHs, this database is best suited for the development of dose-response modeling.

Accidental or occupational exposure of humans to TCDD and related PHAHs variably affects a number of immunological parameters. Unfortunately, evaluation of immune system integrity in humans exposed to PHAHs has provided data that are inconsistent across studies. The broad range of "normal" responses in humans due to the large variability inherent in a heterogenous population, the limited number and sensitivity of tests performed, and the poor exposure characterization of the cohorts in these studies compromise any conclusions about the ability of a given study to detect immune alterations. Consequently, there are insufficient clinical data from these studies to fully assess human sensitivity to PHAH exposure. Nevertheless, the

database of the results of the extensive animal work is sufficient to indicate that immune effects could occur in the human population from exposure to PHAHs at some dose level.

It is interesting that a common thread in several human studies is the observed reduction in $CD4^+$ T helper cells, albeit generally within the "normal" range, in cohorts exposed to PHAHs. These reductions may not translate into clinical effects, but it is important to note that such cells have an important role in regulating immune responses and that their reduction in clinical diseases is associated with immunosuppression. Another important consideration is that a primary antibody response following immunization was not evaluated in any of the human studies. In that this immune parameter has been revealed to be the most sensitive in animal studies, this parameter should be included in future studies of human populations exposed to PHAHs. It is also recommended that research continue on delineating the mechanism(s) underlying PHAH-induced immunotoxicity.

Table 4-1. Acute single dose ID_{50}s for polychlorinated dioxins, furans, and biphenyls based on suppression of the PFC response to SRBCs in Ah-responsive B6 mice

Congener	ID_{50}	Reference
2,3,7,8-TCDD	0.74 µg/kg	Kerkvliet and Brauner, 1990
"	0.65 µg/kg	Vecchi et al., 1980
"	0.77 µg/kg	Davis and Safe, 1988
"	0.60 µg/kg	Kerkvliet et al., 1990a
1,2,3,6,7,8-HxCDD	7.1 µg/kg	Kerkvliet et al., 1985
1,2,3,4,6,7,8-HpCDD	85.0 µg/kg	Kerkvliet et al., 1985
OCDD	>500 µg/kg	Kerkvliet et al., 1985
2,3,4,7,8-PCDF	1.0 µg/kg	Davis and Safe, 1988
2,3,7,8-TCDF	4.3 µg/kg	Davis and Safe, 1988
1,2,3,4,6,7,8-HpCDF	208 µg/kg	Kerkvliet et al., 1985
1,2,3,7,9-PenCDF	239 µg/kg	Davis and Safe, 1988
1,3,6,8-TCDF	11 mg/kg	Davis and Safe, 1988
3,4,3′,4′-TCB	28 mg/kg[a]	Silkworth and Grabstein, 1982
2,3,4,5,3′,4′-HxCB	0.7 mg/kg	Davis and Safe, 1990
2,3,4,5,3′,4′-HxCB	31 mg/kg[a]	Silkworth et al., 1984
2,4,3′,4′,5′,6′-HxCB	43 mg/kg	Davis and Safe, 1990
2,3,4,3′,5′-PenCB	65 mg/kg	Ibid.
2,3,4,5,3′,5′-HxCB	72 mg/kg	Ibid.
2,4,2′,4′-TCB	>100 mg/kg	Silkworth et al., 1984
2,4,5,2′,4′,6′-HxCB	>360 mg/kg	Davis and Safe, 1990
2,4,6,2′,4′,6′-HxCB	>360 mg/kg	Ibid.
2,4,5,2′,4′,5′-HxCB	>360 mg/kg	Biegel et al., 1989
Aroclor 1260	104 mg/kg	Davis and Safe, 1989
Aroclor 1254	118 mg/kg	Ibid.
Aroclor 1254	207 mg/kg	Lubet et al., 1986
Aroclor 1248	190 mg/kg	Davis and Safe, 1989
Aroclor 1242	391 mg/kg	Ibid.
Aroclor 1016	408 mg/kg	Ibid.
Aroclor 1232	464 mg/kg	Ibid.

[a]Interpolated from two data points.

Table 4-2. ID_{50}s for sppression of alloantigen (P8l5)-specific CTL response in C57Bl/6 mice

Congener	ID_{50}	Reference
TCDD	7 µg/kg	Kerkvliet et al., 1990b
3,4,5,3′,4′,5′-HxCB	7 mg/kg	Ibid.
2,3,4,5,3′,4′-HxCB	70 mg/kg[a]	Ibid.
2,4,5,2′,4′,5′-HxCB	>300 mg/kg	Ibid.

[a] Interpolated from two data points.

Table 4-3. Immunotoxic effects of TCDD in the offspring following prenatal/neonatal exposure to TCDD

Protocol[a]	Endpoints	Effect	LOAEL[b]
Study 1			
Pregnant B6 or	PYB6 tumor incidence	Increased	1 µg/kg × 4
$B6C3F_1$ mice given 1, 2, 5,	Allograft rejection time	Increased	2 µg/kg × 4
or 15 µg/kg TCDD orally	Body, thymus, spleen wt	Decreased	5 µg/kg × 4
on day -7, 0, +7, +14	Bone marrow cellularity	Decreased	5 µg/kg × 4
relative to parturition	T cell blastogenesis	Decreased	5 µg/kg × 4
on day 0	*Listeria monocytogenes*-induced mortality	Decreased	5 µg/kg × 4
	Bone marrow colony formation (CFU-S)	Decreased	5 µg/kg × 4
		—	>15 µg/kg × 4
	LPS blastogenesis	—	>15 µg/kg × 4
	Anti-SRBC serum titers		
Study 2			
Pregnant Swiss mice	Endotoxin mortality	Increased	1.0 ppb diet
fed diets containing	Thymus weight	Decreased	2.5 ppb diet
1.0, 2.5, or 5.0 ppb	PFC response to SRBC	Decreased	5.0 ppb diet
TCDD for 7 weeks prenatally	DTH response	Decreased	5.0 ppb diet
and postnatally	Anti-SRBC serum titers	—	>5.0 ppb diet
	T and B cell blastogenesis	—	>5.0 ppb diet
	Listeria-induced mortality	—	>5.0 ppb diet
Study 3			
Pregnant Fischer 344	Allograft rejection time	Increased	5 µg/kg × 4
rats given 1 or 5 µg/kg	T cell blastogenesis	Decreased	5 µg/kg × 4
TCDD orally on day -3, 0,	DTH response	Decreased	5 µg/kg × 4
+7, and +14 relative to	*Listeria*-induced mortality	Decreased	5 µg/kg × 4
parturition on day 0	Body and thymus weight	Decreased	5 µg/kg × 4
	Anti-BGG serum titers	—	>5 µg/kg × 4

[a]Study 1: Vos and Moore, (1974), Luster et al. (1980a); Study 2: Thomas and Hinsdill (1979); Study 3: Vos and Moore, (1974) , Faith and Moore (1977).

[b]Abbreviations used: LOAEL - lowest observable adverse effect level; BGG - bovine gamma globulin; LPS - lipopolysaccharide; PHA - phytohemagglutinin; Con A - Concanavalin A; SRBC - sheep red blood cell; DTH - delayed-type hypersensitivity; PFC - plaque-forming cell; CFU-S - colony-forming units-spleen.

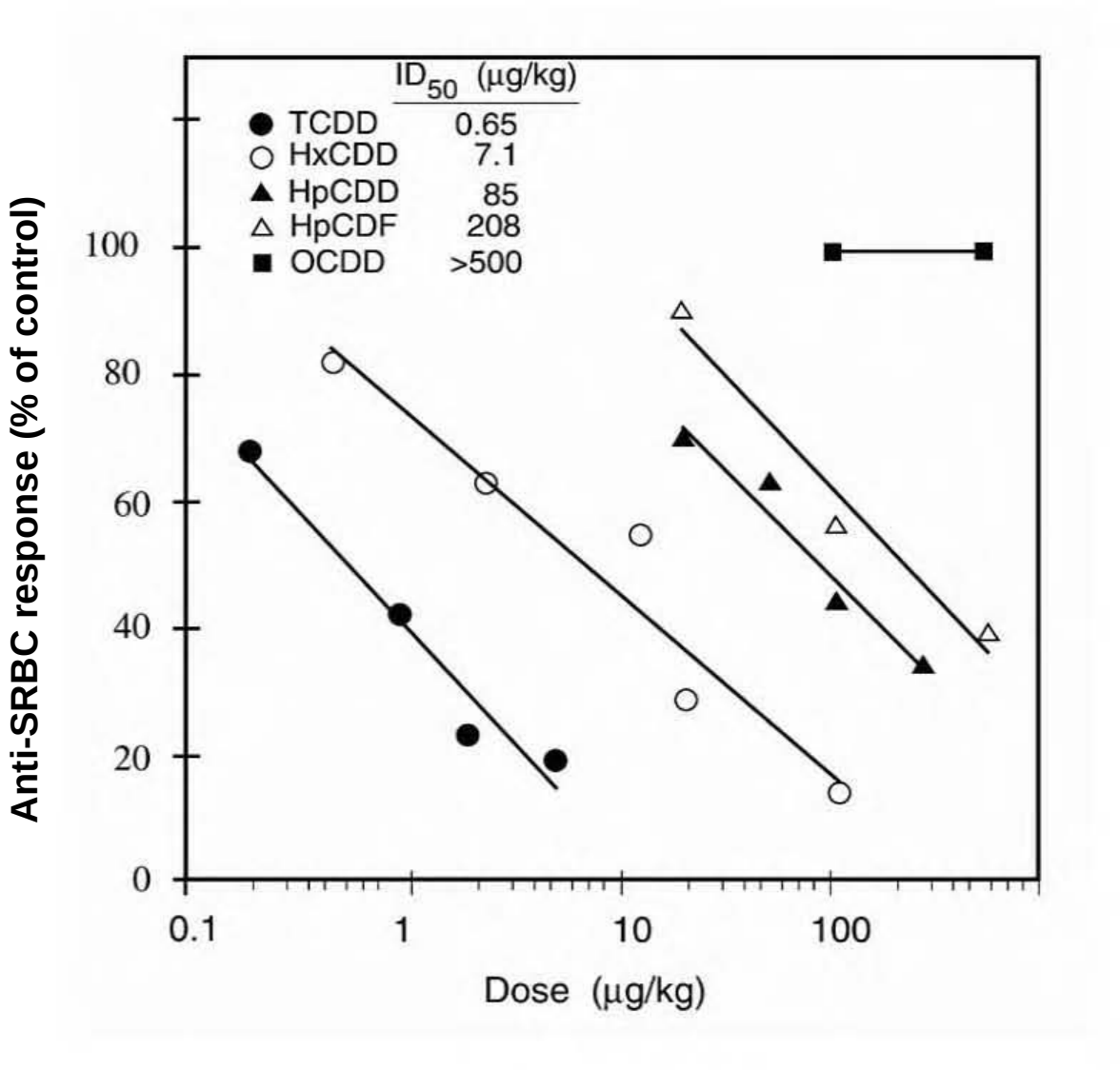

Figure 4-1. Structure-dependent immunotoxicity of some polychlorinated dioxin and furan isomers. Immunotoxicity assessed by suppression of the splenic antibody response to SRBCs (modified from Kerkvliet et al., 1985).

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5. DEVELOPMENTAL AND REPRODUCTIVE TOXICITY*

5.1. INTRODUCTION

The potential for dioxins and related compounds to cause reproductive and developmental toxicity has been recognized for many years. Recent laboratory studies have broadened our knowledge in this area and demonstrate that altered development is among the most sensitive endpoints of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This chapter reviews much of the literature on dioxin's developmental and reproductive toxicity but is not intended to be exhaustive. Special emphasis is placed on that part of the database that has accumulated since the last major EPA review of this topic (Kimmel, 1988; Peterson et al., 1993). In addition, the database is viewed in light of the Ah receptor model of TCDD action that is being examined for its applicability in the current EPA risk assessment.

To focus the analysis of the database, the chapter is divided into developmental toxicity and male and female reproductive toxicity. The authors recognize the interrelatedness of developmental and reproductive events at all levels of biological complexity. Therefore, the reader should not view the chapter subheadings within each of these divisions as defining discrete endpoints that are exclusive of other endpoints. For example, the effects of TCDD on circulating levels of sex hormones or on responsiveness to sex hormones may be translated into reproductive dysfunction if exposure occurs in adulthood or abnormal development of sexual behavior if exposure occurs perinatally. Likewise, even though organ structure and growth are considered separate manifestations in developmental toxicity that are associated with perinatal exposure to TCDD, the normal development of an organ is dependent on normal growth processes, and inhibiting perinatal growth can significantly disrupt the structural integrity of an organ system.

2,3,7,8-TCDD is one of 75 possible CDD congeners and 135 possible CDF congeners. It is one of the most potent of the CDDs, BDDs, CDFs, BDFs, PCBs, and PBBs, and as such serves as the prototype congener for investigating the toxicity elicited by these classes of chemicals. Developmental and reproductive toxicity is generally believed to be caused by the parent compound; there is no evidence that TCDD metabolites are involved. The toxic potency of TCDD is due to the number and position of chlorine substitutions on the dibenzo-*p*-dioxin molecule. CDD congeners with decreased lateral (2, 3, 7, and 8) or increased nonlateral chlorine and bromine substituents are less potent than TCDD (Safe, 1990); however, most of these

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congeners will produce toxicity, and the pattern of responses within animals of the same species, strain, sex, and age will generally be similar to that of TCDD (McConnell and Moore, 1979; Poland and Knutson, 1982). PCB congeners with zero or one *ortho* chlorines, two *para* chlorines, and at least two *meta* chlorines can assume a coplanar conformation sterically similar to TCDD and also produce a pattern of toxic responses similar to that of TCDD. In contrast, PCB congeners with two or more *ortho* chlorines cannot assume a coplanar conformation and do not resemble TCDD in toxicity (Poland and Knutson, 1982; Safe, 1990).

CDD and CDF congeners chlorinated in the lateral positions, as compared with those lacking chlorines in the 2, 3, 7, and 8 positions, are preferentially bioaccumulated by fish, reptiles, birds, and mammals (Stalling et al., 1983; Cook et al., 1991; U.S. EPA, 1991). Furthermore, coplanar PCBs and/or monoortho-chlorine-substituted analogs of the coplanar PCBs bioaccumulate in fish, wildlife, and humans (Tanabe, 1988; Kannan et al., 1988; Mac et al., 1988; Kubiak et al., 1989; Smith et al., 1990). This is of concern because combined effects of the lateral-substituted CDD, BDD, CDF, BDF, PCB, and PBB congeners acting through an Ah receptor mechanism have the potential of decreasing feral fish and wildlife populations secondary to developmental and reproductive toxicity (Gilbertson, 1989; Walker and Peterson, 1991; Walker et al., 1991; Cook et al., 1991). Humans are not exempt from the developmental and reproductive effects of complex halogenated aromatic hydrocarbon mixtures. Such mixtures that contain both TCDD-like congeners and non-TCDD-like congeners have been implicated in causing developmental and reproductive toxicity in the Yusho and Yu-Cheng poisoning incidents in Japan and Taiwan (Kuratsune, 1989; Hsu et al., 1985; Rogan, 1989). Thus, exposure to TCDD-like congeners is a health concern for humans as well as for domestic animals, fish, and wildlife, although the relative contributions of TCDD-like and non-TCDD-like congeners are not known in some exposure situations.

A mechanism of action that CDD, BDD, CDF, BDF, PCB, and PBB congeners substituted in the lateral positions have in common is that they bind to the Ah receptor, which dimerizes with the Ah receptor nuclear translocator protein (ARNT) in the nucleus. These liganded heterodimeric complexes bind to specific sequences of DNA referred to as dioxin-responsive enhancers (DREs), resulting in alterations in gene transcription. There is evidence that this Ah receptor mechanism may be involved in the antiestrogenic action of TCDD and in its ability to produce the structural malformations of cleft palate and hydronephrosis in mice. Recent interest has also focused on the potential nonnuclear interaction of the Ah receptor within the cell (see Chapter 2).

5.2. DEVELOPMENTAL TOXICITY

The manifestations of developmental toxicity from exposure to TCDD have been divided into three categories for convenience in assessing the database with respect to an Ah receptor-mediated response. These categories include death/growth/clinical signs, structural malformations, and postnatal functional alterations. Exposure-related effects on death/growth/clinical signs are described for fish, birds, laboratory mammals, and humans along with structure-activity results that are consistent with, but do not prove, an Ah receptor-mediated mechanism. Structural malformations, particularly cleft palate formation and hydronephrosis, occur in mice. In other mammalian species, however, postnatal functional alterations, some of which may be irreversible, are the most sensitive adverse developmental effects of TCDD-like congeners. These include effects on the male and female reproductive systems in rats and hamsters, and object learning behavior in monkeys.

5.2.1. Death/Growth/Clinical Signs

5.2.1.1. *Fish*

Early life stages of fish appear to be more sensitive to TCDD-induced mortality than adults. This is suggested by the LD_{50} of TCDD in rainbow trout sac fry (0.4 μg/kg egg weight) being 25 times less than that in juvenile rainbow trout (10 μg/kg body weight) (Walker and Peterson, 1991; Kleeman et al., 1988). The significance of this finding is that early life stage mortality caused by high concentrations of TCDD-like congeners in fish eggs may pose the greatest risk to feral fish populations (Walker and Peterson, 1991; Cook et al., 1991). Cooper (1989) reviewed the developmental toxicity of CDDs and CDFs in fish, and Cook et al. (1991) discussed components of an aquatic ecological risk assessment for TCDD in fish. The reader is referred to this literature for more indepth coverage than is presented here.

TCDD is directly toxic to early life stages of fish. This has been demonstrated for Japanese medaka, pike, rainbow trout, and lake trout exposed as fertilized eggs to graded concentrations of waterborne TCDD. In these species, TCDD causes an overt toxicity syndrome characterized by edema, hemorrhages, and arrested growth and development culminating in death (Helder, 1980, 1981; Wisk and Cooper, 1990a; Spitsbergen et al., 1991; Walker et al., 1991; Walker and Peterson, 1991). Histopathologic evaluation of lake trout embryos and sac fry has shown this syndrome to be essentially identical to that of blue sac disease (Helder, 1981; Spitsbergen et al., 1991). Following egg exposure to TCDD, signs of toxicity are not detected in medaka until after the liver rudiment forms (Wisk and Cooper, 1990a), and in lake trout toxicity is first detected ~1 week prior to hatching but becomes fully manifest during the sac fry stage (Spitsbergen et al., 1991; Walker et al., 1991). Among all fish species investigated thus far, lake trout are the most sensitive to TCDD developmental toxicity. Following exposure of fertilized

lake trout eggs to graded waterborne concentrations of TCDD, the no observable adverse effect level (NOAEL) for sac fry mortality is 34 pg TCDD/g egg, the lowest observed adverse effect level (LOAEL) is 55 pg TCDD/g egg, and the egg TCDD concentration that causes 50% mortality above control at swim up (LD_{50}) is 65 pg TCDD/g egg (Walker et al., 1991). Thus, TCDD is a potent developmental toxicant in fish, and the effect is not secondary to maternal toxicity.

The Ah receptor has not been identified in early life stages of fish; however, it is assumed to be present because PCBs induce hepatic cytochrome P-4501A1 in lake trout and brook trout embryos and fry (Binder and Stegeman, 1983; Binder and Lech, 1984). The Ah receptor has been identified in adult rainbow trout liver (Heilmann et al., 1988) and in a rainbow trout hepatoma cell line (Lorenzen and Okey, 1990). CDD and CDF congeners that are approximate isostereomers of TCDD produce essentially the same pattern of toxic responses as TCDD in early life stages of medaka and rainbow trout, suggesting that they may act through a common mechanism (Wisk and Cooper, 1990b; Walker and Peterson, 1991). Also, in rainbow trout their potencies relative to TCDD (i.e., toxic equivalency factors, TEFs) for causing early life stage mortality (TCDD LD_{50}/congener LD_{50}) are in the same range as those proposed for human health risk assessment based on a diverse spectrum of acute and subchronic toxicity tests in mammalian species (Safe, 1990; Walker and Peterson, 1991). However, for the coplanar PCBs and monoortho-chlorinated analogs of the coplanar PCBs, TEFs based on early life stage mortality in rainbow trout are 1/14 to 1/80 less (Walker and Peterson, 1991) than the TEFs proposed for risk assessment (Safe, 1990).

5.2.1.2. *Birds*

Bird embryos are also more sensitive to TCDD toxicity than adults. The LD_{50} of TCDD in the chicken embryo (0.25 μg/kg egg weight) is 100 to 200 times less than the TCDD dose that causes mortality in adult chickens (25-50 μg/kg body weight) (Greig et al., 1973; Allred and Strange, 1977). The LD_{50} of TCDD injected into fertilized ring-necked pheasant eggs (1.1-1.8 μg/kg egg weight) is 14 to 23 times less than the TCDD dose that causes 75% mortality in ring-necked hen pheasants (25 μg/kg body weight) (Nosek et al., 1993).

Among bird species, most developmental toxicity research has been done on chickens. Injection of TCDD or its approximate isostereomers into fertilized chicken eggs causes a toxicity syndrome in the embryo characterized by pericardial and subcutaneous edema, liver lesions, inhibition of lymphoid development in the thymus and bursa of Fabricius, microphthalmia, beak deformities, cardiovascular malformations, and mortality (Cheung et al., 1981a,b; Brunstrom and Darnerud, 1983; Rifkind et al., 1985; Brunstrom and Lund, 1988; Brunstrom and Andersson, 1988; Nikolaidis et al., 1988a,b). On the other hand, injection of a coplanar PCB into fertilized

turkey eggs at a dose high enough to cause microphthalmia, beak deformities, and embryo mortality did not produce liver lesions, edema, or thymic hypoplasia, all hallmark signs of TCDD toxicity in the chicken embryo (Brunstrom and Lund, 1988). This disparity in signs of TCDD embryotoxicity among bird species is not unique to the turkey and chicken. In fertilized eggs of ring-necked pheasants and eastern bluebirds, injection of TCDD produces embryo mortality, but all of the other signs of toxicity seen in the chicken embryo are absent, including cardiovascular malformations (Thiel et al., 1988; Martin et al., 1989; Nosek et al., 1993). Thus, in bird embryos the signs of toxicity elicited by TCDD and its approximate isostereomers are highly species dependent; the only toxic effect common to all bird species is embryo mortality.

There is evidence in chicken embryos that the Ah receptor may be involved in producing developmental toxicity. The Ah receptor has been detected in chicken embryos (Denison et al., 1986; Brunstrom and Lund, 1988) and the rank order potency of PCB congeners for producing chicken embryo mortality (3,3',4,4',5-PCB > 3,3',4,4'-TCB > 3,3',4,4',5,5'-HCB > 2,3,3',4,4'-PCB > 2,3,4,4',5-PCB, with 2,2',4,5'-TCB, 2,2',4,4',5,5'-HCB, and 2,2',3,3',6,6'-HCB being inactive) is similar to that for a classic Ah receptor-mediated response in the chicken embryo, cytochrome P-4501A1 induction (Rifkind et al., 1985; Brunstrom and Andersson, 1988; Brunstrom, 1989). However, although induction of cytochrome P-4501A1 and toxicity may both be part of a pleiotropic response linked to the Ah receptor, they are not otherwise causally related. This is demonstrated by the nonsteroidal anti-inflammatory drug benoxoprofen that suppresses 3,3',4,4'-TCB-induced toxicity in the chicken embryo without altering its ability to induce microsomal enzyme activity (Rifkind and Muschick, 1983). Also, for 3,3',4,4'-TCB, 3,3',4,4',5,5'-HCB, and TCDD there is a marked dissociation of the dose-response relationship for lethality and enzyme induction in the chicken embryo (Rifkind et al., 1985).

A decreased activity of uroporphyrinogen decarboxylase (URO-D) and an increased accumulation of uroporphyrins are effects that are readily produced by exposure of cultured chicken embryo liver cells to TCDD, 3,3',4,4'-TCB, and other PCBs (Sinclair et al., 1984; Marks, 1985; Lambrecht et al., 1988). Coplanar PCB congeners are more potent inhibitors of URO-D activity in cultured chicken embryo liver cells than are noncoplanar PCB congeners (Sassa et al., 1986), suggesting an Ah receptor-mediated mechanism. Unlike the results in cultured cells, however, a lethal dose of TCDD (6 nmol/egg) does not affect URO-D activity or cause an increased accumulation of uroporphyrins in chicken embryos (Rifkind et al., 1985). Thus, TCDD-induced lethality in chicken embryos is not associated with the effects of TCDD on URO-D activity, even though a decrease in URO-D activity might be expected to occur if a sufficient dose of TCDD could be reached without being lethal.

The chicken embryo heart is a target organ for TCDD and other halogenated aromatic hydrocarbons that act by an Ah receptor mechanism. Expression of the Ah receptor occurs

ubiquitously in cardiac myocytes, while ARNT expression is restricted to myocytes that overlay the atrioventricular canal, outflow tract, and atrial and ventricular septa (Walker et al., 1997). Both Ah receptor and ARNT appear to be absent from the endocardium and endocardial- derived mesenchyme. In addition, cardiac expression of cytochrome P-4501A1 is restricted to myocardium that expresses Ah receptor and ARNT. The classic sign of chick embryo toxicity involving the heart is pericardial edema. However, TCDD has other effects on the chick embryo heart that are less well known. These include its ability to produce cardiovascular malformations and to increase cardiac release of arachidonic acid metabolites. When fertilized chicken eggs are injected with graded doses of TCDD, cardiovascular malformations are produced including ventricular septal defects, aortic arch anomalies, and conotruncal malformations. Approximately 1.6 pmol TCDD/egg (9 ng/kg egg, assuming a 55 g egg weight) causes cardiovascular malformations in 46% of treated embryos versus 29% of control embryos (Cheung et al., 1981a,b). The cardiovascular malformation response may be unique to the chicken embryo because in fertilized ring-necked pheasant and eastern bluebird eggs injected with TCDD the incidence of such malformations is not increased (Thiel et al., 1988; Martin et al., 1989; Nosek et al., 1993).

In the chicken embryo heart, arachidonic acid metabolism is stimulated by TCDD, resulting in increased formation of prostaglandins (Quilley and Rifkind, 1986). Dose-response relationships for the release of immunoreactive PGE_2, PGF_{2a}, and TxB_2 from chick embryonic heart are biphasic, with an apparent maximally effective dose of 100 pmol TCDD/egg. When the egg tetrachloroabenzene (TCDD) dose is further increased, release of these prostaglandins tends to decline towards levels in control hearts. Biphasic dose-response curves for cardiac PGE_2 release also were obtained with 3,3',4,4'-TCB and 3,3',4,4',5,5'-HCB (Quilley and Rifkind, 1986). The thymus and bursa of Fabricius are other TCDD target organs in the chicken embryo. TCDD, 3,3',4,4'-TCB, and 3,3',4,4'-TCAOB cause dose-related decreases in the lymphoid development of both of these immune system organs (Nikolaidis et al., 1988a,b, 1990). Cultured thymus anlage from chick embryos are 100 times more sensitive to TCDD's inhibitory effect on lymphoid development than cultured thymus anlage from turkey and duck embryos (Nikolaidis et al., 1988a). This suggests that the reason thymic atrophy was not seen in turkey embryos at egg doses of 3,3',4,4'-TCB that were overtly toxic (Brunstrom and Lund, 1988) was not because the turkey embryo thymus was incapable of responding to 3,3',4,4'-TCB. Rather, turkey embryos appear to be more sensitive to the lethal than to the immunotoxic effect of this coplanar PCB.

Within the same bird species, the signs of developmental toxicity elicited by TCDD and its approximate isostereomers are similar. In the chicken embryo, TCDD, 3,3',4,4',5-PCB, 3,3',4,4'-TCB, and 3,3',4,4',5,5'-HCB all cause pericardial and subcutaneous edema, liver lesions, microphthalmia, beak deformities, and mortality, and TCDD, 3,3',4,4'-TCB, and 3,3',4,4'-

TCAOB inhibit lymphoid development (Cheung et al., 1981a; Brunstrom and Andersson, 1988; Nikolaidis et al., 1988a,b). In pheasant embryos, an altogether different pattern of responses is seen. Nevertheless, the TCDD-like congeners injected into fertilized pheasant eggs, TCDD and 3,3',4,4'-TCB, produce the same pheasant embryo-specific pattern. This pattern consists of embryo mortality in the absence of edema, liver lesions, thymic hypoplasia, and structural malformations (Brunstrom and Reutergardh, 1986; Nosek et al., 1993).

The lethal potency of TCDD and its approximate isostereomers in embryos of different bird species varies widely. The chicken embryo is an outlier in that it is by far the most sensitive of all bird species to TCDD. Turkey, ring-necked pheasant, mallard duck, domestic duck, domestic goose, golden-eye, herring gull, black-headed gull, and eastern bluebird embryos are considerably less sensitive to the embryo-lethal effect of TCDD and TCDD-like congeners (Brunstrom and Reutergardh, 1986; Brunstrom and Lund, 1988; Thiel et al., 1988; Martin et al., 1989; Elliott et al., 1989; Nosek et al., 1993). TCDD is 4 to 7 times more potent in causing embryo mortality in chicken than pheasant embryos, and 3,3',4,4'-TCB is 20 to 100 times more potent in chicken than turkey embryos (Allred and Strange, 1977; Brunstrom and Lund, 1988; Nosek et al., 1989). In chicken embryos, an egg dose of 3,3',4,4'-TCB of 4 μg/kg increased embryo mortality, whereas an egg dose of 100 μg/kg of the same coplanar PCB had no embryotoxic effect in pheasants and mallard ducks and a dose of 1,000 μg/kg egg had no effect on embryo mortality in domestic ducks, domestic geese, golden eyes, herring gulls, and black-headed gulls (Brunstrom, 1988; Brunstrom and Reutergardh, 1986). In contrast to the above species differences, the potency of 3,3',4,4'-TCB in causing embryo mortality among different strains of chickens is quite similar, with the LD_{50} in six different strains varying less than fourfold (Brunstrom, 1988).

Graded doses of TCDD have been administered to fertilized eastern bluebird and ring-necked pheasant eggs for the purpose of determining a LOAEL and NOAEL for embryotoxicity. Mortality was the most sensitive embryotoxic effect in both species. For eastern bluebirds, the LOAEL was 10,000 pg TCDD/g egg and the NOAEL was 1,000 pg TCDD/g egg (Martin et al., 1989). For ring-necked pheasants, the LOAEL was 1,000 pg TCDD/g egg and the NOAEL was 100 pg TCDD/g egg. The LD_{50} for embryo mortality in the ring-necked pheasant is 1,354 pg TCDD/g egg when the dose is injected into the egg albumin and 2,182 pg TCDD/g egg when the dose is injected into the egg yolk (Nosek et al., 1993). In contrast, for chickens the LD_{50} for embryo mortality is 240 pg TCDD/g egg (Allred and Strange, 1977).

5.2.1.3. *Laboratory Mammals*

5.2.1.3.1. ***Developmental expression of Ah receptor and ARNT***. The Ah receptor and its dimerization partner ARNT are expressed in a specific spatial and temporal pattern in the

developing mammalian embryo and fetus, suggesting that they play a fundamental role in development. Preimplantation mouse embryos express Ah receptor mRNA and protein (Peters et al., 1995), and spatial and temporal patterns of ARNT1, ARNT2, and Ah receptor mRNA expression occur in specific developing tissues and organs of the mouse embryo from gestational day 9.5 to 16 (Abbott et al., 1995; Abbott et al., 1995; Jain et al., 1998). On gestational day 9.5, ARNT1 mRNA is highly expressed in the neuroepithelium of the brain and spinal cord, trigeminal ganglion, branchial arches 1 and 2, heart, hepatic primordia, and primitive gut. ARNT2 message is also expressed in the neuroepithelium and in the remainder of the embryo but at comparatively lower levels. Ah receptor mRNA, in contrast to ARNT1 and ARNT2, is not expressed significantly at gestational day 9.5, but by gestational day 10 Ah receptor mRNA was expressed in the neuroepithelium of the developing brain, in the visceral arches, and in the heart. By day 13.5 or 14 of gestation, Ah receptor mRNA was abundantly expressed in the primitive pituitary, palatal shelf, nasal septal cartilage, dorsal surface of the tongue, developing thymus, lung parenchyma, liver, developing gut mucosa, kidney, urogenital sinus, and tip of the genital tubercle. ARNT1 mRNA was expressed to a high extent in various cell types of endodermal and mesodermal origin such as the lung and tongue muscle and was barely above background in the developing nervous system. The tissue distribution of ARNT2 mRNA was the inverse of ARNT1, being highest in the mantle layer of the spinal cord and brain and lowest in the endodermal and mesodermally derived tissues. The expression patterns observed at gestational day 13.5 or 14 continued to be found at gestational day 15.5 or 16 with the additional finding that ARNT2 was clearly expressed in neural crest derivatives like the dorsal root ganglia, adrenal medulla, and in developing tubules in the renal cortex. Thus, the expression of Ah receptor, ARNT1, and ARNT2 mRNAs was specific for cell type, organ/tissue, and developmental stage. Furthermore, immunohistochemical localization of Ah receptor and ARNT1 protein correlated, in general, with in situ localization of Ah receptor and ARNT1 mRNA expression at each gestational age (Abbott et al., 1995; Abbott and Probst, 1995).

5.2.1.3.2. ***Transgenic Ah receptor null mice and ARNT null mice.*** Ah receptor null (knockout) mice have been developed to determine which adverse effects of TCDD exposure are Ah receptor mediated, and to determine the effects of absence of the Ah receptor on organ system development and function. Three lines of Ah receptor null mice have been generated using different targeting methods and they are on the following genetic backgrounds: C57BL/6N x Sv/129 (Fernandez-Salguero et al., 1995), substrain of C57BL/6 x Sv/129 (Schmidt et al., 1996) and C57BL/6J x Sv/129 (Mimura et al., 1997). Ah receptor null mice in all the lines are viable, and offspring of both sexes are fertile and capable of reproduction. However, Abbott et al. (1999) reported adverse reproductive outcomes in homozygous AhR null female mice in the line

of Fernandez-Salguero et al. (1995). The range of adverse reproductive effects included deaths of the females during pregnancy and lactation, small litter size at birth, poor survival of pups during the first 2 weeks after birth, and death of Ah receptor null pups after weaning. Because low survival of the weaned homozygous Ah receptor null pups was independent of genotype of the dam, it was probably not caused by maternal factors like lactational insufficiency or aberrant maternal behaviors. However, the increased mortality of fetuses and pups prior to weaning could be due in part to impaired ability of the homozygous Ah receptor null female to support development of the fetuses, to survive pregnancy and lactation herself, and to rear pups until weaning (Abbott et al., 1999c).

The profile of effects observed in the homozygous Ah receptor null offspring were dependent on the Ah receptor null line investigated and consisted of lesions in the immune system, skin, liver, heart, stomach, spleen, and uterus (Fernandez-Salguero et al., 1995, 1996, 1997; Schmidt et al., 1996). These findings suggest that the AhR signaling pathway plays an important physiological role in development and in maintaining homeostasis as offspring age (Fernandez-Salguero et al., 1996, 1997; Schmidt et al., 1996;). Transgenic mice with a null mutation in the ARNT1 gene have also been evaluated, and unlike their AhR counterparts homozygous ARNT1 null embryos are not viable (Kozak et al., 1997; Maltepe et al., 1997). They are affected by neural tube closure defects, forebrain hypoplasia, delayed rotation of the embryo, placental hemorrhaging, visceral arch abnormalities, and death between gestational days 9.5-10.5 (Kozak et al., 1997). The primary cause of embryo mortality may be failure of the embryonic component of the placenta to vascularize and form the labyrinthine spongiotrophoblast, which is consistent with ARNT1's role in hypoxic induction of angiogenesis (Kozak et al., 1997). Thus, the ARNT1 protein appears to play an indispensable role during development that is essential for embryo survival.

5.2.1.3.3. ***Prenatal mortality.*** When exposed to TCDD during adulthood, laboratory mammals display wide differences in the LD_{50} of TCDD. It is interesting to note, however, that when exposure occurs during prenatal development, the potency of TCDD tends to be more similar across species. The LD_{50} of TCDD in adult hamsters, 1,157 to 5,051 μg/kg, makes adult hamsters three orders of magnitude more resistant to TCDD-induced lethality than are adult guinea pigs (Olson et al., 1980; Henck et al., 1981). Yet, a maternal dose of 18 μg TCDD/kg can increase the incidence of prenatal mortality in the hamster embryo/fetus. Because this dose is only twelvefold higher than the dose (1.5 μg TCDD/kg) that increases the incidence of prenatal mortality in the guinea pig, the hamster embryo/fetus approaches other rodent species in its sensitivity to TCDD-induced lethality (Olson and McGarrigle, 1990, 1991). Thus, the magnitude

of the species differences in lethal potency of TCDD is affected by the timing of TCDD exposure during the life history of the animal.

Exposure to TCDD during pregnancy causes prenatal mortality in the monkey, guinea pig, rabbit, rat, hamster, and mouse (Table 5-1). The rank order of susceptibility from the most sensitive to least sensitive species would appear to be monkey = guinea pig > rabbit = rat = hamster > mouse. However, an important caveat must be applied to the information presented in Table 5-1; i.e., that the time period during which exposure of the embryo/fetus to TCDD occurs is just as important a determinant of prenatal mortality as is the dose of TCDD administered. This point will be illustrated in the text that follows when prenatal mortality is described for different strains of mice.

It is important to note that the concept of a critical time period for exposure makes the analysis of lethality data in the embryo/fetus qualitatively different from that which might be applied to similar data in adult animals. For example, a common dosing regimen used in mice, rats, and rabbits (Table 5-1) is to administer 10 daily doses of TCDD to the pregnant dam on days ~6 to 15 of gestation. This dosing regimen is expected to cover the critical period of early development that results in the greatest incidence of prenatal toxicity. In nearly all species of adult laboratory mammals, however, a single lethal dose of TCDD would be expected to produce a similar delayed-onset death regardless of the age of the adult animal. Susceptibility to TCDD-induced prenatal mortality, in contrast, may be greatly dependent on the age of the embryo/fetus. In this case, multiple doses of TCDD that cover this critical period might result in prenatal mortality, whereas a single dose might miss the critical time and not result in prenatal mortality.

The following paragraphs illustrate a type of analysis using an index of cumulative maternal dose similar to the type of analysis that might be applied to lethality data resulting from multiple dosing of adult animals. After presenting the results of applying this type of analysis to prenatal mortality data from different species, the caveat of critical time dependence will be applied to the data obtained by using different strains of mice. This will illustrate the importance of considering dosage regimen when evaluating prenatal mortality data that are available in the literature. In this case, a difference of 1 gestational day might be critically important. It turns out that the form of analysis using cumulative maternal dose may give the greatest possible degree of species variation. As such, different species may actually be more similar with respect to susceptibility to prenatal mortality than would be apparent from results of this type of analysis.

Using the cumulative dose data that are given in Table 5-1, there appears to be a tenfold to twentyfold difference in the fetolethal potency of TCDD when the monkey/guinea pig is compared with the rabbit/rat/hamster. In the CD-1 mouse treated with TCDD on gestational days 7 to 16, it appears that a daily dose of 200 μg TCDD/kg is required to significantly increase prenatal mortality. Given a ~5.5-day half-life of TCDD in the pregnant dam (Weber and

Birnbaum, 1985), the pregnant CD-1 mouse would be exposed to a maximal accumulated dose of ~1,200 μg TCDD/kg by the lowest dosage regimen that significantly increased prenatal mortality. Therefore, by using the index of cumulative dose, the CD-1 mouse would appear to be ~1,200-fold less sensitive than the monkey/guinea pig for TCDD-induced prenatal mortality. However, in NMRI mice administered TCDD only on day 6 of gestation, prenatal mortality begins to increase after a single dose of 45 μg TCDD/kg (Neubert and Dillman, 1972). The NMRI embryo/fetus is less susceptible to TCDD-induced prenatal mortality when the TCDD is administered on later gestational days up to day 15. Thus, there appears to be only an approximate 45-fold difference between the monkey/guinea pig and the NMRI mouse when the NMRI embryo/fetus is exposed specifically on day 6. In C57BL/6 mice, prenatal mortality is significantly increased after a single maternal dose of 24 μg TCDD/kg given on gestational day 6 (Couture et al., 1990a). This mouse strain, therefore, is about twentyfold to thirtyfold less sensitive to TCDD-induced prenatal mortality than is the monkey/guinea pig when exposed specifically on day 6. As with the NMRI mouse, there was little or no increase in prenatal mortality for the C57BL/6 strain when TCDD was administered to the pregnant dam on gestational days 8, 10, 12, or 14.

Peters et al. (1999) administered a single maternal dose of 25 μg/kg of TCDD on gestational day 10 to Ah receptor wild-type or null female mice (Fernandez-Salguero et al., 1995). In the homozygous Ah receptor wild-type dams and their homozygous Ah receptor wild-type fetuses there was no increase in prenatal mortality. However, in the homozygous Ah receptor null dams and their homozygous Ah receptor null fetuses TCDD increased prenatal mortality, as evidenced by an increase in percentage of resorptions. Mimura et al. (1997) also found that TCDD increased resorptions to a greater extent in Ah receptor null dams compared with Ah receptor wild-type dams. These findings suggest that mechanisms that do not require the Ah receptor may mediate, in part, the increase in prenatal mortality caused by TCDD (Peters et al., 1999).

An important finding about predicting TCDD-induced prenatal mortality is that strain differences in lethal potency of TCDD, when animals are exposed in adulthood, does not predict strain differences in lethal potency of TCDD for causing embryo/fetal mortality. Certain rat strains display wide differences in sensitivity to lethality when TCDD is given in adulthood. The Long Evans rat has a wild-type Ah receptor while the Han/Wistar rat contains a point mutation in its Ah receptor gene that results in a splice variant Ah receptor protein that binds TCDD (Pohjanvirta et al., 1998). While Long Evans and Han/Wistar rats are equally sensitive to TCDD-induced hepatic cytochrome P-4501A1 induction, the Han/Wistar strain is far less sensitive to TCDD-induced lethality than the Long Evans strain when both strains are treated with TCDD in adulthood (Pohjanvirta et al., 1993; Unkila et al., 1994). However, when these

same strains are exposed to TCDD during pregnancy, the maternal doses of TCDD administered on gestational days 8 and 12 that cause fetotoxicity and fetal lethality are similar (Huuskonen et al., 1994).

Mammalian pregnancies (including human) are characterized by critical periods or "windows" during which the embryo/fetus exhibits different susceptibilities and responses to chemical exposures. The susceptibility of any particular endpoint depends on the developmental state of that endpoint at the time of exposure. The embryo/fetus is constantly changing at all biological levels (e.g., cellular, tissue, organism), and the mechanisms of action, response, and repair of a particular endpoint at the time of exposure are the determinants of whether a response to a given exposure will result in a developmental alteration or not.

The concept of a critical window for TCDD-induced lethality in the embryo/fetus suggests an explanation for the apparent insensitivity of the CD-1 mouse embryo/fetus exposed to cumulative doses of TCDD. It could very well be that the critical window for prenatal mortality in the mouse occurs on or before gestational day 6. If the embryo/fetus is not exposed to TCDD by gestational day 6, much larger doses of TCDD are required to produce prenatal mortality. Given that exposure of the pregnant CD-1 dams did not begin until gestational day 7, this interpretation is consistent with the ability of a single 24 μg TCDD/kg dose to increase the incidence of prenatal mortality when administered to pregnant C57BL/6 mice on gestational day 6, but not when administered on gestational days 8, 10, 12, or 14 (Couture et al., 1990a). Similarly, Neubert and Dillman (1972) found that the largest increase in prenatal mortality occurred when a single dose of TCDD was given on gestational day 6 compared with prenatal mortality when the TCDD dose was administered on one of gestational days 7 to 15. In addition, this would suggest that the CD-1 embryo/fetus does not have quite the relative insensitivity to the lethal effects of TCDD compared with the embryo/fetus of other species indicated by using cumulative maternal dose as the index of exposure.

It should be noted that the concept of a critical window for prenatal mortality could potentially alter all of the species comparisons made previously that were based on the cumulative maternal doses shown in Table 5-1. If this turned out to be the case, then the true differences between species with respect to their susceptibility to TCDD-induced prenatal mortality could be substantially less than those indicated by using the cumulative maternal dose. This, of course, would involve a comparison between species using only single doses of TCDD given during the critical time period for each species. At the present time, it is not possible to make such a comparison from the information available in the literature.

Similar to fish and birds, the mammalian embryo/fetus is more sensitive to the lethal action of TCDD than the adult. The maternal dose of TCDD that causes 58% fetal mortality in hamsters is 64 to 280 times less than the LD_{50} of TCDD in adult hamsters (Olson et al., 1980;

Henck et al., 1981; Olson et al., 1990). In Sprague-Dawley rats, the cumulative maternal dose of TCDD that causes 41% prenatal mortality is 5 to 10 times less than the approximate LD_{50} of TCDD in adult rats of the same strain (Sparschu et al., 1971; Seefeld et al., 1984). In rhesus monkeys, the cumulative maternal TCDD dose that causes 81% prenatal mortality is 6 and 25 times less, respectively, than the lowest TCDD dose reported to cause mortality in 1-year-old and adult rhesus monkeys (McNulty, 1977, 1985; Seefeld et al., 1979).

Table 5-1 suggests that in many animal species (guinea pig, rabbit, rat, and mouse), TCDD-induced prenatal mortality is most commonly associated with maternal toxicity that is not severe enough to result in maternal lethality. In each of these species, the dose-response relationship for maternal toxicity, indicated by decreased maternal weight gain and/or marked subcutaneous edema of the dam, is essentially the same as that for increased prenatal mortality. Even in the hamster, where maternal toxicity is far less severe, fetuses exhibit increases in neutrophilic metamyelocytes and bands, and increases in leukocyte number and bands are also found in maternal blood (Olson and McGarrigle, 1991). In mice, it has been shown that TCDD exposure causes rupture of the embryo-maternal vascular barrier, which results in hemorrhage of fetal blood into the maternal circulation (Khera, 1992). Also, pregnant CF1 mice treated with 30 μg TCDD/kg on gestational day 12 exhibited 1.9- and 1.5-fold increases in lipid peroxidation in placental and fetal tissues, respectively, on gestational day 14. This was associated with 1.4- to 2.5-fold increases in lipid metabolite levels of malondialdehyde, formaldehyde, acetaldehyde, and acetone in amniotic fluid (Hassoun et al., 1995).

In spite of this general association between maternal and fetal toxicity, prenatal and postnatal lethality can occur in the absence of overt maternal toxicity. Olson and McGarrigle (1991) reported prenatal death but no maternal toxicity in the hamster at 18 μg/kg TCDD, the highest dose in their study. Likewise, studies in the rat demonstrate that both prenatal death (Bjerke and Peterson, 1994) and postnatal death (Gray et al., 1995) can occur in response to exposure during gestation that does not result in overt maternal toxicity (see Section 5.2.3).

In rhesus monkeys, fewer data are available to make the association between prenatal mortality and maternal toxicity. Nevertheless, the results following dietary exposure to 25 ppt TCDD (Bowman et al., 1989a; Schantz and Bowman, 1989) and 50 ppt TCDD (Allen et al., 1977, 1979; Barsotti et al., 1979; Schantz et al., 1979) before and during pregnancy suggest that TCDD-induced prenatal mortality can occur in monkeys in the absence of overt toxic effects on the mother (see Section 5.3.1). In other studies, developmental toxicity in monkeys exposed to a total cumulative maternal dose of 1 μg TCDD/kg administered during the first trimester indicated a high incidence of prenatal mortality (McNulty, 1984, 1985). However, maternal toxicity occurred in some but not all of the mothers exposed. In these monkeys, 13 of 16 pregnancies resulted in prenatal mortality. Within 20 to 147 days after aborting, 8 of the 13 females that had

aborted showed signs of maternal toxicity and 3 of these monkeys died. Thus, the remaining 5 of 13 instances of prenatal mortality apparently occurred in the absence of overt maternal toxicity. The results of these studies indicate that some levels of TCDD exposure can result in prenatal mortality in monkeys even though overt toxicity seems absent in the mother. As will be described (Section 5.3.1.1), however, only limited attention has been given to female reproductive toxicity in general and to the effects of maternal toxicity during pregnancy on fetal development in particular. Therefore, the relationship between maternal toxicity and prenatal mortality in the monkey is not well established. The integrity of the embryo-vascular barrier, for example, has not been evaluated after TCDD exposure.

Gestational exposure to TCDD produces a characteristic pattern of fetotoxic responses in most laboratory mammals consisting of thymic hypoplasia, subcutaneous edema, decreased fetal growth, and prenatal mortality. Added to these common effects on development are other effects of TCDD that are highly species-specific. Examples of the latter are cleft palate formation in the mouse and intestinal hemorrhage in the rat. Table 5-2 shows those maternal and developmental responses that are produced by gestational exposure to TCDD in various species of laboratory mammals. In the mouse, hydronephrosis is the most sensitive effect of prenatal toxicity, followed by cleft palate formation and atrophy of the thymus at higher doses, and by subcutaneous edema and mortality at maternally toxic doses (Couture et al., 1990b; Courtney, 1976; Courtney and Moore, 1971; Neubert and Dillman, 1972). In the rat, TCDD prenatal toxicity is manifested by intestinal hemorrhage, subcutaneous edema, decreased fetal growth, and mortality (Sparschu et al., 1971; Khera and Ruddick, 1973). Structural abnormalities do occur in the rat, but only at relatively large doses (Couture et al., 1990b). In the hamster fetus, hydronephrosis and renal congestion are the most sensitive effects, followed by subcutaneous edema and prenatal mortality (Olson and McGarrigle, 1991). In the rabbit, an increased incidence of extra ribs and prenatal mortality is found (Giavini et al., 1982a), and in the guinea pig and rhesus monkey, prenatal mortality is seen (Olson and McGarrigle, 1991; McNulty, 1984).

5.2.1.4. *Structure-Activity Relationships in Laboratory Mammals*

The structure-activity relationship for developmental toxicity in laboratory mammals is generally similar to that for Ah receptor binding. Gestational treatment of rats with CDD congeners that do not bind the Ah receptor (2-MCDD, 2,7-DCDD, 2,3-DCDD, or 1,2,3,4-TCDD) do not cause TCDD-like effects on development (Khera and Ruddick, 1973). On the other hand, hexachlorodibenzo-*p*-dioxin, which has intrinsic Ah receptor activity, produces fetotoxic responses in rats that are essentially identical to those of TCDD (Schwetz et al., 1973). Similarly, when administered to pregnant rhesus monkeys or CD-1 mice, PCB congeners that act by an Ah receptor-mediated mechanism (3,3',4,4'-TCB and 3,3',4,4',5,5'-HCB) cause the same

type of developmental effects as TCDD. In contrast, 4,4'-DCB, 3,3',5,5'-TCB, 2,2',4,4',5,5'-HCB, 2,2',4,4',6,6'-HCB, and 2,2',3,3',5,5'-HCB, which have essentially no or a very weak affinity for the Ah receptor, do not produce a TCDD-like pattern of prenatal toxicity in mice (Marks and Staples, 1980; Marks et al., 1981, 1989; McNulty, 1985). Thus, most structure-activity results for overt developmental effects of the halogenated aromatic hydrocarbons are consistent with an Ah receptor-mediated mechanism. Nevertheless, one finding that stands out as being inconsistent is that 2,2',3,3',4,4'-HCB, which has a very weak, if any, affinity for binding to the Ah receptor, causes the same pattern of developmental effects in mice as TCDD (Marks and Staples, 1980).

5.2.1.5. *Humans*

In the Yusho and Yu-Cheng poisoning episodes, developmental toxicity was reported in babies born to affected mothers who consumed rice oil contaminated with PCBs, CDFs, and PCQs (Hsu et al., 1985; Yamashita and Hayashi, 1985; Kuratsune, 1989; Rogan, 1989; Masada, 1994; Hsu et al., 1994). In these incidents, it is essentially impossible to determine the contribution of TCDD-like versus non-TCDD-like congeners to the fetal/neonatal toxicity. Nevertheless, high perinatal mortality was observed among hyperpigmented infants born to affected Yu-Cheng women who themselves did not experience increased mortality (Hsu et al., 1985). Thus, in humans the developing embryo/fetus may be more sensitive than the intoxicated mother to mortality caused by halogenated aromatic hydrocarbons.

In most cases, women who had affected children in the Yusho and Yu-Cheng episodes had chloracne themselves (Rogan, 1982). Based on this evidence, Rogan (1982) suggested that "exposure to amounts insufficient to produce some effect on the mother probably lessens the chance of fetopathy considerably." In support of this interpretation, overt signs of halogenated aromatic hydrocarbon toxicity were not observed in infants born to apparently unaffected mothers in the Seveso, Italy, and Times Beach, Missouri, TCDD incidents (Reggiani, 1989; Hoffman and Stehr-Green, 1989).

Effects of chemical exposure on normal development of the human fetus can have four outcomes depending on the dose and time during gestation when exposure occurs: fetal death, growth retardation, structural malformations, and organ system dysfunction. In the Yusho and/or Yu-Cheng incidents, all of these outcomes were found (Yamashita and Hayashi, 1985; Kuratsune, 1989; Rogan, 1989; Masada; 1994; Hsu et al., 1994). Increased prenatal mortality and low birthweight suggesting fetal growth retardation were observed in affected Yusho and Yu-Cheng women (Wong and Hwang, 1981; Law et al., 1981; Yamashita and Hayashi, 1985; Hsu et al., 1985; Miller, 1985; Lan et al., 1989; Rogan et al., 1988). In a follow-up of the Yu-Cheng children at elementary school age, Guo et al. (1994) reported decreased height and muscle

development in children who were the first born to women who were exposed. A structural malformation, rocker bottom heel, was observed in Yusho infants (Yamashita and Hayashi, 1985). Organ dysfunction involving the central nervous system (CNS) that was characterized by delays in attaining developmental milestones and by neurobehavioral abnormalities was reported in Yu-Cheng children exposed transplacentally (Rogan et al., 1988).

Organs and tissues that originate from embryonic ectoderm are well-known targets for toxicity following exposure to TCDD-like halogenated aromatic hydrocarbons. For example, treatment of adult monkeys with TCDD results in effects involving the skin, meibomian glands, and nails (Allen et al., 1977). Similarly, a hallmark sign of fetal/neonatal toxicity in the Yusho and Yu-Cheng episodes is an ectodermal dysplasia syndrome. It is characterized by hyperpigmentation of the skin and mucous membranes, hyperpigmentation and deformation of fingernails and toenails, hypersecretion of the meibomian glands, conjunctivitis, gingival hyperplasia, presence of erupted teeth in newborn infants, altered eruption of permanent teeth, missing permanent teeth, and abnormally shaped tooth roots (Taki et al., 1969; Yamaguchi et al., 1971; Funatsu et al., 1971; Wong and Hwang, 1981; Hsu et al., 1985; Yamashita and Hayashi, 1985; Rogan et al., 1988; Kuratsune, 1989; Rogan, 1989; Lan et al., 1989). Accelerated tooth eruption has been observed in newborn mice exposed to TCDD by lactation (Madhukar et al., 1984), as well as in the human infants mentioned above. In addition, other effects have been reported in Yusho and Yu-Cheng exposed infants that resemble those observed following TCDD exposure in adult monkeys. These include subcutaneous edema of the face and eyelids (Allen et al., 1977; Moore et al., 1979; Law et al., 1981; Yamashita and Hayashi, 1985; Rogan et al., 1988). Also, larger and wider fontanels and abnormal lung auscultation were found in the human infants (Law et al., 1981; Yamashita and Hayashi, 1985; Rogan et al., 1988). The similarities between certain effects reported in human infants exposed during the Yusho and Yu-Cheng incidents, as well as in adult monkeys and neonatal mice exposed to TCDD, enhance the probability that certain effects reported in human infants were caused by the TCDD-like PCB and CDF congeners in the contaminated rice oil ingested by the mothers of these infants.

Although chloracne is the most often cited effect of TCDD exposure involving the skin in adult humans, has an animal correlate in the hairless mouse, and can be studied by using a mouse teratoma cell line in tissue culture (Poland and Knutson, 1982), it has rarely been recognized in the TCDD literature that the nervous system, like the skin, is derived from embryonic ectoderm (Balinsky, 1970). As will be described in Section 5.2.3.2, neurobehavioral effects occur following transplacental and neonatal exposure to TCDD-like congeners in mice, as well as transplacental exposure to TCDD itself in monkeys. In addition, in some of the Yu-Cheng children who were exposed transplacentally to PCBs, PCDFs, and PCQs, there was a clinical impression of developmental delay or psychomotor delay including impairment of intellectual

development (Rogan et al., 1988). As there is a clustering of effects due to TCDD-induced toxicity in organs derived from ectoderm, it is possible to speculate that direct effects of TCDD-like congeners on the CNS are responsible for some of the neurobehavioral effects observed in these children. Effects of TCDD on EGF receptors are associated with certain aspects of the ectodermal dysplasia syndrome such as hyperkeratinization of the skin (Osborne and Greenlee, 1985) and accelerated tooth eruption (Madhukar et al., 1984). Decreased autophosphorylation of the EGF receptor in human placentas is associated with decreased birthweight in infants born to exposed mothers 4 years after the initial Yu-Cheng exposure incident (Sunahara et al., 1987). This last result supports the earlier conclusion that careful study is needed to define the relationship between maternal toxicity, placental toxicity, and developmental toxicity in humans. In addition, further research is needed to characterize and elucidate the mechanisms by which TCDD affects the nervous system.

5.2.2. Structural Malformations

Developmental effects consisting of cleft palate, hydronephrosis, and thymic hypoplasia are produced in mice following in utero exposure to halogenated dibenzo-*p*-dioxin, dibenzofuran, biphenyl, and naphthalene congeners, which bind stereospecifically to the Ah receptor (Weber et al., 1985; Miller and Birnbaum, 1986; Birnbaum et al., 1987a,b, 1991). Of these effects in the mouse, cleft palate is less responsive than hydronephrosis, as the latter is induced in the absence of cleft palate (Couture et al., 1990b). Both responses can be induced at TCDD doses that are not otherwise overtly toxic (Couture et al., 1990a). The oral surface of the palate in the mouse is characterized by 8 or 9 pairs of transverse ridges, rugae. TCDD and 3,3',4,4',5-PCB (PCB 126) produce palatal ruga anomalies in mice (Yasuda et al., 1999). The potency of TCDD for producing teratogenesis in the mouse is clearly evident when one considers that only 0.0003% of a maternally administered dose can be isolated from the fetal palatal shelves or kidneys. More specifically, a maternal TCDD dose of 30 μg/kg administered on gestational day 11 results in a tissue concentration of 0.65 pg TCDD/mg in the palatal shelves 3 days after dosing, and the same tissue concentration of TCDD is present in the kidneys at that time (Abbott et al., 1989).

Susceptibility to the developmental actions of TCDD in mice depends on two factors: genotype of the fetus and stage of development at the time of exposure. One genetically encoded parameter that determines the responsiveness of different mouse strains is the Ah receptor protein. The Ah receptor is thought to mediate the structural malformations caused by TCDD in the mouse, namely cleft palate and hydronephrosis (Poland and Knutson, 1982). After gestational day 12, the Ah receptor and its dimerization partner ARNT are expressed in the embryonic palate and developing urinary tract of the C57BL/6 mouse fetus. Expression of Ah receptor and ARNT mRNA increases significantly during palatal shelf outgrowth from

gestational day 12 to 14. While the increase in Ah receptor expression was not affected by a maternal dose of 24 μg/kg of TCDD administered on gestational day 12, there was a decrease in the expression of ARNT (Abbott et al., 1999b). Similarly, Ah receptor protein levels in the mouse urinary tract increase from gestational days 12 to 14 regardless of exposure to 12 μg/kg of TCDD on gestational day 10, whereas the expression of ARNT protein on gestational day 14 is reduced by TCDD (Bryant et al., 1997). Thus, Ah receptor and ARNT are expressed in the developing palate and urinary tract, and the opportunity exists for the Ah receptor-ARNT complex to regulate gene expression in these developing tissues. It may be important for normal development that an appropriate relative expression of these genes is maintained, and decreasing the availability of ARNT could be a significant factor in the response of the embryonic palate and urinary tract to TCDD.

Mouse strains that produce Ah receptors with relatively high affinity for TCDD respond to lower doses of TCDD than mouse strains that produce relatively low-affinity Ah receptors (Poland and Glover, 1980; Hassoun et al., 1984a). The differences that exist between mouse strains with respect to developmental responsiveness to these chemicals are not absolute, as all strains, including those with Ah receptors of relatively low affinity, respond when exposed to sufficiently large doses during the critical period of organogenesis (Birnbaum, 1991). In the mouse, the peak times of fetal sensitivity vary slightly depending on which developmental effect is used as the endpoint. However, exposure between days 6 and 15 of gestation will produce teratogenesis (Couture et al., 1990a,b).

In inbred strains of mice, the developmental response, characterized by altered cellular proliferation, metaplasia, and modified terminal differentiation of epithelial tissues (Poland and Knutson, 1982), is extremely organ-specific, occurring only in the palate, kidney, and thymus (Birnbaum, 1991). Pharmacokinetic differences are not responsible for this high degree of tissue specificity, and Ah receptors are not found exclusively in the affected organs (Carlstedt-Duke, 1979; Gasiewicz et al., 1983). Therefore, other factors intrinsic to the palate, kidney, and thymus appear to play a role along with the Ah receptors in these tissues in producing the structural malformations. For certain developmental effects, the time at which exposure occurs is important, as there may be a critical period during which the toxicant must be present in order to produce the effect. This critical period can be different for different organs and tissues.

Differences exist between mammalian species with respect to susceptibility to the developmental effects of TCDD. Although genetic differences between species or strains might affect absorption, biotransformation, and/or elimination of TCDD by the maternal system and its absorption across the placenta, such species differences do not account for the lack of cleft palate formation in species other than mice (Birnbaum, 1991). Rather, the species differences in susceptibility to cleft palate formation appear due to differences in the interaction between

TCDD and the developing palatal shelves themselves. This is demonstrated by the occurrence of similar responses when palatal shelves from different species are exposed to TCDD in organ culture (Abbott et al., 1989; Abbott and Birnbaum, 1990a, 1991). The key difference is that in other species much higher concentrations of TCDD are required to elicit essentially the same palatal response that is seen in the mouse (Table 5-3). Thus, since palatal shelves of the mouse are 200 times more sensitive to TCDD than those of the human, it is considered unlikely that human embryos would be exposed to high enough concentrations of TCDD to cause changes in palatal differentiation sufficient to produce cleft palate (Abbott et al., 1999a).

With respect to the occurrence of similar developmental effects in mammalian species other than the mouse, no other species develops cleft palate except at maternal doses that are fetotoxic and maternally toxic (Couture et al., 1990a; Birnbaum, 1991). In mice and hamsters, hydronephrosis can be elicited at TCDD doses that are neither fetotoxic nor maternally toxic (Olson and McGarrigle, 1991), whereas thymic hypoplasia is a fetal response to TCDD observed in virtually all laboratory mammalian species that have been tested (Vos and Moore, 1974). Studies in humans have not clearly identified an association between TCDD exposure and structural malformations (Fara and Del Corno, 1985; Mastroiacovo et al., 1988; Stockbauer et al., 1988; Reggiani, 1989).

5.2.2.1. *Cleft Palate*

5.2.2.1.1. ***Characterization of TCDD effect.*** Palatal shelves in the mouse originate as outgrowths of the maxillary process. Eventually, they come to lie vertically within the oral cavity on both sides of the tongue. In order to form the barrier between the oral and nasal cavities, the shelves in the mouse must reorient themselves from a vertical direction to a horizontal direction. Once they come together horizontally, their medial aspects bring apposing epithelia into close contact (Coleman, 1965; Greene and Pratt, 1976). At this stage, the apposing medial edge epithelia of the separate palatal shelves each consist of an outer layer of periderm that overlays a strata of cuboidal-shaped basal cells. These basal cells, in turn, rest on top of a continuous basal lamina. There is a sloughing of the outer periderm cells followed by the formation of junctions between the newly apposing basal epithelial cells. The midline seam so formed consists of the two layers of basal cells, all of which appear healthy, even though the outer periderm cells are shed before adhesion occurs. As fusion proceeds, the bilayer seam breaks up into small islands of cells. Eventually, the basal lamina disappears and the elongating former basal cells within the small islands extend filopodia into the adjacent connective tissue. During this process, the former basal cells lose epithelial characteristics and gain fibroblast-like features. Essentially, the medial edge epithelium is an ectoderm that retains the ability to transform into mesenchymal cells. Upon completion of this epithelial to mesenchyme transformation, the once separate and

apposing palatal shelves are fused so that a single continuous tissue is formed (Fitchett and Hay, 1989; Shuler et al., 1992).

Cleft palate can result from a failure of the shelves to grow and come together or a failure of the shelves to fuse once they are in close apposition (Pratt et al., 1985). TCDD and other Ah receptor agonists are unusual inducers of cleft palate because the shelves grow and make contact, but the subsequent processes involving loss of periderm, shelf adhesion, and the epithelial to mesenchyme transformation does not occur. Therefore, a cleft is formed as the palatal shelves continue to grow without fusing. When TCDD is administered to pregnant mice on gestational days 6 to 12, the incidence of cleft palate formation increases with time. However, day 12 is a critical window, after which the incidence of cleft palate formation decreases. No cleft palates are formed when TCDD is administered on day 14, since fusion has already occurred (Couture et al., 1990b).

Palatal shelves of the mouse, rat, and human can be removed from the fetus and placed into organ culture. Under these conditions, when the separate shelves are placed in an apposing condition in vitro, sloughing periderm cells are trapped within the seam (Fitchett and Hay, 1989). Thus, due to the presence of these trapped dead cells, the fusion process was previously believed to require programmed cell death to remove epithelial cells at the fusion seam (Coleman, 1965; Greene and Pratt, 1976; Pratt et al., 1984). However, the newer model, which involves transformation of the basal epithelial cells into mesenchyme rather than their death, is believed to be valid under explant conditions in vitro, as well as in vivo (Fitchett and Hay, 1989). When exposed to TCDD as explants in vitro, the palatal shelves of the mouse, rat, and human all respond to TCDD in a similar way by retaining medial epithelial cells that proliferate and differentiate into a stratified epithelium (Abbott et al., 1989; Abbott and Birnbaum, 1989, 1990a, 1991). The epithelial to mesenchyme transformation of the basal epithelial cells does not occur, and instead there is a differentiation into a stratified squamous epithelium such that these cells resemble the squamous keratinizing oral cells within the tissue.

Table 5-3 shows the lowest TCDD concentration that prevents the epithelial to mesenchyme transformation process in isolated palatal shelves (lowest observed effect level, LOEL), TCDD concentration that produces a 100% maximal response (EC_{100}), and lowest concentration of TCDD that produces cytotoxicity. Palatal shelves of rats and humans respond to TCDD in a manner identical to the mouse; however, higher concentrations of TCDD are required to induce the epithelial responses. The relative insensitivity of rat palatal shelves may explain the lack of cleft palate when fetal rats are exposed to nonmaternally toxic doses of TCDD. Sensitivity of human palatal shelves to TCDD in vitro is similar to the rat. This suggests that exposure to maternally toxic and fetotoxic doses of TCDD may be required to cause cleft palate formation in humans.

A disruption in the normal spatial and temporal expression of EGF, thyroid growth factor (TGF)-α, TGF-β1,and TGF-β2 correlates with altered proliferation and differentiation in the medial region of the developing palate, resulting in a palatal cleft. Thus, the abnormal proliferation and differentiation of TCDD-exposed medial cells may be related to reduced expression of EGF and TGF-α. Also, decreased levels of immunohistochemically detectable TGF-β1 could contribute to the continued proliferation and altered differentiation of medial cells (Abbott and Birnbaum, 1990b). It is important to note that EGF and TGF-α both exert their actions by binding to EGF receptors.

Based on these results, biochemical and genetic differences between mouse and human palates have been described that may explain the different sensitivities to cleft palate formation in the mouse and human. Ah receptor concentrations in the mouse palate are 346 times greater than those in the human, and ARNT levels are also greater in the mouse (Abbott et al., 1999a). In addition, gene expression studies have demonstrated that human and mouse palates cultured in vitro are dissimilar with respect to their particular spatial and temporal patterns of EGF, EGF receptor, TGF-α, and TGF-β3 mRNA expression. Because the proteins that are the translation products of these mRNAs are important for palatal development, it has been suggested that species differences in the expression patterns of these genes could contribute to the lower sensitivity of human palates to TCDD when compared with the mouse (Abbott et al., 1998).

The differentiation of basal cells to a stratified squamous epithelium, which resembles the keratinizing oral epithelium within the developing palate that is mentioned above, is similar to certain effects of TCDD that can be studied in cultured human keratinocytes. These effects in cultured human keratinocytes involve altered EGF binding to those cells. In addition, the Ah receptor is implicated in producing this response in cultured cells (Osborne and Greenlee, 1985). Thus, the mechanisms by which TCDD produces a palatal cleft in the mouse may have similarities to the mechanisms by which TCDD produces other effects that are part of the ectodermal dysplasia syndrome. This is consistent with the description given by Fitchett and Hay (1989) that the medial edge epithelium within the developing palate is essentially an ectoderm that retains the ability to transform into mesenchymal cells.

5.2.2.1.2. *Evidence for an Ah receptor mechanism.*

5.2.2.1.2.1. *Genetic.* When wild-type C57BL/6 (Ah^bAh^b) mice are crossed with DBA/2 (Ah^dAh^d) mice that contain a mutation at the Ah locus, all of the heterozygous B6D2F1 progeny (Ah^bAh^d) resemble the wild-type parent in that AHH activity is inducible by TCDD and other halogenated aromatic hydrocarbons (Nebert and Gielen, 1972). Test crosses between the B6D2F1 progeny and each original parent strain, and other B6D2F1 progeny mice, demonstrate that in the C57BL/6 and DBA/2 strains, susceptibility to AHH induction segregates as a simple

dominant trait in the backcross and F_2 progeny. Thus, the trait of AHH induction is expressed in progeny that contain the Ah^bAh^b and Ah^bAh^d genotypes, but is not expressed in the Ah^dAh^d progeny from these crosses. Certain other effects of TCDD, such as its binding affinity for the hepatic Ah receptor (Okey et al., 1979), thymic atrophy (Poland and Glover, 1980), hepatic porphyria (Jones and Sweeney, 1980), and immunosuppressive effects (Vecchi et al., 1983; Nagarkatti et al., 1984) have been shown in similar genetic crosses and test crosses to segregate with the Ah locus that permits AHH induction. Thus, for these effects of TCDD, genetic evidence demonstrates an involvement of the Ah locus (Poland and Knutson, 1982).

Nebert's group was the first to relate developmental toxicity to the Ah locus in mice (Lambert and Nebert, 1977; Shum et al., 1979). Subsequently, Poland and Glover (1980) administered a single 30 μg TCDD/kg dose to pregnant mice on gestational day 10. A 54% incidence of cleft palate was found in homozygous C57BL/6 (Ah^bAh^b) fetuses, a 13% incidence in heterozygous B6D2F1 (C57BL/6 and DBA/2 hybrid, Ah^bAh^d) fetuses, and only a 2% incidence in homozygous DBA/2 (Ah^dAh^d) fetuses. This pattern of inheritance, in which the incidence of developmental toxicity in the heterozygous F1 generation is intermediate between that of the homozygous parental strains, is consistent with the autosomal dominant pattern of inheritance described for AHH inducibility and the Ah locus (Nebert and Gielen, 1972), even if dominance is incomplete in the case of developmental toxicity. However, the pattern of inheritance for developmental toxicity described when Poland and Glover (1980) crossed C57BL/6 and DBA/2 mice is not sufficient proof that the Ah locus is the genetic locus that controls susceptibility to TCDD-induced developmental toxicity in these mouse strains.

To provide such proof, it is necessary to show genetic linkage between the susceptibility for developmental toxicity and the Ah locus. The standard of proof would be that developmental toxicity and a particular allele at the Ah locus must always segregate together in genetic crosses because if the loci are the same there can be no recombination between the loci. This is generally accomplished by demonstrating cosegregation between the two loci, not only in crosses between the two homozygous parental strains, which in and of itself is insufficient proof of genetic linkage, but also in test crosses or backcrosses between the heterozygous F1 hybrids with each homozygous parental strain.

It was stated previously that certain effects of TCDD are well known to segregate with the Ah locus due to the results of appropriate crosses and backcrosses between responsive and nonresponsive mouse strains and their hybrid F1 progeny. With this standard of proof in mind, the evidence that specifically links certain endpoints of developmental toxicity with the Ah locus can be described. It is intended that this information be provided with a considerable degree of detail, so the reader can independently determine whether the standard of proof has been satisfied by the evidence available.

To strengthen their conclusion based on the results of simple crosses between C57BL/6 and DBA/2 mice, Poland and Glover (1980) planned to perform a backcross between the hybrid B6D2F1 and DBA/2. However, the low incidence of cleft palate in B6D2F1 mice would have required characterizing and phenotyping a prohibitively large number of fetuses. Alternatively, the backcross between B6D2F1 and C57BL/6 was considered, in which Ah^bAh^b and Ah^bAh^d progeny would have been distinguished by the amount of high-affinity specific binding for TCDD in fetal liver. In this case, however, overlap between individual mice would have made the results uncertain in some of the progeny. Therefore, it was not possible to obtain satisfactory results from either backcross.

Instead, Poland and Glover (1980) examined the incidence of cleft palate in 10 inbred strains of mice: 5 strains with high-affinity Ah receptors and 5 strains with low-affinity receptors. In the five latter strains, there was only a 0% to 3% incidence of cleft palate formation, whereas four of the five strains with high-affinity Ah receptors developed a ~50% incidence. The one strain with high-affinity Ah receptors that did not follow the pattern, CBA strain, is also resistant to cleft palate formation induced by glucocorticoids. Overall, these results indicate that cleft palate formation probably segregates with the Ah locus.

The incidence of cleft palate formation was studied in fetuses from a cross between C57BL/6 and AKR/NBom mice administered 3,3',4,4'-TCAOB on gestational day 12 (Hassoun et al., 1984b). Although C57BL/6 mice are responsive for AHH induction and cleft palate formation, AKR mice are less responsive, requiring higher doses for both effects. In a manner unlike the result of a cross between C57BL/6 and DBA/2, the incidence of cleft palate formation in the B6AKF1 progeny was <2%, showing that nonresponsiveness segregates as the dominant trait when C57BL/6 mice are crossed with AKR mice. Similarly, cleft palate formation was virtually absent in the progeny of a backcross between AKR/NBom and B6AKF1, demonstrating dominance of the noninducible trait. Although Ah phenotyping of the backcross progeny was not performed in this particular study, Robinson et al. (1974) had previously evaluated segregation of the Ah locus in backcrosses between C57BL/6 and AKR/N mice. They found in these two strains that noninducibility for AHH activity segregates as the dominant trait. Thus, inducibility for cleft palate formation and AHH activity both segregate as dominant traits when C57BL/6 mice are crossed with DBA/2, but noninducibility is dominant for both traits when C57BL/6 mice are crossed with AKR/N. These results are consistent with the interpretation that cleft palate induction probably segregates with the Ah locus.

Like Poland and Glover (1980), Hassoun et al. (1984a) were unable to determine whether cleft palate formation segregates with the Ah locus in C57BL/6 and DBA/2 mice by performing simple backcrosses. Instead, they evaluated cosegregation of the Ah locus and 2,3,7,8-TCDF-induced cleft palate formation using a series of recombinant strains called BXD mice. These

strains are fixed recombinants produced from an original cross between the two parental strains C57BL/6J and DBA/2J. Hybrid B6D2F1 mice were crossed to produce F_2 progeny and these were strictly inbred by sister and brother matings into several parallel strains. The mice used in this study were from the F_{42} and F_{58} generations of inbreeding. It was found that the incidence of TCDF-induced cleft palate formation after matings within eight different BXD strains with high-affinity Ah receptors is >85%. After similar matings with eight different BXD strains with low-affinity Ah receptors, the incidence of TCDF-induced cleft palate formation is <2%. These results of Hassoun et al. (1984a) corroborate those of Poland and Glover (1980) and provide further evidence that cleft palate formation segregates with the Ah locus. Thus, the Ah locus and the Ah receptor are involved in the formation of palatal clefts that are induced by TCDD-like congeners.

Consistent with this interpretation, the Ah receptor null mouse line of Mimura et al. (1997) is completely resistant to TCDD-induced cleft palate formation and the Ah receptor null line of Fernandez-Salguero et al. (1995) is almost entirely resistant to this teratogenic effect of TCDD (Peters et al., 1999). Taken together, these findings support the conclusion that the Ah receptor plays a key role in TCDD-induced cleft palate formation. However, because 9% of the homozygous Ah receptor null fetuses of the Fernandez-Salguero et al. (1995) transgenic line developed cleft palate when exposed to TCDD (compared with 0% of vehicle-exposed wild-type and 0% of vehicle-exposed Ah receptor null fetuses), a TCDD-induced alteration in processes that do not require the Ah receptor might also be involved. Further research is needed to explore this possibility.

As additional evidence for an Ah receptor-mediated mechanism for cleft palate formation by TCDD and related compounds, stereospecific, high-affinity Ah receptors can be isolated from cytosol fractions prepared from embryonic palatal shelves. These receptors are present in palatal shelves of Ah^bAh^b, C57BL/6 fetuses but are not detectable in similar tissue from Ah^dAh^d, AKR/J fetuses (Dencker and Pratt, 1981). However, the significance of this finding may be mitigated to some extent by the following observation. In cytosols prepared from homogenates of whole embryo/fetal tissue (minus head, limbs, tail, and viscera), the concentration of specific binding TCDD receptors is 256 fmol/mg protein in C57BL/6 mice, compared with a concentration of 21 fmol/mg protein in the less responsive DBA/2 strain, 15 fmol/mg protein in the less responsive AKR/J strain, and 19 fmol/mg protein in the less responsive SWR/J strain. However, when embryonic tissue is cultured, the differences between the strains in receptor number are less pronounced, and in the receptors isolated from cultured embryonic cells of different strains, there is only about a twofold difference in the relative binding affinity for ^{3}H-TCDD. The mechanistic reasons for the diminished degree of difference between responsive and less responsive mouse strains during embryonic cell culture are not known (Harper et al., 1991).

The possible influence of maternal toxicity on cleft palate formation was evaluated by performing reciprocal blastocyst transfer experiments using the high-affinity-Ah receptor NMRI and lower affinity-Ah receptor DBA strains of mice (D'Argy et al., 1984). After administration of 30 μg TCDD/kg or 8 mg TCAOB/kg to pregnant dams on gestational day 12, 75% to 100% of all NMRI fetuses developed cleft palates. This is true whether the fetuses remained within the uterus of their natural mother or were transferred into the uterus of a DBA mouse. Under the same conditions, none of the 24 DBA fetuses transferred into an NMRI mother developed a cleft palate, even though 89% of their NMRI litter mates were affected. Thus, these results, along with the presence of Ah receptors in palatal shelves and responsiveness of palatal shelves in organ culture to TCDD, indicate that cleft palate formation in mice is due to a direct effect of TCDD on the palatal shelf itself and is not secondary to maternal toxicity.

5.2.2.1.2.2. ***Structure activity.*** As genetic evidence in mice indicates that the Ah receptor mediates TCDD-induced cleft palate formation and hydronephrosis (see Section 5.3.2.2.2.1), structure-activity requirements based on Ah receptor-binding characteristics should predict the relative potencies of different agonists for producing cleft palate and hydronephrosis. Of the halogenated aromatic hydrocarbons, TCDD has the greatest affinity for binding to the Ah receptor and it is the most potent teratogen in inbred mouse strains. Table 5-4 shows the relative potencies for cleft palate induction and hydronephrosis in C57BL/6 mice for a number of TCDD-like congeners. As TCDD is the most potent, it is assigned a value of 1.000. When examined by probit analysis, the dose-response curve of each congener, compared with all of the others, did not deviate from parallelism. Therefore, the relative potencies of the congeners are valid for any given incidence of cleft palate formation or hydronephrosis. The main finding, however, is that the rank order potency of the various congeners for producing these two developmental effects is generally similar to that for binding to the Ah receptor (see Table 5-4), with the notable exception that the apparent binding affinities for the brominated dibenzofurans have not yet been reported. There are additional ligands for the Ah receptor that cause cleft palate formation in C57BL/6 mice at nonmaternally toxic doses, but they are not listed in the table. These include 3,3',4,4'-TCAOB (Hassoun et al., 1984a), 3,3',4,4'-tetrachlorobiphenyl (Marks et al., 1989), 3,3',4,4',5,5'-hexachlorobiphenyl (Marks et al., 1981), and a mixture that contained 1,2,3,4,6,7- and 2,3,4,5,6,7-hexabromonaphthalenes (Miller and Birnbaum, 1986).

Also consistent with the structure-activity relationships for binding to the Ah receptor is the finding that a number of hexachlorobiphenyls do not induce cleft palate formation. These congeners either lack sufficient lateral substitution or are substituted in such a manner that they cannot achieve a planar conformation. Included in this category are the diortho and tetraortho chlorine-substituted 2,2',3,3',5,5'-; 2,2',3,3',6,6'-; 2,2',4,4'5,5'-; and 2,2',4,4',6,6'-hexachloro-

biphenyls (Marks and Staples, 1980). In addition, it is consistent with the structure-activity relationships that the monoortho chlorine-substituted 2,3,4,5,3',4'-HCB is a weak teratogen. Its potency relative to that of TCDD varies from 3×10^{-5} to 9×10^{-5} for cleft palate formation, AHH induction, and hydronephrosis (see Table 5-4) (Kannan et al., 1988).

A result that would not be expected according to the structure-activity relationships for binding to the Ah receptor is that the diortho chlorine-substituted 2,2',3,3',4,4'-hexachlorobiphenyl causes cleft palate formation and hydronephrosis in mice (Marks and Staples, 1980). However, another diortho chlorine-substituted PCB congener, 2,2',4,4',5,5'-hexachlorobiphenyl, also can cause hydronephrosis and is a very weak inducer of 7-ethoxyresorufin-O-deethylase (EROD) activity (Biegel et al., 1989; Morrissey et al., 1992). It is consistent with the interpretation that 2,2',4,4',5,5'-hexachlorobiphenyl is a partial Ah receptor agonist, that it can competitively displace TCDD from the murine hepatic cytosolic receptor, and that at large enough doses it can inhibit TCDD-induced cleft palate formation and immunotoxicity in C57BL/6 mice (Biegel et al., 1989; Morrissey et al., 1992). These results suggest that PCB congeners do not have to be in a strictly planar configuration to cause teratogenesis.

5.2.2.1.3. ***Species differences.*** Cleft palate is induced in rats only at maternally toxic TCDD doses that are associated with a high incidence of fetal lethality. Schwetz et al. (1973) reported an increased incidence of cleft palate after maternal administration of 100 μg hexachlorodibenzo-*p*-dioxin/kg/day to Sprague-Dawley rats on days 6 to 15 of gestation. Couture et al. (1989) also observed an increased incidence of cleft palate formation after a single dose of 300 μg/kg of 2,3,4,7,8-pentachlorodibenzofuran given to Fischer 344 rats. In Long Evans rats administered 5 μg/kg of TCDD on gestational day 8 there was a 71.4% incidence of cleft palate (Huuskonen et al., 1994). However, in Han/Wistar rats that have a mutated form of the Ah receptor, exposure to 10 μg/kg of TCDD on gestational day 8 failed to cause cleft palate formation (Huuskonen et al., 1994). Thus, there are rat strain differences in susceptibility to cleft palate formation as has been shown for mice. Cleft palate also can be produced in fetal hamsters following maternally toxic and fetotoxic doses of TCDD (Olson et al., 1990).

In monkeys, bifid uvula (Zingeser, 1979) and bony defects in the hard palate (McNulty, 1985) were reported, but there were no corresponding soft tissue defects or clefts of the secondary palate. Cleft palates have not been reported in human fetuses of mothers accidentally exposed to TCDD or mixtures of PCBs and CDFs (Fara and Del Corno, 1985; Mastroiacovo et al., 1988; Stockbauer et al., 1988; Rogan, 1989). Thus, sensitivity of the palate in mice to TCDD is unique. In other species, including humans, other forms of fetal toxicity occur at doses lower than those required for cleft palate formation.

5.2.2.2. *Hydronephrosis*

5.2.2.2.1. ***Characterization of TCDD effect.*** Hydronephrosis is the most sensitive developmental response elicited by TCDD in mice. It is produced by maternal doses of TCDD too low to cause palatal clefting and is characterized as a progressive hydronephrosis preferentially occurring in the right kidney, which can be accompanied by hydroureter and/or abnormal nephron development (Courtney and Moore, 1971; Moore et al., 1973; Birnbaum et al., 1985; Weber et al., 1985; Abbott et al., 1987a,b). Hyperplasia of the ureteric lumenal epithelium results in ureteric obstruction. Therefore, the TCDD-induced kidney malformation in the mouse is a true hydronephrosis in that blockage of urine flow results in back pressure damaging or destroying the renal papilla (Abbott et al., 1987a). In addition, mRNA and protein for both the Ah receptor and ARNT are expressed in the fetal ureters and metanephric tubules of the mouse (Bryant et al., 1997), so it is possible that hydronephrosis is caused by a direct action of TCDD on the developing kidney.

When dissected on gestational day 12 from control embryos, isolated ureters exposed to 1×10^{-10} M TCDD in vitro display evidence of epithelial cell hyperplasia (Abbott and Birnbaum, 1990c). This is significant in that it shows that the hydronephrosis response is due to a direct effect of TCDD on the ureteric epithelium. Embryonic cell proliferation within the ureter may be regulated by the actions of growth factors, including EGF (Abbott and Birnbaum, 1990c). In control ureteric epithelia, the expression of EGF receptors decreases with advancing development, whereas after TCDD exposure the rate of ^{3}H-thymidine incorporation and expression of EGF receptor does not decline. Therefore, in TCDD-treated mice there is a correlation between excessive proliferation of ureteric epithelial cells and inappropriate expression of EGF receptors.

Other effects of TCDD on the developing kidney involve changes in the extracellular matrix components and basal lamina (Abbott et al., 1987b). In TCDD-exposed fetal kidneys, extracellular matrix fibers are of a diameter consistent with Type III collagen similar to such fibers in unexposed fetal kidneys. However, the abundance of these Type III collagen fibers is reduced by TCDD treatment. In the developing kidney, these collagen fibers are associated with undifferentiated mesenchymal cells. Similarly, the expression of fibronectin, which is also associated with undifferentiated mesenchymal cells, is decreased by TCDD exposure. In the glomerular basement membrane, the distribution of laminin and Type IV collagen is altered by TCDD exposure. These changes in the glomerular basement membrane may affect the functional integrity of the filtration barrier and could exacerbate the hydronephrosis and hydroureter. The proteins within the extracellular matrix and basal lamina that are altered by TCDD exposure (laminin, fibronectin, and collagen) are considered markers of a commitment to differentiate into epithelial structures. In the mouse embryo/fetus, TCDD exposure also blocks differentiation

within the epithelium of the developing palate. Although there are effects of TCDD exposure on EGF in the developing ureter as well as the developing palate, the urinary system, unlike parts of the soft palate, is derived from mesoderm. Thus, it is important to note that the ectodermal dysplasia syndrome is intended to denote a clustering of effects that appears to involve ectoderm-derived organs. It is not intended to imply that all TCDD-induced developmental toxicity involves organs derived from ectoderm.

5.2.2.2.2. ***Evidence for an Ah receptor mechanism.***

5.2.2.2.2.1. ***Genetic.*** With respect to involvement of the Ah locus in TCDD-induced hydronephrosis, very few genetic studies have been done. Prior to the discovery of the Ah locus, however, Courtney and Moore (1971) reported a 62% incidence of hydronephrosis in C57BL/6 mice exposed to a maternal TCDD dose of 3 μg/kg/day on days 6 to 15 of gestation, whereas the incidence in similarly exposed DBA/2 mice was only 26%. More recently, Silkworth et al. (1989) reported that when TCDD is administered on gestational days 6 to 15, the incidence of hydronephrosis is dose related. As the maternal dose of TCDD is increased from 0.5 to 4μg/kg/day, the incidence of hydronephrosis in C57BL/6 mice increases from 31% to 92%, whereas in DBA/2 mice the incidence varies from 5% to 37% over the same dose range. In DBA/2 mice the incidence of hydronephrosis increases to 60% when the largest dose of TCDD administered is doubled to 8 μg/kg/day (but does not reach the 92% level seen in C57BL/6 mice at 4μg TCDD/kg). Thus, the incidence of hydronephrosis is higher in the mouse strain that produces high-affinity Ah receptors (C57BL/6) compared with that strain (DBA/2) that produces Ah receptors having lower ligand-binding affinity (Okey et al., 1989). The largest dose of TCDD used in these experiments resulted in hydronephrosis of the fetus without affecting the mean body weight or body weight gain of the dam. In the BXD strains (Hassoun et al., 1984a), the incidence of 2,3,7,8-TCDF-induced hydronephrosis is 34% to 48% in eight strains with high-affinity Ah receptors and 3% to 4% in eight strains with low-affinity Ah receptors. These results obtained in the BXD strains of mice provide the best evidence currently available of an association between the ability of TCDD-like congeners to induce hydronephrosis and the wild-type Ah^b allele. Thus, the Ah locus and the Ah receptor are involved in the hydronephrosis that is induced by TCDD-like congeners.

More recently, transgenic Ah receptor null mutant mice have been used to study the effects of Ah receptor deletion on the ability of TCDD exposure to cause hydronephrosis. Female mice heterozygous for Ah receptor expression were mated to males of the same genotype and exposed during pregnancy to 40 μg TCDD/kg on gestational day 12.5 (Mimura et al., 1997). Nearly all TCDD-exposed wild-type and heterozygous progeny developed hydronephrosis. In sharp contrast, there was no hydronephrosis in offspring from the same litters that were

homozygous for the Ah receptor null mutation. Similarly, Ah receptor null mice generated by a different targeting method (Fernandez-Salguero et al., 1995) were also completely resistant to TCDD-induced hydronephrosis (Peters et al., 1999). These results, coupled with the difference in incidence of TCDD- or TCDF-induced hydronephrosis in C57BL/6 and DBA/2 mouse strains, demonstrate that this teratogenic response to TCDD is Ah receptor mediated. Since haplo-insufficiency was observed for the cleft palate response, but not for hydronephrosis, Mimura and coworkers suggest that the mechanisms by which the Ah receptor mediates these two teratogenic effects of TCDD may be different (Mimura et al., 1997).

5.2.2.2.2.2. ***Structure activity.*** The rank order of potencies for various halogenated aromatic hydrocarbon congeners to cause hydronephrosis in mice is consistent with the structure-activity requirements for binding to the Ah receptor (see Table 5-4). This provides further evidence that the Ah receptor mediates the effects of these TCDD-like congeners on the developing mouse kidney.

5.2.2.2.2.3. ***Species differences.*** Hydronephrosis has been reported after administration of low maternal doses of TCDD to rats and hamsters. Possibly due to the small numbers of fetuses examined, the observed incidences of hydronephrosis in rats after exposure to cumulative maternal doses <2 μg TCDD/kg have not been statistically significant (Courtney and Moore, 1971; Giavini et al., 1983). There are also interstrain differences in rats in susceptibility to hydronephrosis. This is illustrated in the TCDD-resistant Han/Wistar and TCDD-sensitive Long Evans rat strains by 1 and 10 μg/kg of TCDD administered on gestational day 8 causing 3% and 11.9% hydronephrosis in the Han/Wistar strain while a 5 μg/kg dose of TCDD administered on the same day of gestation failing to cause hydronephrosis in the Long Evans strain (Huuskonen et al., 1994). Following a 1.5 μg TCDD/kg dose administered on gestational days 7 and 9, the incidence of hydronephrosis in hamster fetuses was 11% and 4.2%, respectively. This is in contrast to an incidence of <1% in control hamster fetuses. Accordingly, hydronephrosis is one of the most sensitive indicators of prenatal toxicity in hamsters (Olson and McGarrigle, 1991).

5.2.2.3. *Tooth Development*

The interpretation that lactational exposure to CDDs and CDFs may lead to mineralization defects in the first molars of human infants (Alaluusua et al., 1996, 1999) was further investigated in experiments where primordial mandibular molar teeth from mouse embryos were cultured in the presence of 1 μM TCDD (Partanen et al., 1998). In these cultured primordial teeth, TCDD caused toxicity to odonotoblasts and ameloblasts. This led to a failure of dentin to undergo mineralization and a lack of enamel deposition. Cuspal morphology also

was disrupted by TCDD exposure in the cultured teeth. While the concentration of TCDD required to produce these effects was high, 1 μM, the authors suggest that barriers to diffusion inherent in tooth structure may result in TCDD concentrations at the cellular site of action in the primordial teeth being much lower than that in the culture medium (Partanen et al., 1998). Exposure to EGF (10 μg/L) similarly retarded molar tooth development in cultured explants from wild-type embryos, because layers of mineralized dentin and the enamel matrix were thinner than those in vehicle-exposed explants. In cultured primordial molar teeth from EGF receptor null embryos, the effects of EGF were completely ameliorated, and TCDD had only a mild effect. When cultured explants from wild-type mouse embryos were simultaneously exposed to EGF and TCDD, the adverse effects of TCDD on mineralization and enamel deposition were largely, but not completely prevented (Partanen et al., 1998). In utero and lactational exposure of male Holtzman rats to 0.064, 0.16, 0.40, or 1.0 μg/kg of TCDD on gestational day 15 failed to accelerate the age at which incisor eruption occurred. At the highest TCDD dose used there was a tendency for incisor eruption to be accelerated by about 1 day (9.9 days in the control versus 8.9 days in the TCDD group), but the effect was not statistically significant (Mably et al., 1992a). Taken together, these results are consistent with the interpretation that TCDD alters tooth development in organ culture by interfering with EGF receptor signaling. However, TCDD also may affect tooth development by perturbing other signaling pathways, which either act in concert with or interfere with EGF receptor signaling, and probably involve additional mechanisms of cell and/or tissue interactions. Finally, the involvement of EGF receptor signaling in this effect of TCDD is consistent with aberrant tooth development being a part of the TCDD ectodermal dysplasia syndrome.

5.2.3. Postnatal Effects

5.2.3.1. *Eye Opening*

In utero and lactational exposure to TCDD caused external developmental effects in male rodent offspring that are not androgen dependent. The most prominent of these is accelerated eye opening. Mably et al. (1992a) reported that the age of eye opening was accelerated by 1.0 μg/kg of TCDD administered on gestational day 15. Lower doses of TCDD that affected growth and development of several male reproductive tract organs, however, had no effect on eye opening, demonstrating that this endpoint could be clearly dissociated from the more sensitive male reproductive endpoints by the dose of TCDD needed to cause them. Gray et al. (1997) found accelerated eye opening to be one of the most sensitive endpoints in the Long Evans rat, occurring at 0.05 μg/kg of TCDD administered on gestational day 15. This was the lowest dose used in their study, and it also significantly decreased ejaculated sperm numbers, by 25%. In the ICR mouse exposure to 15, 30, or 60 μg/kg of TCDD on gestational day 14 accelerated eye

opening in male pups at all dosage levels (Theobald and Peterson, 1997). However, there was no effect on age to eye opening in female pups from the same TCDD-exposed mouse litters.

5.2.3.2. *Male Reproductive System*

TCDD has been shown to decrease plasma androgen concentrations in the adult male rat (see Section 5.3.2.2). Because TCDD is known to be transferred from mother to young in utero and during lactation (Moore et al., 1976; van den Berg et al., 1987), it can be expected to have an impact on the male reproductive system during early development (Mably et al., 1991). Testosterone and/or its active metabolite 5α-dihydrotestosterone (DHT) are essential prenatally and/or during the early postnatal stage for imprinting and development of accessory sex organs (Chung and Raymond, 1976; Rajfer and Coffey, 1979; Coffey, 1988) and for initiation of spermatogenesis (Steinberger and Steinberger, 1989). For example, exposure of the male rat fetus on gestational days 14 to 16 to a 5α-reductase inhibitor, which inhibits conversion of testosterone to DHT, impairs development of urogenital sinus-derived accessory sex organs such as the prostate (Clark et al., 1993). If perinatal imprinting fails to occur in the Wolffian duct or urogenital sinus-derived accessory sex organs of a neonatal male rat, the result could be that these male sex organs do not develop a normal trophic response to androgenic stimulation and do not grow and develop normally as the animal matures. In addition, aromatization of testosterone to 17ß-estradiol within the CNS is required perinatally for the imprinting of typical adult male patterns of reproductive behavior (Gorski, 1974) and luteinizing hormone (LH) secretion (Barraclough, 1980). Thus, normal development of male reproductive organs and imprinting of typical adult sexual behavior patterns require sufficient testosterone to be secreted by the fetal and neonatal testis at critical times in early development before and shortly after birth (MacLusky and Naftolin, 1981; Wilson et al., 1981).

To determine how the male reproductive system is affected by in utero and lactational TCDD exposure, Mably et al. (1991, 1992a,b,c) treated pregnant rats with a single oral dose of TCDD (0.064, 0.16, 0.4, or 1.0 μg/kg) or vehicle on day 15 of gestation (day 0 = sperm positive). Day 15 was chosen because most organogenesis in the fetus is complete by this time and the hypothalamic/pituitary/testis axis is just beginning to function (Warren et al., 1975, 1984; Aubert et al., 1985). The pups were weaned 21 days after birth. The consequences of this single, maternal TCDD exposure for the male offspring were characterized at various stages of postnatal sexual development. These original studies of male sexual development following in utero and lactational TCDD exposure have been expanded and further defined in subsequent studies using Holtzman, Long Evans, Sprague-Dawley, and Wistar rats, Syrian hamsters, and mice. These studies have been conducted in five different laboratories and in the vast majority of the studies, TCDD was used as the prototype Ah receptor agonist. However, some studies used 3,3'4,4',5-

PCB (PCB 126), 3,3',4,4',5,5'-HCB (PCB 169), and 2,3,4,7,8-PCDF. In general, the collective findings have produced qualitatively similar results that define a significant effect of TCDD and related Ah receptor agonists on the developing male reproductive system. The effects do not appear to result from reduced plasma androgen concentrations during the perinatal period as originally hypothesized by Mably et al. (1992a) and do not overlap completely with developmental effects of known antiandrogens (Roman et al., 1998b; Gray et al., 1999).

5.2.3.2.1. ***Overt toxicity assessment.*** Mably et al. (1992a) found that TCDD treatment had no effect on daily feed intake during pregnancy and the first 10 days after delivery, nor did it have an effect on the body weight of dams on day 20 of gestation or on days 1, 7, 14, or 21 postpartum. Treating dams with graded doses of TCDD on day 15 of gestation had no effect on gestation index, length of gestation, or litter size. Except for an 8% decrease at the highest maternal dose, TCDD had no effect on live birth index. Neither the 4-day nor 21-day survival index was significantly affected by TCDD. In all dosage groups, the number of dead offspring was equally distributed between males and females, and of the females that failed to deliver litters, none were pregnant. Signs of overt toxicity among the offspring were limited to the above-mentioned 8% decrease in live birth index (highest dose only), initial 10% to 15% decreases in body weight (two highest doses), and initial 10% to 20% decreases in feed intake (measured for males only, two highest doses). The latter two effects disappeared by early adulthood, after which the body weights of the maternally exposed and nonexposed rats were similar.

These findings have essentially been confirmed by both Gray's and Peterson's laboratories (Bjerke et al., 1994a; Gray et al., 1995a, 1997; Roman et al., 1995). A single oral exposure of 1 μg/kg TCDD on day 15 of gestation does not result in maternal toxicity, but compromises perinatal viability and growth of the offspring. A difference in the findings was that the reduced viability occurred prenatally in the studies using the Holtzman rat (Bjerke et al., 1994a; Roman et al., 1995) and postnatally in the Long Evans rat (Gray et al., 1995a).

5.2.3.2.2. ***Prenatal plasma androgen levels and testicular androgen production***. Exposure of Holtzman rats to 1.0 μg/kg of TCDD on gestational day 15 was originally reported to decrease plasma testosterone concentrations in male fetuses from gestational days 17 to 21 and in neonates 2 hours after birth (Mably et al., 1992a). However, a subsequent study from the same laboratory was not able to reproduce these findings (Chen et al., 1993). They found, contrary to their original study (Mably et al., 1992a), that exposure of Holtzman rats to 1.0 μg/kg of TCDD on gestational day 15 did not reduce plasma testosterone concentrations in male fetuses on gestational days 18 or 20 or in male neonates 2 hours after birth. Furthermore, perinatal TCDD exposure did not decrease intratesticular testosterone content or interfere with the ability of the

LH analog, human chorionic gonadotropin (hCG), to stimulate testosterone production from bisected testis preparations at these times (Chen et al., 1993). No other studies have examined the effects of in utero and lactational TCDD exposure on plasma testosterone levels or testicular testosterone production in rat fetuses or neonates at these specific times perinatally when plasma testosterone concentrations are elevated. In control rats the neonatal testosterone peak that occurs 2 hours after birth is followed from 6 hours to 5 days after birth by plasma testosterone concentrations that are 70% to 80% lower than the neonatal peak concentration. When evaluated at these times there was no effect of 1.0 μg/kg of TCDD administered on gestational day 15 on plasma testosterone concentrations in male offspring of either the Holtzman or Long Evans strains (Mably et al., 1992a; Gray et al., 1995a). Also, when evaluated 6 hours after birth there was no effect on LH-stimulated testosterone production in neonatal rats of the Long Evans strain exposed perinatally to TCDD (Gray et al., 1995a). Taken together, these results suggest that effects of in utero and lactational TCDD exposure on the male rat reproductive system cannot be explained by decreased testicular testosterone production or plasma testosterone concentrations during perinatal development (Roman and Peterson, 1998b).

5.2.3.2.3. ***Postnatal plasma androgen levels and testicular androgen production.*** Mably et al. (1992a) failed to find a significant decrease in plasma testosterone or 5α-DHT concentrations in male Holtzman rat offspring that were 32, 49, 63, or 120 days of age and had been exposed on gestational day 15 to either 0.064, 0.16, 0.40, or 1.0 μg/kg of TCDD. Consistent with these negative results, Roman et al. (1995) and Loeffler and Peterson (1999) were also unable to observe any consistent pattern of reduction of plasma testosterone or 5α-androstane-3α,17β-diol concentration in male Holtzman rats that were 21, 32, 49, and 63 days of age and had been exposed to 0.25 or 1.0 μg/kg of TCDD on gestational day 15. Similarly, at the three dosage regimens used for in utero and lactational exposure to TCDD, there was no effect on plasma testosterone concentration in male Wistar rat offspring at postnatal day 70 and only at the highest TCDD dosage regimen was there a reduction in plasma testosterone at postnatal day 170 (Faqi et al., 1998). Gray et al. (1995a) found no effect on serum testosterone concentrations or on basal or LH-stimulated testicular testosterone production from in utero and lactational exposure to 1.0 μg/kg of TCDD administered on gestational day 8 or 15 in male Long Evans rats at 49 or 270 days of age. These investigators also reported that there was no effect of in utero and lactational exposure to 2.0 μg/kg of TCDD administered on gestational day 11 on serum testosterone concentrations of male Syrian hamsters at 140 days of age (Gray et al., 1995a). Theobald and Peterson (1997) failed to find a significant decrease in plasma testosterone concentrations in male ICR mouse offspring that were 44, 65, or 114 days of age and had been exposed on gestational day 14 to either 15, 30, or 60 μg/kg of TCDD. In utero and lactational exposure of rats to other

Ah receptor agonists have produced results similar to those caused by TCDD. 3,3'4,4'5-PCB (PCB 126), 2,3',4,4',5-PCB (PCB 118), or 2,3,4,7,8-PCDF administered on gestational day 1 had no effect on plasma testosterone concentrations in male Wistar rat offspring at 112 days of age (Bouwman et al., 1996). Overall, these findings suggest that the spectrum of effects caused by in utero and lactational exposure to TCDD on the male reproductive system cannot be explained by decreased postnatal testicular androgen production or plasma androgen concentrations (Gray et al., 1995a; Roman and Peterson, 1998b).

5.2.3.2.4. ***External indicators of androgenic status*****.** The androgenic status of the male offspring can be determined from the structure and function of androgen-dependent systems and from the levels of circulating androgens. Anogenital distance, which is dependent on both circulating androgen concentrations and androgenic responsiveness (Neumann et al., 1970), was reduced in 1- and 4-day-old Holtzman male pups by a single maternal TCDD dose as low as 0.16 μg/kg, even when slight decreases in body length were considered (Mably et al., 1992a). However, this effect was not observed in subsequent studies in Holtzman and Long Evans rats exposed perinatally to TCDD when anogenital distance was determined relative to body weight (Gray et al., 1993; 1995a) or crown-rump length (Bjerke et al., 1994a,b; Roman et al, 1995). Also, when Wistar rats were exposed in utero and via lactation to TCDD or 3,3',4,4',5,5'-HCB (PCB 169), anogenital distance was not affected (Faqi et al., 1998a; Smits-van Prooije et al., 1994). This lack of effect on relative anogenital distance was also found when Long Evans rats were exposed to 3,3'4,4'5,5'-HCB (PCB 169) on gestational day 15 (Gray et al., 1999). Thus, these findings suggest that androgenic status of the male rat neonate is not affected by perinatal exposure to TCDD and PCB 169.

Two other external indicators of androgenic status are time to testis descent and time to preputial separation (Rajfer and Walsh, 1977; Korenbrot et al., 1977). These occur in control rats between postnatal days 20-23 and 42-45, respectively. Exposure to 0.16, 0.40, or 1.0 μg/kg of TCDD on gestational day 15 delayed testis descent in the Holtzman rat strain by 1.0 to 1.6 days (Mably et al., 1992a). However, this effect was significant in only two of four rat studies (Mably et al., 1992a; Bjerke et al., 1994a,b; Faqi et al., 1998a) and in the ICR mouse TCDD had no effect on the age at testis descent (Theobald and Peterson, 1997). Puberty, assessed by age at preputial separation, was more reproducibly affected by TCDD across rat strains and species. It was delayed by as much as 3.6 days in Long Evans rats exposed to 1.0 μg/kg TCDD on gestational day 15 (Gray et al., 1995, 1997). The effect was dose-related and significant at a maternal TCDD dose as low as 0.20 μg/kg (Gray et al., 1997). Delays in age at preputial separation were also reported in Holtzman and Wistar rats and in the Syrian hamster following in utero and lactational exposure to TCDD (Bjerke et al., 1994a,b; Roman et al., 1995; Gray et al.,

1995a; Faqi et al., 1998a). The only species studied where TCDD failed to delay the age at preputial separation was the ICR mouse (Theobald and Peterson, 1997). The ability of TCDD to delay puberty in the Long Evans rat was also observed following in utero and lactational exposure to 1.8 mg/kg of 3,3'4,4'5,5'-HCB (PCB 169) administered on gestational day 8 (Gray et al., 1999).

The spectrum of external effects caused by in utero and lactational exposure to TCDD and 3,3',4,4',5,5'-HCB (PCB 169) have been interpreted not to resemble those caused by known antiandrogens such as flutamide (Gray et al., 1999). This is evident in Holtzman and Long Evans rats by perinatal exposure to TCDD or 3,3',4,4',5,5'-HCB (PCB 169) failing to affect external androgen-dependent tissues either by reducing relative anogenital distance or by inducing areolas, retained nipples, or hypospadias (Roman and Peterson, 1998b; Loeffler and Peterson, 1999; Gray et al., 1999). Flank gland development, an androgen-dependent process that occurs in young adulthood in male hamsters, also was not affected by in utero and lactational exposure to TCDD (Gray et al., 1995a). However, other effects of in utero and lactational exposure to TCDD on the androgen-dependent endpoints of preputial separation (weight of the ventral prostate, seminal vesicle, glans penis, testis, and epididymis; daily sperm production; cauda epididymal sperm number; epididymal malformation; demasculinized and feminized sexual behavior; and feminized regulation of LH secretion) resemble effects caused by antiandrogens (Roman and Peterson, 1998b).

5.2.3.2.5. ***Prostate*****.** One of the most sensitive effects of in utero and lactational exposure to TCDD in the male Holtzman rat is a dose-related reduction in ventral prostate weight. The lowest dose of TCDD that caused this effect was 0.064 μg/kg administered on gestational day 15. It reduced ventral prostate weight in male offspring at 32 days of age (Mably et al., 1992a). However, when expressed on a relative body weight basis, 0.16 μg/kg of TCDD was the lowest dose that caused a significant reduction in ventral prostate weight. At a maternal TCDD dose of 1.0 μg/kg, significant decreases in ventral prostate weight have been detected in Holtzman rats as early as postnatal day 14 and as late as postnatal day 120 (Roman and Peterson, 1998; Mably et al., 1992a). In addition to weight of the ventral prostate being reduced by in utero and lactational TCDD exposure in Holtzman rats (Mably et al., 1992a; Bjerke et al., 1994a,b; Roman et al., 1995; Roman and Peterson, 1998), this effect of perinatal TCDD exposure has also been observed in Long Evans and Sprague-Dawley rats (Gray et al., 1997; Wilker et al., 1996) and in ICR and C57BL/6 mice (Theobald and Peterson, 1997; Sommer and Peterson, 1997; Lin et al., 2000). Although a decrease in ventral prostate weight following in utero and lactational exposure to TCDD was not observed in Wistar rats, this may have been caused by the low level of TCDD exposure used in this study (Faqi et al., 1998a). When the same investigators

administered 10 μg/kg of 3,3'4,4'5-PCB (PCB 126) on gestational day 15 to Wistar rats, ventral prostate weights in 70- and 170-day-old offspring were reduced (Faqi et al., 1998b). Administration of 1.8 mg/kg of 3,3',4,4',5',5-HCB (PCB 169) on gestational day 8 reduced ventral prostate weight in Long Evans rats at 65, 260, and 600 days of age (Gray et al., 1999). However, exposure to 100 μg/kg of 3,3'4,4'-TCB (PCB 77) on gestational day 15 had no effect on ventral prostate weight of Wistar rats at 70 and 170 days of age (Faqi et al., 1998b). Taken together, these results demonstrate that in utero and lactational exposure to certain Ah receptor agonists, namely, TCDD, PCB 126, and PCB 169, are capable of reducing ventral prostate weight in various strains of rats and mice. PCB 77 does not appear to share this effect with the other Ah receptor agonists, and this may be due to the more rapid rate of metabolism and elimination of PCB 77 in the rat than TCDD and the other coplanar PCB congeners tested.

The ability of in utero and lactational exposure to TCDD to decrease ventral prostate weight in the rat is greatest from the earliest age at which the organ can be accurately weighed until just after puberty (50 days of age). Thereafter, the magnitude of the weight reduction is progressively attenuated with advancing age, either completely or partially, depending on the dose of TCDD administered during pregnancy (Mably et al., 1992a). At minimally effective doses the reduction in ventral prostate weight is transient and not seen in adulthood. However, at maximally effective doses ventral prostate weight of adult males is reduced significantly. This has been demonstrated for TCDD in Holtzman rats, PCB 169 in Long Evans rats, PCB 126 in Wistar rats, and TCDD in ICR mice (Mably et al., 1992a; Gray et al., 1999; Faqi et al., 1998b; Theobald and Peterson, 1997). In utero and lactational exposure to TCDD also decreases weight of the dorsolateral prostate and anterior prostate (coagulating gland) in the Holtzman rat, ICR mouse, and C57BL/6 mouse (Roman et al., 1995; Theobald and Peterson, 1997; Sommer and Peterson, 1997; Roman and Peterson, 1998; Loeffler and Peterson, 1999; Lin et al., 2000). Thus, TCDD exposure is capable of interfering with ventral, dorsolateral, and/or anterior prostate growth and morphogenensis early in development. Depending on the dose administered during pregnancy, timing of the exposure, species or strain of animal, and lobe of the prostate, TCDD is capable of causing a prostate lesion that cannot be compensated for later in life. Besides size of the ventral prostate being smaller in adulthood, its responsiveness to testosterone stimulation in adulthoood is also impaired by perinatal exposure to TCDD (Bjerke et al., 1994b).

The mechanism by which in utero and lactational exposure to TCDD impairs prostate growth and development is unknown. It cannot be explained in Holtzman rats by TCDD decreasing plasma androgen concentrations (Chen et al., 1993; Roman et al., 1995; Gray et al., 1995a) or inhibiting the conversion of circulating androgens to DHT in the prostate (Roman et al., 1995; Theobald et al., 2000). TCDD probably acts directly on the urogenital sinus from which the prostate develops and on the developing lobes of the prostate as they undergo

differentiation. The Ah receptor and ARNT are expressed in both the rat urogenital sinus and the developing ventral and dorsolateral prostate (Roman et al., 1998a; Sommer et al., 1998) and the infantile rat ventral prostate is responsive to in utero and lactational TCDD exposure in terms of CYP1A induction (Roman and Peterson, 1998). Also, various androgen-regulated mRNAs that code for secretory proteins that are produced by prostate luminal epithelial cells and are markers for functional differentiation of these cells show transient decreases in response to perinatal TCDD exposure in the Holtzman rat (Roman and Peterson, 1998a).

In utero and lactational exposure to TCDD begins to impair rat prostate development during fetal life (Roman et al., 1998a). Therefore, it is important to determine the concentration of TCDD that is present in the fetal urogenital tract after gestational day 15 because this is when fetal prostate development is initiated in the rat. Administration of 1.15 μg/kg of TCDD on gestational day 8 to Long Evans rats results in concentrations of TCDD in the urogenital tract of the fetus of 0.04 and 1.1 pg/g on gestational days 16 and 21, respectively (Hurst et al., 1998). This is significant because a slightly lower dose of TCDD, 1.0 μg/kg, administered to Long Evans rats on either gestational day 8 or 15, causes a decrease in ventral prostate weight of the offspring peripubertally that disappears in adulthood (Gray et al., 1993, 1995a, 1997, 1999). Furthermore, 1.0 μg/kg of TCDD administered on gestational day 15 to Holtzman rats impairs prostate growth and development postnatally (Roman and Peterson, 1998b) and reduces the number of prostatic buds that emerge from the fetal urogenital sinus on gestational day 20 to form the various lobes of the prostate (Roman et al., 1998a). In addition, this same dose of TCDD decreased cell proliferation in the ventral prostate of Holtzman rat neonates that were 1 day of age (Roman et al., 1998a). Subsequent analysis of the effects of TCDD on early postnatal development of the ventral prostate revealed that differentiation of both smooth muscle cells and luminal epithelial cells was delayed and striking alterations in histology of the ventral prostate were apparent in male offspring at 32 days of age (Roman et al., 1998a). These alterations consisted of epithelial hyperplasia, decreased abundance of fully differentiated luminal epithelial cells, increased density of basal epithelial cells, altered spatial distribution of the androgen receptor, and increased thickness of the periductal smooth muscle sheath. Thus, the effects of in utero and lactational TCDD exposure on prostate growth and development are contributed by impaired growth of the developing organ prenatally and neonatally and by delayed and/or impaired differentiation postnatally that, if the dose of TCDD is high enough, could be permanent.

Essentially nothing is known about the long-term consequences of in utero and lactational exposure to Ah receptor agonists on the prostate of laboratory rodent species during old age. The only study available found that the incidence of acute prostatitis in the dorsolateral prostate of 600-day-old Long Evans rats was increased significantly by exposure to a single dose of 1.8

mg/kg of 3,3',4,4',5,5'-HCB on gestational day 8 (Gray et al., 1999). Also, 1 of 9 males displayed diffuse epithelial hypertrophy of the ventral prostate compared with 0 of 15 control males (Gray et al., 1999).

To understand the mechanism by which TCDD impairs the initial step in rat prostate formation, it is important to note that both the Ah receptor and ARNT proteins are expressed in high concentrations in the fetal Holtzman rat urogenital sinus (Sommer et al., 1999). The fetal rat prostate develops from the urogenital sinus. Solid cords of basal epithelial cells (prostatic buds) emerge from the urogenital sinus and invade the surrounding mesenchyme on gestational day 18.5. By gestational day 20.5 this budding process, which TCDD partially blocks (Roman et al., 1998a), is complete. Ah receptor and ARNT proteins were expressed at high levels in the rat urogenital sinus on gestational days 16, 18, and 20, with mean concentrations of 600 fmoles Ah receptor and 140 fmoles ARNT per mg total tissue lysate (Sommer et al., 1999). From a mechanism point of view, it is significant that Ah receptor protein levels were approximately four times greater than ARNT. Since ARNT dimerizes with several members of the bHLH PAS family of transcription factors, it raises the possibility that TCDD activation of the Ah receptor in the urogenital sinus might sequester ARNT from participating in endogenous protein-protein interactions that may be essential for prostate development. Whatever the mechanism, it is clear that the Ah receptor plays a role. The recent finding that impairment of ventral prostate growth and development in Ah receptor wild-type mice by in utero and lactational exposure to 5 μg/kg of TCDD on gestational day 14 is blocked in Ah receptor knockout mice administered the same dose of TCDD supports this view (Lin et al., 2000).

Ah receptor and ARNT proteins are also expressed in human fetal, benign hyperplastic, and malignant prostate (Kashani et al., 1998). Also, TCDD exposure in a human prostate cancer cell line, LNCaP, dose-dependently inhibits androgen-dependent transcriptional activity and prostate-specific antigen expression (Jana et al., 1999). Thus, the human prostate, like the rat and mouse prostate, is capable of responding to TCDD.

5.2.3.2.6. ***Seminal vesicle*****.** Weight of the seminal vesicle is decreased in Holtzman, Sprague-Dawley, and Long Evans rats and Syrian hamsters by in utero and lactational exposure to TCDD (Mably et al., 1992a; Bjerke and Peterson, 1994; Gray et al., 1995a; Wilker et al., 1996; Gray et al., 1997). The same effect has been observed in Long Evans rats with 3,3',4,4',5,5'-HCB (PCB 169) and in Wistar rats with 3,3'4,4'-TCB (TCB-77) (Gray and Kelce, 1996; Gray et al., 1999; Faqi et al., 1998b). The lowest maternal dose of TCDD to decrease seminal vesicle weight was 0.16 μg/kg administered on gestational day 15. It significantly decreased seminal vesicle weight in Holtzman rat offspring at 32 and 63 days of age (Mably et al., 1992a).

In Wistar rats a multiple dosing regimen with TCDD that caused a significant decrease in cauda epididymal sperm numbers, daily sperm production, and sperm morphology failed to decrease seminal vesicle weight (Faqi et al., 1998a). This implies that the TCDD-induced decrease in seminal vesicle weight is not the most sensitive effect of TCDD on the developing male reproductive system. 3,3',4,4',5-PCB (PCB 126) administered as a single dose of 10 μg/kg on gestational day 15 also had no effect on seminal vesicle weight in the Wistar rat even though it did significantly decrease ventral prostate weight (Faqi et al., 1998b). Thus, the TCDD-induced reduction in seminal vesicle weight is not as sensitive as some of the other developmental reproductive system endpoints in the Wistar rat (Faqi et al., 1998a). Similarly, in Holtzman rats and ICR mice sensitivity of the seminal vesicle to TCDD is not as great as that of the ventral prostate (Mably et al., 1992a; Roman et al., 1995; Theobald and Peterson, 1997). In Long Evans rats the two accessory sex organs seem equivalent in their sensitivity to TCDD administered on day 15 of gestation (Gray et al., 1997).

The time course of the response of the prostate and seminal vesicle to in utero and lactational TCDD exposure in the Holtzman rat is very different (Roman et al., 1995). The ventral and dorsolateral prostate respond with the greatest relative weight reduction early in development and the magnitude of the response lessens with increasing age. In the case of the seminal vesicle, the opposite is true. Significant TCDD-induced decreases in weight are generally not detected until the peripubertal stage when androgen concentrations are rapidly increasing (Roman et al., 1995). Also, the magnitude of the decrease in seminal vesicle relative weight is not as great as it is for the prostate. The difference in time course of weight reduction between the seminal vesicle and prostate suggest that small TCDD-induced reductions in plasma androgen concentrations peripubertally might account for the small decreases in weight of the seminal vesicles in Holtzman rats at this age (Roman et al., 1995; Roman and Peterson, 1998a). A deficiency in number of androgen receptors in the seminal vesicle is not involved, because the decrease in seminal vesicle weight in 330-day-old Long Evans rat exposed to 1.0 μg/kg of TCDD on gestational day 15 was not associated with a decrease in the concentration of androgen receptors in the seminal vesicle (Gray et al., 1995a).

Another difference between the two accessory sex organs is the effect of in utero and lactational exposure to TCDD on their responsiveness to androgenic stimulation in adulthood. The adult ventral prostate is clearly affected by such exposure and is relatively refractory in its responsiveness to androgens. On the other hand, responsiveness of the adult seminal vesicle to testosterone stimulation is not affected by in utero and lactational exposure to TCDD (Bjerke et al., 1994b).

Consistent with the findings in Holtzman rats (Roman et al., 1995), Long Evans rats exposed on gestational day 15 to 1.0 μg/kg of TCDD and assessed on postnatal days 15, 25, 32,

49, 63, and 120 did not exhibit a decrease in weight of the paired seminal vesicles and attached coagulating glands until postnatal day 32 (Hamm et al., 2000). Furthermore, in utero and lactational exposure to TCDD reduced the amount of secretory fluid contained in the seminal vesicles at this age, which contributed to their decreased weight (Hamm et al., 2000). As with the TCDD-exposed ventral prostate at 32 days of age (Roman et al., 1998a), there were striking alterations in histology of the seminal vesicle at 32 days of age (Hamm et al., 2000). Compared with control animals where seminal vesicle epithelium displayed extensive branching, TCDD-exposed rats had seminal vesicles with fewer and shorter epithelial branches. The epithelium of control rats was characterized by tall columnar cells, whereas that of TCDD-exposed rats contained smaller cells with a lower cytoplasmic-volume to nuclear-volume ratio (Hamm et al., 1999, 2000). Immunostaining for proliferating cell nuclear antigen (PCNA) in control seminal vesicles at 32 days of age was localized to undifferentiated basal cells and no immunoreactivity was observed in terminally differentiated luminal epithelial cells. In contrast, the undifferentiated seminal vesicles of TCDD-exposed rats at the same age exhibited PCNA immunoreactivity at both the basal and luminal surfaces of poorly branched glands (Hamm et al., 2000). Thus, the collective database demonstrates that in utero and lactational exposure to TCDD interferes with epithelial proliferation and differentiation in the seminal vesicle as has been reported for the rat prostate (Hamm et al., 2000; Roman et al., 1998a).

5.2.3.2.7. ***Glans penis.*** Like the prostate and seminal vesicle, the glans penis is an androgen-dependent tissue. In utero and lactational exposure to 1.0 μg/kg of TCDD on gestational day 15 decreased glans penis diameter and absolute weight in Holtzman rats at 63 days of age, but had no effect on glans penis length or relative weight (Bjerke and Peterson, 1994). Weight of the glans penis was reduced in 450-day-old Long Evans rats exposed on gestational day 15 to either 0.20 or 0.80 μg/kg of TCDD (Gray et al., 1997).

5.2.3.2.8. ***Testis weight.*** In utero and lactational exposure to a single dose of TCDD administered on gestational day 15 decreases testis weight in Holtzman, Long Evans, and Sprague-Dawley rats (Mably et al., 1992c; Gray et al., 1995a; Wilker et al., 1996). The effect is transient, being manifested to the greatest extent peripubertally and then decreasing with age. It is not as sensitive an endpoint as the decrease in ventral prostate weight or reduction in cauda epididymal sperm numbers in Holtzman rats or the decrease in ejaculated sperm numbers in Long Evans rats (Mably et al., 1992a,c; Gray et al., 1995a, 1997). Also, in Wistar rats exposed in utero and via lactation to TCDD in a multiple dosing regimen, testis weight is not affected at levels of TCDD exposure that decrease daily sperm production (Faqi et al., 1998a). In utero and lactational exposure to TCDD had no effect on testis weight in the ICR mouse, but did decrease

it in the Syrian hamster (Theobald and Peterson, 1997; Gray et al., 1995a). Thus, among laboratory rodent species there are both strain and species differences in susceptibility to TCDD-induced decreases in testis weight.

There is also variability in the extent to which in utero and lactational exposure to individual non-ortho-substituted PCB congeners are capable of producing this effect. Exposure to 3,3',4,4',5,5'-HCB (PCB 169) on gestational day 8, or to 3,3',4,4'-TCB on gestational day 15, reduced testis weight in Wistar rat offspring (Gray and Kelce, 1996; Gray et al., 1999; Faqi et al., 1998b). However, exposure to 3,3',4,4',5-PCB (PCB 126) on gestational day 15 had no effect on testis weight in the Wistar rat strain (Faqi et al., 1998b).

5.2.3.2.9. ***Epididymis weight and malformation.*** In utero and lactational exposure to TCDD has been shown to reduce epididymal weight in Holtzman, Long Evans, and Sprague-Dawley rat strains (Mably et al., 1992c; Bjerke and Peterson, 1994; Gray et al., 1995a, 1997, 1999; Wilker et al., 1996). In these studies TCDD was administered on gestational day 15, except for the studies by Gray et al. (1995a), where it was also administered on gestational day 8. In the Wistar rat strain a multiple dosing regimen was used for in utero and lactational TCDD exposure and it was not associated with a reduction in the epididymal weight of the progeny (Faqi et al., 1998a). Weight of the epididymis was also not reduced by in utero and lactational TCDD exposure in the ICR mouse (Theobald and Peterson, 1997), but cauda epididymal weight was reduced by TCDD exposure on gestational day 11 in the Sryrian hamster (Gray et al., 1995a). In rat strains that responded to perinatal TCDD exposure by reducing epididymal weight in progeny, certain non-ortho-substituted PCB congeners had the same effect. Administration of 3,3'4,4'5,5'-HCB (PCB 169) on gestational day 8 decreased whole epididymal weight in Long Evans rats, whereas weight of the epididymides in Wistar rats was either not affected or slightly reduced by 3,3',4,4'-TCB (PCB 77) or 3,3',4,4',5-PCB (PCB 126) administered on gestational day 15 (Gray and Kelce, 1996; Gray et al., 1999; Faqi et al., 1998b) .

Compared with decreased testis weight, decreased epididymis and cauda epididymis weights in the Holtzman rat were more sensitive and persistent effects of in utero and lactational TCDD exposure. This is demonstrated by dose-related decreases in weight of the cauda epididymis occurring in Holtzman rats at 120 days of age and cauda epididymal weight being reduced significantly at this age by the lowest dose of TCDD used in the study, 0.064 μg/kg (Mably et al., 1992c). The lowest dose of TCDD reported to decrease epididymal weight in other studies was 0.20 μg/kg in the Long Evans rat (Gray et al., 1997) and the lowest dose tested in the Sprague-Dawley rat, 0.5 μg/kg (Wilker et al., 1996).

The reduction in epididymal weight following in utero and lactational exposure to 1.0 μg/kg of TCDD on gestational day 15 could be permanent in certain rat strains. Significant

decreases in whole epididymal or cauda epididymal weights have been observed in 120-day-old Holtzman rats and 240- to 330-day-old Long Evans rats (Mably et al., 1992c; Gray et al., 1995a). Since epididymal growth is androgen dependent, a TCDD-induced androgenic deficiency and/or decrease in androgen responsiveness of the epididymis could account for decreased size of the organ (Setty and Jehan, 1977; Dhar and Setty, 1990). However, if an antiandrogenic mechanism is involved, it does not appear to be associated with decreases in plasma androgen levels or epididymal androgen receptor levels. This is because in utero and lactational exposure to TCDD has been shown not to reduce circulating androgen concentrations in Holtzman or Long Evans rats at various stages of postnatal development (Roman et al., 1995; Gray et al., 1995a). Also TCDD does not reduce androgen receptor concentrations in either the caput or corpus epididymis when measured in 240- to 330-day-old Long Evans rat progeny exposed perinatally to TCDD (Gray et al., 1995a).

The highest dose of TCDD to be investigated on epididymal development was 2.0 μg/kg administered on gestational day 15 to Sprague-Dawley rats (Wilker et al., 1996). The effects of this high dose on morphological development of the rat epididymis are useful in providing insight into possible mechanisms of action of TCDD on the epididymis. More specifically, this dose of TCDD induced a high incidence of malformations in the epididymis (27%) that were characterized by the segmental absence of regions of the epididymis (Wilker et al., 1996). This high incidence is similar to that reported for rats and mice exposed in utero to the antiandrogen flutamide (van der Schoot, 1992; Cain et al., 1994a,b) and suggests that TCDD may alter testosterone-dependent differentiation of the Wolffian duct into the epididymis (Wilker et al., 1996).

5.2.3.2.10. ***Testicular and epididymal sperm numbers.*** Among the most robust, sensitive, persistent, and reproducible effects of in utero and lactational TCDD exposure in rats, hamsters, and mice are reductions in sperm numbers (Roman and Peterson, 1998b). Generally when TCDD is administered as a single dose during pregnancy, daily sperm production is affected the least. Caput epididymal sperm numbers are reduced to a greater extent than daily sperm production (Gray et al., 1997). Cauda epididymal sperm numbers are reduced more than caput epididymal sperm numbers by in utero and lactational exposure to TCDD. In fact, statistically significant, dose-related reductions in cauda epididymal sperm numbers have been reported for four strains of rats, mice, and hamsters following in utero and lactational exposure to TCDD (Mably et al., 1992c; Gray et al., 1995a, 1997; Wilker et al., 1996; Theobald and Peterson, 1997; Faqi et al., 1998a). The greatest magnitude of reduction in sperm numbers at any given dose of TCDD, however, has been reported for ejaculated sperm numbers in two strains of rats and the hamster (Gray et al., 1995a, 1997; Sommer et al., 1996). Thus, the overall effect of exposure to a

single dose of TCDD administered on gestational day 15 in rats and hamsters is that it causes a progressively greater percentage decrease in sperm numbers in going from the testis (daily sperm production), to caput epididymal sperm numbers, to cauda epididymal sperm numbers, to ejaculated sperm numbers. Taken together, these results imply that in utero and lactational TCDD exposure alters epididymal function such that epididymal sperm storage is permanently reduced (Gray et al., 1995a).

An entirely different profile of inhibitory effects of in utero and lactational exposure to TCDD on sperm numbers, however, was observed in Wistar rats that were exposed to multiple doses of TCDD during mating, pregnancy, and lactation (Faqi et al., 1998b). With this multiple-dosage TCDD exposure paradigm in Wistar rats, the percentage decrease in daily sperm production was greater than the percentage decrease in cauda epididymal sperm numbers (Faqi et al., 1998a)—just the opposite of what was observed in Long Evans and Holtzman rats where TCDD was administered as a single dose (Gray et al., 1995a, 1997; Sommer et al., 1996). It is possible that the difference in rat strain or the TCDD exposure paradigm between these studies accounts for the testis being more sensitive than the cauda epididymis to TCDD-induced decreases in sperm numbers in the study by Faqi and coworkers (1998a).

The lowest single dose of TCDD to decrease cauda epididymal sperm numbers in 120-day-old Holtzman rats was 0.064 μg/kg administered on gestational day 15 (Mably et al., 1992c). The lowest single dose to decrease ejaculated sperm numbers in 450 day old Long Evans rats was 0.050 μg/kg of TCDD administered on gestational day 15 (Gray et al., 1997). Faqi and coworkers (1998a), using a multiple dosing regimen for in utero and lactational exposure of Wistar rat progeny to TCDD, found that the lowest dosing regimen to significantly decrease daily sperm production and cauda epididymal sperm numbers in 170-day-old Wistar rats was a 0.025 μg TCDD/kg loading dose followed by a 0.005 μg TCDD/kg weekly maintenance dose (Faqi et al., 1998a). When the male offspring exposed in utero and via lactation to TCDD in this manner were weaned at 22 days of age, the mean concentration of TCDD in the testis and liver was 0.25 ng/g and 0.24 ng/g, respectively (Faqi et al., 1998a).

5.2.3.2.10.1. ***Daily sperm production.*** In utero and lactational exposure to TCDD in Holtzman rats caused a dose-related decrease in daily sperm production in progeny at 49, 63, and 120 days of age (Mably et al., 1992c). The lowest dose of TCDD administered on gestational day 15 to reduce daily sperm production in 120-day-old Holtzman rats was 0.064 μg/kg. Other studies have also reported that in utero and lactational exposure to TCDD is capable of significantly decreasing daily sperm production in Holtzman, Long Evans, and Wistar rats (Bjerke and Peterson, 1994; Sommer et al., 1996; Gray et al., 1997; Faqi et al., 1998b), but this effect was not observed in Sprague-Dawley rats (Wilker et al., 1996), ICR mice (Theobald and Peterson, 1997),

or Syrian hamsters (Gray et al., 1995a). In the three rat strains where decreased daily sperm production is observed, the response lessens in severity as the progeny age and in some cases returns to control levels (Mably et al., 1992c; Gray et al., 1995a). The Long Evans rat is an example of a rat strain where the decrease in daily sperm production caused by perinatal TCDD exposure is transient (Gray et al., 1995a, 1997). Among the most persistent effects of TCDD on daily sperm production was found in 170-day-old Wistar rats exposed to TCDD dosing during mating, pregnancy, and lactation (Faqi et al., 1998b). It has also been observed in Long Evans rats that administration of TCDD on gestational day 15 is more effective than administering it on gestational day 8 (Gray et al., 1995a; Gray and Kelce, 1996).

Effects on daily sperm production in Long Evans and Wistar rat strains by certain non-ortho-substituted PCBs was variable. In utero and lactational exposure to 3,3',4,4',5',5-HCB (PCB 169) on gestational day 8 reduced daily sperm production in Long Evans rats (Gray et al., 1995b, 1999; Gray and Kelce, 1996). However, exposure of Wistar rats on gestational day 15 to 3,3',4,4',5-PCB (PCB 126) had no effect (Faqi et al., 1998b). Furthermore, in utero and lactational exposure to 3,3',4,4'-TCB (PCB 77) increased both testis size and daily sperm production in 65- and 140-day-old Wistar rats. It was hypothesized that this latter paradoxical effect for an Ah receptor agonist of increasing daily sperm production may be secondary to a possible non-Ah receptor-mediated effect of PCB 77, such as neonatal hypothyroidism (Faqi et al., 1998b).

While severe undernutrition of rat pups and weanlings can adversely affect the male reproductive system and decrease spermatogenesis (Ghafoorunissa, 1980; Jean-Faucher et al., 1982a,b; Glass et al., 1986), it is unlikely that this was involved in reducing daily sperm production caused by in utero and lactational exposure of Holtzman rats to TCDD (Mably et al., 1992c). At the two highest maternal TCDD doses, 0.40 and 1.0 μg/kg, feed consumption and body weight of male offspring were decreased up to 21%, but there was essentially no effect on feed intake or body weight at the two lowest doses, 0.160 and 0.064 μg/kg. However, reduction in daily sperm production, cauda epididymal sperm numbers, and certain sex organ weights, occurred at the two lowest doses. Thus, undernutrition cannot account for these effects (Mably et al., 1992a,c).

Because follicle-stimulating hormone (FSH) and testosterone are essential for quantitatively normal spermatogenesis (Steinberger and Steinberger, 1989), an alternative explanation for the decreases in daily sperm production is a decrease in FSH and/or testosterone levels. In rats, the duration of spermatogenesis is 58 days (Blazak et al., 1985; Amann, 1986; Working and Hurtt, 1987), so the decreases in plasma FSH concentrations in 32-day-old male offspring could contribute to the reductions in daily sperm production when the progeny were 49 and 63 days of age (Mably et al., 1992c). However, the modest depressant effect of perinatal

TCDD exposure on plasma FSH concentrations was transitory, with no effect on plasma FSH levels being found when the offspring were 49, 63, and 120 days old (Mably et al., 1992c). Therefore, it was concluded that reduced daily sperm production in 120-day-old rats perinatally exposed to TCDD is not due to decreases in plasma FSH levels when the animals were 49 to 120 days of age (Mably et al., 1992c). Also, administration of 1.0 μg/kg of TCDD on gestational day 15 to Holtzman rats did not affect testicular testosterone production of their progeny at either prenatal or postnatal stages of development (Chen et al., 1993; Roman et al., 1995). Therefore, a reduction in intratesticular testosterone levels following such TCDD exposure would not be sufficient to reduce spermatogenesis (Zirkin et al., 1989; Mably et al., 1992c; Gray et al., 1993).

In normal rats, daily sperm production does not reach a maximum until 100 to 125 days of age (Robb et al., 1978), but in rats perinatally exposed to TCDD it takes longer for sperm production to reach the adult level. Furthermore, the length of the delay for daily sperm production to attain control levels appears to be directly related to TCDD dose (Mably et al., 1992c). If the dose is high enough, the reduction in daily sperm production may be permanent. This is suggested by in utero and lactational exposure to TCDD decreasing daily sperm production in 170-day-old Wistar rats (Faqi et al., 1998b) and 300-day-old Holtzman rats (Moore et al., 1992). However, in Long Evans rat the TCDD-induced reduction in daily sperm production is transient and does not last beyond the peripubertal stage of development (Gray et al., 1997).

5.2.3.2.10.2. *Testis histology*. A key observation for postulating mechanisms by which perinatal TCDD exposure reduces spermatogenesis in the Holtzman rat strain in adulthood is the finding that the ratio of leptotene spermatocytes per Sertoli cell in the testes of 49-, 63-, and 120-day-old Holtzman rats is not affected by in utero and lactational TCDD exposure even though daily sperm production is reduced (Mably et al., 1992c). Because Sertoli cells provide spermatogenic cells with functional and structural support (Bardin et al., 1988) and the upper limit of daily sperm production in adult rats is directly dependent on the number of Sertoli cells per testis (Russell and Peterson, 1984), three possible mechanisms for the decrease in daily sperm production in Holtzman rats may be involved. TCDD could increase the degeneration of cells intermediate in development between leptotene spermatocytes and terminal-stage spermatids (the cell type used to calculate daily sperm production); decrease postleptotene spermatocyte cell division (meiosis); and/or decrease the number of Sertoli cells per testis (Orth et al., 1988). In a histological study of the testis in Holtzman rats exposed to TCDD in utero and via lactation, it was found that spermatogenesis was qualitatively normal; there was no indication of a gross histological lesion nor any evidence of germ cell degeneration (Shinomiya et al., 1994).

In Long Evans rats exposed in utero and via lactation to TCDD, testicular histopathology was not typically affected (Gray et al., 1995a). That is, there was generally no histological evidence for degeneration of the seminiferous tubules, Sertoli cell abnormalities, or retained spermatids in progeny exposed in utero and via lactation to TCDD (Gray et al., 1997). On occasion, however, both Long Evans rat progeny and Syrian hamster progeny of dams exposed to TCDD exhibited severe atrophy of the seminiferous tubules that was associated with a marked loss of spermatogenic activity (Gray et al., 1997).

In Wistar rats that were exposed to TCDD using a multiple dosing regimen during mating, pregnancy, and lactation, the decrease in daily sperm production observed at the two lowest TCDD exposure levels was not associated with any testicular pathology (Faqi et al., 1998a). However, at the highest level of in utero and lactational TCDD exposure some seminiferous tubuli showed pyknotic nuclei and cell debris in the lumen (Faqi et al., 1998a). In utero and lactational exposure to 1.0 μg/kg of TCDD on gestational day 15 did not cause abnormal testicular histology in 62-day-old Sprague-Dawley rats (Wilker et al., 1996). The number of Sertoli cells per testis and number of Sertoli cells per gram testis was not affected by TCDD. However, the ratio of the number of elongated spermatids in testicular homogenates to the number of Sertoli cells per testis was significantly lower in TCDD-exposed progeny (Wilker et al., 1996).

5.2.3.2.10.3. ***Epididymal sperm numbers.*** The epididymis has two functions: in the caput and corpus epididymis, proximal regions of the organ, spermatozoa mature gaining the capacity for motility and fertility, whereas in the cauda epididymis, the distal region, mature sperm are stored before ejaculation (Robaire and Hermo, 1989). Mably et al. (1991, 1992c) found that motility and morphology of sperm taken from the cauda epididymis on postnatal days 63 and 120 were unaffected by perinatal TCDD exposure. Exposure of Wistar rats to TCDD in a multiple-dosing regimen during mating, pregnancy, and lactation caused small but significant increases in the percentage of abnormal sperm in 170-day-old male offspring (Faqi et al., 1998a). However, in Wistar rats exposed in utero and via lactation to a single dose of 3,3',4,4'-TCB (PCB 77) or 3,3',4,4',5-PCB (PCB 126) on gestational day 15, no effect on the percentage of abnormal sperm was found in 65- or 140-day-old male progeny (Faqi et al., 1998b).

It bears repeating at this time that the most sensitive, robust, persistent, and reproducible effect of in utero and lactational exposure to TCDD on the male reproductive system of laboratory rodents is a decrease in cauda epididymal sperm numbers. This effect has been demonstrated for Holtzman, Long Evans, Sprague-Dawley, and Wistar rats as well as ICR mice and Syrian hamsters (Mably et al., 1992c; Gray et al., 1995a, 1997; Wilker et al., 1996; Theobald

and Peterson, 1997; Faqi et al., 1998a). The lowest dose of TCDD to produce this effect is 0.064 μg/kg administered on gestational day 15 to Holtzman rats (Mably et al., 1992c).

Following in utero and lactational exposure to a single dose of TCDD there is a graded decline in sperm numbers as they travel from the testis through the caput, corpus, and cauda epididymis and are ejaculated (Gray et al., 1995a, 1997; Sommer et al., 1996). While these results suggest that sperm transit rate through the epididymis should be increased by in utero and lactational TCDD exposure, three studies that have determined epididymal sperm transit rates have reached different conclusions. The most rigorous examination of this endpoint was the study by Sommer et al. (1996). They found that in Holtzman rats administered TCDD on gestational day 15 there was no effect on epididymal sperm transit rate. This rules out the possibilities of sperm loss via spontaneous ejaculation or abnormal introduction of sperm into urine (Sommer et al., 1996). In contrast, in utero and lactational exposure of Sprague-Dawley rats to TCDD on gestational day 15 was reported to increase in epididymal sperm transit rate (Wilker et al., 1996), and using a multiple-dosing regimen for in utero and lactational TCDD exposure in Wistar rats, a decrease in epididymal sperm transit rate was found (Faqi et al., 1998a).

In association with the reduction in cauda epididymal sperm numbers, there is a distinct tendency for an increased incidence of a chronic inflammatory reaction in the epididymis of Long Evans rats exposed in utero and via lactation to 3,3',4,4',5,5'-HCB (PCB 169) (Gray et al., 1999) and in Holtzman rats exposed to TCDD (Sommer and Peterson, unpublished results). Furthermore, the decrease in cauda epididymal sperm numbers in adult hamsters following in utero and lactational exposure to TCDD is associated with an increased incidence of sperm granulomas in epididymides and/or testes. This lesion was characterized by a nodular accumulation of fibrous connective tissue and mixed inflammatory cells surrounding degenerating sperm in the interstitium of the epididymides and testes. Taken together, these findings suggest that the reduction in cauda epididymal sperm numbers caused by in utero and lactational exposure to TCDD in the hamster are due in part to sperm resorption from the epididymis. Furthermore, since resorption of sperm in the epididymis is often associated with the accumulation of inflammatory cells in the organ, sperm resorption from the epididymis might also be occurring in postpubertal Holtzman rats exposed to TCDD in utero and via lactation (Sommer and Peterson, unpublished results).

5.2.3.2.10.4. ***Ejaculated sperm numbers.*** Although it has been assessed in only two rat strains, Long Evans and Holtzman, and in the Syrian hamster, the effect on the male reproductive system that is detected at the lowest dose of TCDD administered during pregnancy is that which causes a decrease in ejaculated sperm numbers. The lowest single dose of TCDD administered during

pregnancy that causes this effect is 0.050 μg/kg administered on gestational day 15 in the Long Evans rat with ejaculated sperm numbers assessed in adulthood (Gray et al., 1997). In addition to the reduction in total number of sperm ejaculated during the mating period there was also a reduction in the number of sperm in copulatory plugs. The small reduction in sperm produced by the testis of Long Evans rats, exposed perinatally to TCDD, was not sufficient to account for the larger reductions in cauda epididymal sperm numbers and ejaculated sperm numbers. Finally, there was no reduction in the number of copulatory plugs produced by TCDD-exposed males, indicating no interference with copulation (Gray et al., 1995a).

5.2.3.2.11. ***Reproductive capability.*** To assess reproductive capability, male Holtzman rats born to dams given TCDD (0.064, 0.16, 0.40, or 1.0 μg/kg) or vehicle on day 15 of gestation were mated with control virgin females when the males were 70 and 120 days of age (Mably et al., 1991, 1992c). The fertility index of the males is defined as number of males impregnating females divided by number of males mated. The two highest maternal TCDD doses decreased the fertility index of the male offspring by 11% and 22%, respectively. However, these decreases were not statistically significant, and at lower doses the fertility index was not reduced. The gestation index, defined as the percentage of control dams mated with TCDD-exposed males that delivered at least one live offspring, was also not affected by in utero and lactational TCDD exposure.

With respect to progeny of these matings, the results of the above study (Mably et al., 1992c) and more recent studies are somewhat inconsistent possibly due to differences in the rat strain used. Gray et al. (1995a) reported in the Long Evans that there were fewer implants in females mated to gestational day 15 TCDD-treated male offspring. On the other hand, all male Wistar rat offspring exposed during mating, pregnancy, and lactation to TCDD were able to impregnate unexposed female rats and to produce viable fetuses (Faqi et al., 1998a). For these TCDD-exposed male rat progeny, their mating, pregnancy, and fertility indices were similar to control. Also, the number of implantations, resorption rate, number of viable and dead fetuses, and sex ratio of the progeny were similar among control and TCDD treatment groups (Faqi et al., 1998a). Similar to the results in Wistar rats, Mably et al. (1992c) reported that there was no effect on litter size, live birth index, or 21-day survival index for male Holtzman rat offspring that were mated to unexposed females.

Effects of in utero and lactational exposure to non-ortho-substituted PCB congeners has also been investigated on the reproductive capability of male rat progeny when they reach sexual maturity. Exposure to 1.8 mg/kg of 3,3',4,4',5,5'-HCB (PCB 169) on gestational day 1 reduced the fertility of the PCB 169-exposed male Wistar rat progeny when they were mated with unexposed control females (Smits-van Prooije et al., 1993). In contrast, treatment with either

3,3',4,4'-TCB (PCB 77) or 3,3',4,4',5-PCB (PCB 126) on gestational day 15 had no effect on the outcomes of matings between PCB 77- or PCB 126-exposed male Wistar rat progeny mated with unexposed females for the following endpoints: implantations per litter, viable fetuses per litter, or percentage resorptions (Faqi et al., 1998b).

Since rats produce and ejaculate 10 times more sperm than is necessary for normal fertility and litter size (Aafjes et al., 1980; Amann, 1982), the absence of a reduction in fertility of male rats exposed perinatally to TCDD is not inconsistent with the substantial reductions in testicular spermatogenesis and epididymal sperm reserves. In contrast, reproductive efficiency in human males is very low, the number of sperm per ejaculate being close to that required for fertility (Working, 1988). Thus, measures of fertility using rats are not appropriate for low-dose extrapolation in humans (Meistrich, 1992). A percentage reduction in daily sperm production in humans, similar in magnitude to that observed in rats (Mably et al., 1991, 1992c), could be associated with reduced fertility in men.

5.2.3.2.12. Possible mechanisms for effects on male reproductive tract growth and development. The mechanisms by which TCDD and related compounds impair male reproductive tract development are not known. Several possibilities exist and since these have been reviewed recently (Roman and Peterson, 1998b), only an overview will be presented here. It is generally assumed that most effects of in utero and lactational exposure to TCDD on development of the male reproductive system are Ah receptor mediated. While this is probable, it has not yet been proven conclusively for these endpoints. A comparison of male reproductive endpoints in wild-type and Ah receptor knockout mice, following in utero and lactational exposure to TCDD, is needed to provide this insight. Such studies in Ah receptor wild-type and Ah receptor knockout mice have shown that the decrease in prostate and seminal vesicle weight caused by perinatal exposure to TCDD is dependent on the Ah receptor (Lin et al., 2000). However, this kind of information is not available for any of the other male reproductive endpoints. Three possible Ah receptor-dependent mechanisms by which in utero and lactational exposure to TCDD could impair male reproductive development are as follows. First, the liganded Ah receptor could dimerize with ARNT and this complex could then bind to dioxin-responsive elements in the 5' regulatory regions of genes and alter their transcription in male reproductive tissues during the endocrine phase of fetal and neonatal sexual differentiation. Second, the liganded Ah receptor could compete with other PAS proteins for dimerization with ARNT at critical periods of male repoductive tract development and downregulate genes dependent on ARNT and an alternative dimerization partner for transcription. Third, the ligand-activated Ah receptor could be rapidly depleted from cells, thereby decreasing the pool of Ah receptor available for binding of an endogenous ligand or activating the transcription of genes

important in normal male reproductive development at the cellular level. Treatment of adult rats with TCDD is known to downregulate Ah receptor expression in several male rat reproductive tract tissues (Roman et al., 1998c). However, it was recently found that this does not occur in the developing rat prostate when 1.0 μg/kg of TCDD is administered on gestational day 15, making this latter Ah receptor mechanism seem less likely (Sommer et al., 1999).

In utero and lactational exposure to TCDD produces a novel constellation of growth and developmental alterations in the male rat reproductive system. These consist of decreases in accessory sex organ weights, delays in preputial separation, decreases in daily sperm production by the testis and sperm storage in the cauda epididymis, decreases in ejaculated sperm numbers, and partial demasculization of sexual behavior and partial feminization of sexual behavior and the regulation of LH secretion. Taken together, these effects are consistent with decreased testicular androgen production and/or circulating androgen concentrations. But these parameters have not been shown to be affected perinatally or at later times by perinatal exposure to TCDD (Mably et al., 1992a; Chen et al., 1993; Roman et al., 1995; Gray et al., 1995a). Nevertheless, the possibility remains that the androgenic deficiency-like syndrome caused by developmental exposure to TCDD could be the result of interference with androgen action at the level of the androgen receptor. While no effect of in utero and lactational exposure to TCDD on androgen receptor concentrations in the caput epididymis, cauda epididymis, ventral prostate, or seminal vesicle was found in 336- to 339-day-old Long Evans rats (Gray et al., 1995a), alterations in the spatial distribution of the androgen receptor were found in the ventral prostate of infantile and weanling Holtzman rats exposed perinatally to TCDD (Roman et al., 1998a). This latter effect of TCDD may explain why the ventral prostate exhibits decreased growth and abnormal differentiation in the presence of normal circulating levels of androgens (Roman et al., 1998a). Thus, it is possible that TCDD acts at or beyond the androgen receptor to interfere with prostate development.

Just because development of androgen-dependent tissues such as the prostate, seminal vesicle, epididymis, and testis are affected by in utero and lactational TCDD exposure does not necessarily mean that an antiandrogenic action of TCDD is the only mechanism by which TCDD could disrupt their development (Roman and Peterson, 1998b; Gray et al., 1999). Impaired growth and development of these organs could arise by TCDD acting on multiple components of the endocrine axis to alter concentrations of other hormones, growth factors and/or their receptors. Epidermal growth factor, prolactin, thyroid hormones, and growth hormones can influence development of certain of these organs, and their signaling pathways may be modulated by perinatal exposure to TCDD (Gray et al., 1999). Also, an important finding is that the spectrum of TCDD's effects on male reproductive system development and function does not quite match that which is produced by perinatal exposure to known antiandrogens, 5α-reductase

inhibitors, or antiestrogens (Roman and Peterson, 1998b; Gray et al., 1999). Therefore, it is possible that TCDD modulates cell proliferation and differentiation in these tissues by interfering with nonhormonal aspects of these processes. For example, prostatic budding and ductal morphogenesis are of course androgen-dependent but they also involve important mesenchymal-epithelial interactions occurring downstream of androgen receptor action that might be modulated by TCDD (Roman and Peterson, 1998b).

5.2.3.2.13. ***Sexual differentiation of the CNS*****.** Sexual differentiation of the CNS is dependent on the presence of androgens during early development. In rats, the critical period of sexual differentiation extends from late fetal life through the first week of postnatal life (MacLusky and Naftolin, 1981). In the absence of adequate circulating levels of testicular androgen during this time, adult rats display high levels of feminine sexual behavior (e.g., lordosis), low levels of masculine sexual behavior, and a cyclic (i.e., feminine) pattern of LH secretion (Gorski, 1974; Barraclough, 1980). In contrast, perinatal androgen exposure of rats will result in the masculinization of sexually dimorphic neural parameters, including reproductive behaviors, regulation of LH secretion, and several morphological indices (Raisman and Field, 1973; Gorski et al., 1978). The mechanism by which androgens cause sexual differentiation of the CNS is not completely understood. In the rat, it appears that 17ß-estradiol, formed by the aromatization of testosterone within the CNS, is one of the principal active steroids responsible for mediating sexual differentiation (McEwen, 1978); however, androgens also are involved.

5.2.3.2.13.1. ***Demasculinization of sexual behavior*****.** Mably et al. (1991, 1992b) assessed sexually dimorphic functions in male rats born to dams given graded doses of TCDD or vehicle on day 15 of gestation. Masculine sexual behavior was assessed in male offspring at 60, 75, and 115 days of age by placing a male rat in a cage with a receptive control female and observing the first ejaculatory series and subsequent postejaculatory interval. The number of mounts and intromissions (mounts with vaginal penetration) before ejaculation was increased by a maternal TCDD dose of 1.0 μg/kg. The same males exhibited twelvefold and elevenfold increases in mount and intromission latencies, respectively, and a twofold increase in ejaculation latency. All latency effects were dose related and significant at a maternal TCDD dose as low as 0.064 μg/kg (intromission latency) and 0.16 μg/kg (mount and ejaculation latencies). Copulatory rates (number of mounts + intromissions/time from first mount to ejaculation) were decreased to less than 43% of the control rate (Mably et al., 1992b). This effect on copulatory rates was dose related, and a statistically significant effect was observed at maternal TCDD doses as low as 0.16 μg/kg. Postejaculatory intervals were increased 35% above the control interval, and a statistically

significant effect was observed at maternal doses of TCDD as low as 0.40 μg/kg. Collectively, these results demonstrate that perinatal TCDD exposure demasculinizes sexual behavior.

Because perinatal exposure to a maternal TCDD dose of 1.0 μg/kg has no effect on the open field locomotor activity of adult male rats (Schantz et al., 1991), the increased mount, intromission, and ejaculation latencies in Holtzman rats (Mably et al., 1992b) appear to be specific for these masculine sexual behaviors, not secondary to a depressant effect of TCDD on motor activity. The reported postpubertal plasma testosterone and DHT concentrations in litter mates of the rats evaluated for masculine sexual behavior were as low as 56% and 62%, respectively, of controls (Mably et al., 1991, 1992a). However, plasma testosterone concentrations that were only 33% of controls are still sufficient to masculinize sexual behavior of adult male rats (Demassa et al., 1977). Therefore, the modest reductions in adult plasma androgen concentrations following perinatal TCDD exposure were not of sufficient magnitude to demasculinize sexual behavior.

Reductions in perinatal androgenic stimulation can inhibit penile development and subsequent sensitivity to sexual stimulation in adulthood (Nadler, 1969; Södersten and Hansen, 1978). Therefore, the demasculinization of sexual behavior could, to some extent, be secondary to decreased androgen-dependent penile development. However, perinatal TCDD exposure had no effect on gross appearance of the rat penis. In addition, TCDD-exposed males exhibited deficits in such masculine sexual behaviors as mount latency and postejaculatory interval, which do not depend on stimulation of the penis for expression (Sachs and Barfeld, 1976). Thus, although some effects of TCDD, such as decreased copulatory rate and prolonged latency until ejaculation, could be due to reduced sensitivity of the penis to sexual stimulation, the twelvefold increase in mount latency and increase in postejaculatory interval cannot be explained by this mechanism.

The effect of in utero and lactational exposure to 0.7 μg/kg of TCDD on gestational day 15 on the expression of masculine sexual behavior was assessed in male Holtzman rats at 61-65 and 75-79 days of age (Bjerke et al., 1994). A partial demasculinization of sexual behavior was evidenced by increased intromission latencies and a greater number of intromissions prior to ejaculation. Overall, the effects were more similar to those observed in Holtzman rats exposed on gestational day 15 to 0.4 μg/kg of TCDD (Mably et al., 1992b).

The effect of in utero and lactational exposure to 1.0 μg/kg of TCDD administered on gestational day 8 or 15 on masculine sexual behavior was assessed in Long Evans rats (Gray et al., 1998a). The expression of masculine sexual behaviors was altered to a greater extent in rats exposed to TCDD on gestational day 15 than gestational day 8. In males exposed to TCDD on gestational day 15, partial demasculinization of sexual behavior was evidenced by increases in total number of mounts prior to ejaculation, number of mounts with intromissions prior to

ejaculation, number of mounts without intromissions prior to ejaculation, and latency prior to ejaculation (Gray et al., 1995a). While the same profile of results was obtained in males exposed to TCDD on gestational day 8, the effects were not as great and were not statistically significant (Gray et al., 1995a).

Masculine sexual behavior was also assessed in male Wistar rats exposed in utero and via lactation to TCDD administered to dams during mating, pregnancy, and lactation (Faqi et al., 1998a). Mount latency and intromission latency were increased at two of three TCDD exposure levels. However, ejaculation latency, number of mounts with intromissions prior to ejaculation, and intromission frequency were not affected. Of the five endpoints of masculine sexual behavior assessed in male Wistar rat progeny that were exposed to 10 μg/kg of 3,3',4,4',5-PCB (PCB 126) on gestational day 15, only one endpoint was affected, the number of mounts with intromissions prior to ejaculation, and it was increased (Faqi et al., 1998b).

Taken together, these results demonstrate in three different rat strains, Holtzman, Long Evans, and Wistar, that in utero and lactational exposure to TCDD affects some, but not all, endpoints of masculine sexual behavior. Therefore, TCDD only partially demasculinizes sexual behavior. The response is not as robust as other endpoints, and the degree to which TCDD affects the expression of masculine sexual behavior depends on the rat strain, Ah receptor agonist, and dose administered. It is notable that male hamster progeny do not exhibit demasculinized sexual behavior following perinatal exposure to TCDD, making it difficult to extrapolate this response with certainty to other species.

5.2.3.2.13.2. ***Feminization of sexual behavior*****.** Mably et al. (1991, 1992b) determined if the potential of adult male rats to display feminine sexual behavior was altered by perinatal TCDD exposure. Male offspring of dams treated on day 15 of gestation with various doses of TCDD up to 1 μg/kg or vehicle were castrated at ~120 days of age, and beginning at ~160 days of age were injected weekly for 3 weeks with 17ß-estradiol benzoate, followed 42 hours later by progesterone. Four to six hours after the progesterone injection at weeks 2 and 3, the male was placed in a cage with a sexually excited control stud male. The frequency of lordosis in response to being mounted by the stud male was increased from 18% (control) to 54% by the highest maternal TCDD dose, 1.0 μg/kg. Lordosis intensity, scored after Hardy and DeBold (1972) as 1 for light lordosis, 2 for moderate lordosis, and 3 for a full spinal dorsoflexion, was increased in male rats by perinatal TCDD exposure. Both effects on lordosis behavior in males were dose related and significant at maternal TCDD doses as low as 0.16 μg/kg (increased lordotic frequency) and 0.40 μg/kg (increased lordotic intensity). Together, they indicate a feminization of sexual behavior in these animals. Although severe undernutrition from 5 to 45 days after birth potentiates the display of lordosis behavior in adult male rats (Forsberg et al., 1985), the

increased frequency of lordotic behavior was seen at a maternal TCDD dose of 0.16 μg/kg, which had no effect on feed intake or body weight. It was concluded that perinatal TCDD exposure feminizes sexual behavior in adult male rats independent of undernutrition.

Defeminization of sexual behavior in male rats occurs during the first week or so after birth (Goy and McEwen, 1980; Perakis and Stylianopoulou, 1985). Therefore it was hypothesized that if TCDD interferes with defeminization of sexual behavior that lactational exposure to TCDD would be more important than in utero exposure. A subsequent study by Bjerke and Peterson (1994) is consistent with this hypothesis. In their cross-fostering study on the effects of in utero versus lactational TCDD exposure in the Holtzman rat, it was found, as predicted, that feminization of male sexual behavior required lactational exposure. When exposure was restricted to the in utero period, the male offspring did not display a significant increase in lordotic behavior, whereas such behavior was increased following exposure during the lactational period, either alone or in combination with in utero exposure. Also, in a separate study it was shown following in utero and lactational exposure to 1.0 μg/kg of TCDD administered on gestational day 15 that feminine sexual behavior of male rats was partially feminized as indicated by an increase in lordosis quotient (Bjerke et al., 1994b).

In contrast to the above three studies that show in utero and lactational TCDD exposure increases the expression of feminine sexual behavior in male Holtzman rats (Mably et al., 1992b; Bjerke and Peterson, 1994; Bjerke et al., 1994b), this effect was not observed in male Long Evans rats (Gray et al., 1995a). They showed no significant increase in lordotic behavior as adults following in utero and lactational exposure to 1.0 μg/kg of TCDD on gestational day 8 or 15 (Gray et al., 1995a). This may be due to a rat strain difference in susceptibility to this endpoint.

5.2.3.2.13.3. ***Feminization of LH secretion regulation.*** The effect of perinatal TCDD exposure on regulation of LH secretion by ovarian steroids was determined in male offspring at ~270 days of age. There is normally a distinct sexual dimorphism to this response. In rats castrated as adults, estrogen-primed females greatly increase their plasma LH concentrations when injected with progesterone, whereas similarly treated males fail to respond (Taleisnik et al., 1969). Progesterone had little effect on plasma LH concentrations in estrogen-primed control males, but significant increases were seen in males exposed to maternal TCDD doses as low as 0.40 μg/kg. Thus, perinatal TCDD exposure increases pituitary and/or hypothalamic responsiveness of male rats to ovarian steroids in adulthood, indicating that regulation of LH secretion is permanently feminized.

5.2.3.2.13.4. ***Estrogen receptor concentrations in the brain and volumes of sexually dimorphic brain nuclei.*** In the Holtzman rat, in utero and lactational exposure to TCDD partially demasculinizes and feminizes sexual behavior in adult male rats, possibly by causing incomplete sexual differentiation of the CNS. To determine if TCDD exposure affects other aspects of sexual differentiation of the CNS in this rat strain, the effects of perinatal exposure to 0.7 μg/kg of TCDD administered on gestational day 15 on estrogen receptor binding in specific brain nuclei was examined along with effects on the volumes of brain nuclei that are dependent on hormone stimulation during the period of CNS sexual differentiation (Bjerke et al., 1994b). It was found that estrogen receptor concentrations in three brain nuclei—the medial preoptic nucleus (MPO), the ventrolateral aspect of the ventromedial nucleus, and the periventricular preoptic area—were higher in control females than males, but in utero and lactational exposure to TCDD had no effect on estrogen receptor concentrations in these sexually dimorphic brain nuclei (Bjerke and Peterson, 1994). It also had no effect on estrogen receptor concentrations in other brain nuclei where there was not a sex difference in estrogen receptor concentrations.

The volumes of sexually dimorphic brain nuclei were also not affected by in utero and lactational exposure to TCDD in Holtzman rats. In control rats the volume of the sexually dimorphic nucleus of the preoptic area (SDN-POA) is greater in males, whereas the MPO is greater in females. Perinatal TCDD exposure had no effect on the volume of either nucleus in male and female Holtzman rat offspring in adulthood (Bjerke and Peterson, 1994). Thus, in utero and lactational TCDD exposure is capable of partially demasculinizing and partially feminizing sexual behavior of Holtzman rat progeny (Mably et al., 1992b; Bjerke and Peterson, 1994; Bjerke et al., 1994b), but it is not associated with an effect on sexual differentiation of the estrogen receptor system in the brain or the volume of sexually dimorphic brain nuclei (Bjerke et al., 1994b; MacLusky et al., 1998).

5.2.3.2.13.5. ***Comparison to other Ah receptor-mediated responses.*** The induction of hepatic cytochrome P-4501A1 and its associated EROD activity are extremely sensitive Ah receptor-mediated responses to TCDD exposure. Yet in 120-day-old male Holtzman rats that had been exposed to TCDD perinatally, alterations in sexual behavior, LH secretion, sex organ weights, and sperm numbers were observed when induction of hepatic EROD activity could no longer be detected (Mably et al., 1991, 1992a,b,c). These results suggest that TCDD affects sexual behavior, gonadotrophic function, and sperm counts when virtually no TCDD remains in the body. Therefore, the partial demasculinization and feminization of sexual behavior, partial feminization of LH secretion, and reduced cauda epididymal sperm numbers caused by in utero and lactational exposure to TCDD have the potential to be irreversible effects of transient

exposure to TCDD during the endocrine phase of fetal and neonatal sexual differentiation (Mably et al., 1992b,c).

5.2.3.2.13.6. ***Possible mechanisms for effects on sexual behavior*.** The most plausible explanation for the demasculinization of sexual behavior and feminization of sexual behavior and LH secretion is that perinatal exposure to TCDD impairs sexual differentiation of the CNS. Neither undernutrition, altered locomotor activity, reduced sensitivity of the penis to sexual stimulation, nor modest reductions in adult plasma androgen concentrations of the male offspring can account for this effect (Mably et al., 1992b). On the other hand, exposure of the developing brain to testosterone, conversion of testosterone into 17ß-estradiol within the brain, and events initiated by the binding of 17ß-estradiol to its receptor are all critical for sexual differentiation of the CNS and have the potential to be modulated by TCDD. If TCDD interferes with any of these processes during late gestation and/or early neonatal life, it could irreversibly demasculinize and feminize sexual behavior (Hart, 1972; McEwen et al., 1977; Whalen and Olson, 1981) and feminize the regulation of LH secretion (Gogan et al., 1980, 1981) in male rats in adulthood. However, results that argue against this hypothesis are that in utero and lactational exposure to TCDD does not alter either estrogen receptor concentrations in various brain nuclei or volumes of sexually differentiated brain nuclei of male and female Holtzman rat progeny at doses that affect the expression of masculine and feminine sexual behavior (Bjerke et al., 1994). Also, while in utero and/or lactational exposure to TCDD may cause similar effects on sexual behavior in other animal species, including nonhuman primates (Pomerantz et al., 1986; Thornton and Goy, 1986; Goy et al., 1988), in which sexual differentiation is under androgenic control; this was not able to be demonstrated for male hamster progeny exposed in utero and via lactation to TCDD (Gray et al., 1995a). In humans, there is evidence that social factors account for much of the variation in sexually dimorphic behavior; there is also evidence that prenatal androgenization influences both the sexual differentiation of such behavior and brain hypothalamic structure (Erhardt and Meyer-Bahlburg, 1981; Hines, 1982; LeVay, 1991).

5.2.3.2.14. ***Cross-species comparisons*.** Gray et al. (1995a) demonstrated that many of the results observed on male rat reproductive system development following in utero and lactational TCDD exposure are also observed in male hamster offspring exposed perinatally to TCDD. Pregnant hamsters were exposed to 2 μg/kg of TCDD on gestational day 11. This exposure level caused no maternal toxicity or decrease in viability of the offspring. The number of litters in the study was small (three dams/treatment group). Nevertheless, growth retardation, reduced adrenal and brain weight at postnatal day 136 to 140, delayed eye opening, and reduced sperm in the epididymis and ejaculate were observed in the male hamster offspring exposed to TCDD.

Anogenital distance and testicular sperm number were not affected. As regards androgen-dependent organ development, age at preputial separation was delayed and seminal vesicle weight was reduced, but flank gland development was not affected. In contrast to the rat, none of the masculine sexual behavior parameters measured in male hamster offspring appeared to be altered. At sacrifice (postnatal day 136 to 140), there was an increase in sperm granulomas and in the severity of kidney lesions in the TCDD-exposed male hamster progeny. While the findings of this study show some species specificity in the hamster's response to in utero and lactational TCDD exposure, they generally support the above findings in male rat offspring.

Male ICR mice, CD-1 derived, exposed in utero and via lactation to TCDD are also affected by developmental toxicity to the reproductive system (Theobald et al., 1997). The doses of TCDD used in this study did not alter maternal or offspring body weights and were not associated with prenatal or postnatal mortality. However, ventral prostate weight assessed on postnatal days 44, 65, and 114 was significantly decreased in male offspring after exposure to 15 μg TCDD/kg administered on gestational day 14. Coagulating gland weight was also reduced on the same postnatal days, but this lobe of the prostate was not as sensitive as the ventral prostate because larger doses of TCDD were required to produce the effect. The dorsal prostate in the ICR mouse was not affected even at the largest maternal TCDD dose (60 μg/kg). There was no statistically significant decrease in daily sperm production after TCDD exposure, but whole epididymal sperm numbers were decreased at maternal doses of 30 and 60 μg TCDD/kg. Thus, ventral prostate weight in this strain of mouse was a more sensitive endpoint of TCDD exposure than the reduction in epididymal sperm number. The C57BL/6 mouse is more sensitive to the developmental effects of TCDD on accessory sex organ growth (Lin et al., 2000). Ventral prostate, dorsolateral prostate, and coagulating gland weight in mouse progeny exposed to 5 μg/kg of TCDD on gestational day 13 were all significantly reduced when assessed on postnatal days 21 to 90. Histological examination revealed an impairment of ductal development in the ventral prostate on postnatal day 21, and only 50% of the luminal epithelial cells in ventral prostate from TCDD-exposed mice expressed androgen receptors, compared with 100% of the epithelial cells in tissue from vehicle-exposed mice. Urogenital sinus epithelial complexes from male offspring exposed to a single maternal dose of 5 μg/kg of TCDD administered on gestational day 13 were examined by scanning electron microscopy, and complete agenesis of ventral prostate buds on gestation day 18 was found. In Ah receptor knockout mice obtained from Bradfield (Schmidt et al., 1996) and backcrossed into C57BL/6, there was no reduction in seminal vesicle or prostate weight due to in utero and lactational TCDD exposure, and prostatic bud formation occurred normally by gestational day 18. Therefore, these effects on the prostate and seminal vesicle of perinatal TCDD exposure in the mouse appear to be Ah receptor mediated.

Taken together, these results indicate that there is species specificity in sensitivity to certain effects of in utero and lactational TCDD exposure on male reproductive system development. In general, however, the results reported in the hamster and mouse are consistent with those reported in male rat offspring. There is evidence that at least some of these effects are Ah receptor mediated, namely those that occur in the prostate and seminal vesicle. Because the fetal human prostate expresses the Ah receptor (Kashani et al., 1998), it is plausible that the human prostate could be affected by sufficient exposure to TCDD and TCDD-like Ah receptor agonists during development.

5.2.3.3. *Female Reproductive System*

Effects of in utero and lactational exposure to TCDD on female reproductive system development has not been investigated for as long as the male reproductive system. However, the results from these studies clearly show that the effects of gestational exposure to TCDD is not limited to the male offspring.

5.2.3.3.1. ***Vaginal thread malformation.*** One of the most sensitive effects of in utero and lactational exposure to TCDD on the female reproductive system is the occurrence of a vaginal thread malformation. It has been detected in two strains of rats, Long Evans and Holtzman, but not in ICR mice or Syrian hamsters (Gray et al., 1995; Flaws et al., 1997; Theobald and Peterson, 1997; Gray et al., 1997b; Wolf et al., 1999; Dienhart et al. 2000). The lowest dose of TCDD to significantly increase the incidence of vaginal threads in female progeny is 0.20 μg/kg administered on gestational day 15 to Long Evans rat dams (Gray et al., 1997b). This dose was effective in increasing the incidence of the malformation when expressed either as percentage of females with a temporary or permanent vaginal thread or as percentage of females with a permanent vaginal thread (Gray et al., 1997b). In utero and lactational exposure to other Ah receptor agonists are also capable of producing this same type of malformation in Long Evans rats. 3,3',4,4',5,5'-HCB (PCB 169) administered on gestational day 8 at a dose of 1.8 mg/kg caused a significant increase in the percentage of female progeny with vaginal threads (Gray et al., 1999).

The original study to report an increase in vaginal thread malformation following in utero and lactational exposure to TCDD was that of Gray and Ostby (1995). They reported on the effects in Long Evans rats of a single maternal exposure to 1 μg/kg of TCDD on either gestational day 8 or 15 on postnatal vaginal development in female offspring. Both exposures were associated with incomplete (vaginal thread) or absent vaginal opening, and a smaller vaginal orifice. Similar malformations involving the vaginal canal have been reported for Holtzman rats (Gray and Ostby, 1995; Flaws et al., 1997). The incidence of vaginal threads was

greater in the Long Evans rat when TCDD was administered on gestational day 15 compared with gestational day 8 (Gray and Ostby, 1995). On the other hand, in the Holtzman rat the incidence of vaginal threads was essentially the same when TCDD was administered on gestational days 11, 15, or 18 (Flaws et al., 1997).

The vaginal thread is manifested in pubertal rats as a persistent thread of mesenchymal tissue surrounded by keratinized epithelium that partially occludes the vaginal opening (Flaws et al., 1997). However, it was not known how early in development this abnormality could be detected. Vaginal threads in TCDD-exposed Holtzman rat offspring were identified in histological sections of the developing vagina in 2-day-old pups, demonstrating that this malformation was actually present at birth (Flaws et al., 1997). This suggested that prenatal exposure to TCDD should be sufficient to cause the vaginal thread malformation. This was confirmed in a cross-fostering study in Long Evans rats (Gray et al., 1997b) where female progeny that received prenatal TCDD exposure developed vaginal threads but those that received only postnatal exposure to TCDD did not. The earliest time during fetal development that morphologic signs of this malformation were present was gestational day 19 in Holtzman rats (Dienhart et al., 2000) and gestational day 18 in Long Evans rats (Hurst et al., 1999). At this time there was an increased thickness of mesenchymal tissue between the caudal Mullerian ducts. The presence of this mesenchymal tissue caused the Mullerian ducts to fail to fuse, a process that is normally completed prior to birth. TCDD was also found to block regression of the Wolffian ducts, which contributed to the changes in morphology of the vagina (Dienhart et al., 2000). Thus, prenatal TCDD exposure leads to altered development of the rat vagina as early as gestational day 18 or 19 depending on the strain, 3 or 4 days after treatment of the dams. This effect is produced by TCDD interfering with two critical morphogenetic events involved in the formation of the female reproductive tract, namely, regression of the Wolffian ducts and fusion of the Mullerian ducts (Hurst et al., 1999; Dienhart et al., 2000).

The mechanisms by which TCDD produces these effects at the molecular level are unknown. TCDD modulates cellular responses to both hormones and growth factors including androgens, estrogens, EGF, and TGF (Abbott, 1997; Birnbaum, 1998; Roman and Peterson, 1998b). Developmental processes such as the timing of morphogenetic signals and events like cell proliferation, cell movement, receptor expression, apoptosis, and terminal differentiation are tightly regulated by these and other hormones and growth factors. Thus, TCDD modulation or interference with the activity of hormones and/or growth factors in the female rat reproductive tract may play a role in causing the vaginal thread malformation (Dienhart et al., 2000).

5.2.3.3.2. ***Cleft phallus and mild hypospadias*****.** Other morphological effects of in utero and lactational exposure to TCDD on the female reproductive tract are cleft phallus and mild

hypospadias. The hypospadias are considered mild because the urethral opening was always separate from the vaginal opening. These two types of malformations have been observed in rats and hamsters, but not in mice (Gray and Ostby, 1995; Flaws et al., 1997; Theobald and Peterson, 1997; Gray et al., 1997b; Wolf et al., 1999; Dienhart et al., 2000). The lowest dose of TCDD to significantly increase the incidence of cleft phallus and mild hypospadias is 0.80 and 0.20 μg/kg of TCDD, respectively, administered on gestational day 15 in Long Evans rats (Gray et al., 1997b). The morphometric indices of mild hypospadias that were significantly affected by exposure to 0.2 μg/kg of TCDD on gestational day 15 were length of the urethral slit (increased by TCDD), distance from the tip of the phallus to the urethral opening (increased by TCDD), and distance from the urethral to vaginal opening (decreased by TCDD) (Gray et al., 1997b). Other Ah receptor agonists are also capable of producing cleft phallus and mild hypospadias in female Long Evans rats. 3,3',4,4',5,5'-HCB (PCB 169) administered on gestational day 8 at a dose of 1.8 mg/kg caused a significant increase in the percentage of female progeny with cleft phallus (Gray et al., 1999). It also caused the female offspring to have a significantly longer urethral slit and a shorter distance between the urethral and vaginal openings (Gray et al., 1999). The incidence of cleft phallus was greater in female Long Evans rat progeny administered TCDD on gestational day 15 compared to gestational day 8 (Gray and Ostby, 1995). In Holtzman rats the incidence was greater when TCDD was administered on gestational day 11 compared with gestational day 15 or 18 (Flaws et al., 1997).

These TCDD-induced malformations of the external genitalia in female rats and hamsters (cleft phallus and mild hypospadias) closely resemble the mild form of hypospadias caused by in utero exposure to diethylstilbestrol (DES) and other potent estrogens. In hamsters estradiol causes cleft phallus (Whitsett et al., 1978) and in rats DES and the synthetic estrogen RU2858 are capable of producing a mild form of hypospadias (Voherr et al., 1979; Vannier et al., 1980). This raises the possibility that TCDD, which is often characterized as being an antiestrogen, might cause these effects through an estrogen-like developmental action (Gray et al., 1997b). In this context, it is important to stress that the other type of malformation produced by in utero and lactational exposure to TCDD in the female rodent, vaginal thread formation, is unique to TCDD and TCDD-like Ah receptor agonists. Vaginal thread formation, which can be detected as early as gestational day 19 in the rat, is not known to be produced by any other class of chemical, including potent estrogens like DES.

Gray and Ostby reported that in utero and lactational exposure to TCDD caused a significant reduction in ovarian and brain weights when necropsied as adults (Gray and Ostby, 1995). Hamster offspring, like rats, display clefting of the phallus, mild hypospadias, and reduced ovarian weight, but not formation of the vaginal thread (Gray and Ostby, 1995; Gray et al., 1997b; Wolf et al., 1999). Female ICR mouse offspring were not susceptible to either cleft

phallus or vaginal thread malformations nor were their ovarian or brain weights reduced by perinatal TCDD exposure (Theobald and Peterson, 1997).

5.2.3.3.3. ***Ovary.*** In utero and lactational exposure to TCDD decreased ovarian weight in the rat and hamster but not in the mouse (Gray and Ostby, 1995; Theobald and Peterson, 1997; Wolf et al., 1999). Shiverick and Muther (1983) reported that there was no change in circulating levels of estradiol in the rat after exposure to 1 μg/kg/day on gestational days 4 to 15. Similarly, Gray et al. have found no effect on serum estradiol levels after perinatal exposure to a single maternal dose of 1 μg TCDD/kg administered on gestational day 15 in the Long Evans rat, evaluated on postnatal days 21 and 28 (Gray et al., 1997b). In addition, these authors found no effect on ovarian estradiol production when ovaries from vehicle- and TCDD-exposed rats removed on postnatal days 21 and 28 were placed in organ culture for 3 hours. However, Chaffin et al. found that serum estradiol and ovarian secretion of estradiol in vitro were decreased by a similar exposure regimen in the Holtzman rat (Chaffin et al., 1996, 1997). Histologic examination of ovaries from 21- to 22-day-old rats that had been exposed to a single maternal dose of 1 μg TCDD/kg in utero and via lactation revealed decreases, compared with vehicle-exposed rats, in the number of ovarian follicles without alterations in ovarian size, or apoptosis in the affected follicular regions (Heimler et al., 1998). Similarly, the administration of a single maternal dose of 0.6 mg/kg of 3,3',4,4',5,5'-HCB (PCB 169) on gestational day 1, combined with daily doses of 1 mg/kg of 3,3',4,4'-TCB (PCB 77) on gestational days 2-18 resulted in a statistically significant increase in the incidence of cystic dilated ovarian follicles (Smits-van Prooije et al., 1994).

5.2.3.3.4. ***Estrous cyclicity and reproductive performance.***

5.2.3.3.4.1. ***Rats.*** With regard to effects on estrous cyclicity and reproductive performance, Long Evans rats exposed on gestational day 8 to 1.0 μg/kg of TCDD had a significantly increased number of the female offspring displaying constant estrus by 1 year of age (Gray and Ostby, 1995). This was accompanied by a significant reduction in fertility during a continuous breeding trial. The gestational day 15 exposure did not have the same effect on cyclicity, and the occurrence of constant estrus was not significantly different from control rats. There was also no effect on female sexual behavior. Nevertheless, the number of mounts of control males and the latency to ejaculation were increased in matings with females exposed to TCDD on gestational day 15. This was possibly due to the vaginal abnormalities interfering with normal copulation.

Gray and Ostby (1995) also compared the gestational day 15 exposure to 1.0 μg/kg of TCDD in the Long Evans female offspring with that in the Holtzman. There was a greater reduction in neonatal viability in Holtzman than Long Evans female offspring (50% vs. 11%, respectively) following TCDD exposure. In the surviving Holtzman offspring, the

morphological effects were similar to those in the Long Evans offspring, including genital clefting and vaginal threads. Reproductive behavior was not assessed in the Holtzman strain.

As Gray and Ostby (1995) have noted, their observations are consistent with previous reports of infertility in female offspring after in utero exposure to TCDD (Khera and Ruddick, 1973) and are likely due to the alterations in estrous cyclicity and ovarian function. In utero and lactational exposure of Wistar rats to 0.5 μg/kg/day of TCDD administered on gestational days 6 to 15 caused infertility in both sexes (Khera and Ruddick, 1973). Also, in utero and lactational exposure to 1.8 mg/kg of 3,3',4,4',5,5'-HCB (PCB 169) on gestational day 1 decreased mating success and female fecundity in female Wistar rat progeny (Smits-van Prooije et al., 1994). Taken together, in utero and lactational exposure to TCDD and TCDD-like Ah receptor agonists in the rat causes morphological and functional reproductive alterations in female offspring at relatively low doses that do not induce overt maternal toxicity.

5.2.3.3.4.2. ***Hamsters.*** TCDD produced adverse effects in female hamsters that persisted through two generations (F1 and F2). This occurred despite the F1 generation being the only generation that was exposed in utero and via lactation to 2.0 μg/kg of TCDD administered on gestational day 11.5 (Wolf et al., 1999). In the female progeny of the F1 generation, vaginal opening was delayed and vaginal estrous cycles were altered. However, most TCDD-exposed females had regular 4-day behavioral estrous cycles. This suggests in utero and lactational TCDD exposure did not cause a marked disruption in the hypothalamic-pituitary-gonadal hormonal cyclicity. While the F1 TCDD-exposed females mated successfully with a control male, 20% of them did not become pregnant and 38% of those that did become pregnant died near term. Both the number of implants in pregnant TCDD-exposed hamsters and the number of pups they produced that were born alive were reduced significantly.

An important finding was that survival of F2 generation offspring through weaning was virtually eliminated by treating with TCDD the dams that produced the F1 generation (Wolf et al., 1999). The cause of death of the F2 generation offspring has not been reported.

5.2.3.3.5. ***Histopathology of the aging female reproductive tract.*** In utero and lactational exposure to TCDD affects the histopathology of the female rat reproductive tract (Gray et al., 1997b). In the ovary of TCDD-exposed female offspring, cystic follicles with luteinization and sertoliform hyperplasia were observed. Diffuse squamous hyperplasia of the cervix and hyperkeratosis of the vagina were seen in the TCDD-exposed progeny, but not in the controls.

5.2.3.3.6. ***Ovarian and mammary gland tumors.*** Ovarian tumors were found in female rats following in utero and lactational exposure to TCDD, but not in control rats (Gray et al., 1997b).

In addition, in utero and lactational exposure of rats to 1.0 μg/kg of TCDD on gestational day 15 rendered mammary glands of the female offspring more susceptible to tumor formation induced by 7,12-dimethylbenz[a]anthracene (DMBA) (Brown et al., 1998).

5.2.3.4. *Neurobehavior*

Because differentiated tissues derived from ectoderm, namely, skin, conjunctiva, nails, and teeth, are sites of action of halogenated aromatic hydrocarbons in transplacentally exposed human infants, another highly differentiated tissue derived from ectoderm, the CNS, should be considered a potential site of TCDD action. In support of this possibility, sexual differentiation of the CNS in adult male rats is irreversibly altered in a dose-related fashion by perinatal exposure to TCDD (Mably et al., 1991, 1992b). As will be shown below, the central nervous systems of mice transplacentally exposed to 3,3′,4,4′-TCB, monkeys perinatally exposed to TCDD, and children transplacentally exposed to a mixture of PCBs, CDFs, and PCQs in the Yu-Cheng incident are also affected. Thus, functional CNS alterations, which may or may not be irreversible, are observed following perinatal exposure to halogenated aromatic hydrocarbons.

5.2.3.4.1. ***Ah receptor and ARNT in the central nervous system.*** Ah receptors have been identified in rat brain (Carlstedt-Duke, 1979). However, while an early study suggested the Ah receptor may be associated with glial cells rather than neurons (Silbergeld, 1992), a more recent study of the adult male rat brain that used in situ hybridization to localize mRNAs for the Ah receptor and ARNT proteins found mRNAs for both proteins in the same neuronal populations in the olfactory bulb, hippocampus, cerebral, and cerebellar cortices (Kainu et al., 1995). Unexpectedly, detectable levels of Ah receptor mRNA were not detected in the hypothalamus. The significance of these findings is that they suggest that TCDD and related Ah receptor agonists may act in discrete neuronal populations in the brain.

Following administration of ^{14}C-TCDD in the rat, the highest concentrations of TCDD-derived ^{14}C are found in the hypothalamus and pituitary. Much lower concentrations are found in the cerebral cortex and cerebellum (Pohjanvirta et al., 1990). In another study, the Ah receptor was not detected in whole rat or mouse brain but was detected in the cerebrum of the hamster and cerebrum and cerebellum of the guinea pig (Gasiewicz, 1983).

5.2.3.4.2. ***Neurobehavior in mice.*** CD-1 mice exposed transplacentally to 3,3',4,4'-TCB at a maternal oral dose of 32 mg/kg administered on days 10 to 16 of gestation exhibited neurobehavioral, neuropathological, and neurochemical alterations in adulthood (Tilson et al., 1979; Chou et al., 1979; Agrawal et al., 1981). The neurobehavioral effects consisted of circling, head bobbing, hyperactivity, impaired forelimb grip strength, impaired ability to traverse a wire

rod, impaired visual placement responding, and impaired learning of a one-way avoidance task (Tilson et al., 1979). The brain pathology in adult mice exhibiting this syndrome consisted, in part, of alterations in synapses of the nucleus accumbens (Chou et al., 1979). This suggested that in utero exposure to 3,3',4,4'-TCB may interfere with synaptogenesis of dopaminergic systems. In support of this possibility, Agrawal et al. (1981) found that adult mice transplacentally exposed to 3,3',4,4'-TCB had decreased dopamine levels and decreased dopamine receptor binding in the corpus striatum, both of which were associated with elevated levels of motor activity. It was concluded that transplacental exposure to 3,3',4,4'-TCB in mice may permanently alter development of striatal synapses in the brain.

Eriksson (1988) examined the neurobehavioral effects of 3,3',4,4'-TCB in NMRI mice exposed to a single oral dose of 0.41 or 41 mg/kg on postnatal day 10. Following sacrifice of the mice on day 17, muscarinic receptor concentrations in the brain were significantly decreased at both dose levels. This effect was shown to occur in the hippocampus but not in the cortex. More recently (Eriksson et al., 1991), NMRI mice were exposed to the same two doses of 3,3',4,4'-TCB similarly administered on postnatal day 10. At 4 months of age, the effects of the PCB on locomotor activity were assessed. At both dose levels, abnormal activity patterns were exhibited in that the treated mice were significantly less active than controls at the onset of testing, but were more active than controls at the end of the test period. This pattern of effects can be interpreted as a failure to habituate to the test apparatus. In contrast to the previous results with CD-1 mice, circling or head bobbing activities were not observed in these animals. Upon sacrifice after the activity testing was complete, a small but statistically significant increase (as opposed to the decrease found after sacrifice on postnatal day 17) in the muscarinic receptor concentration of the hippocampus was found in animals from the high-dose group. These results suggest that the neurochemical effects of 3,3',4,4'-TCB are complex. Cholinergeric as well as dopaminergic systems in the brain are involved.

Of all the developmental and reproductive endpoints reported in this chapter for laboratory animals, the only ones that have not yet been demonstrated to occur following perinatal exposure to TCDD are the above neurotoxic effects in mice. These have only been studied following perinatal exposure to 3,3'4,4'-TCB. In addition, there is as yet no evidence to show (1) that among inbred mouse strains having low- and high-affinity Ah receptors, susceptibility to 3,3',4,4'-TCB-induced neurotoxicity segregates with the Ah locus or (2) that the rank order binding affinity of congeners for the Ah receptor correlates with their rank order potency for causing these neurotoxic effects in mice. The rapid metabolism of 3,3',4,4'-TCB compared with the relatively slow metabolism of TCDD in mice causes some uncertainty about the potential involvement of the Ah receptor in 3,3',4,4'-TCB-induced neurotoxicity. Contributing to this uncertainty is the hypothesis that 3,3',4,4'-TCB might produce CNS effects

by being converted to a hydroxylated metabolite that is neurotoxic. Although there is no evidence for or against this hypothesis, there is also no evidence for or against the Ah receptor mechanism hypothesis of 3,3',4,4'-TCB neurotoxicity. Further research is needed to test these hypotheses. In so doing, it should become apparent whether 3,3',4,4'-TCB-induced neurotoxicity effects are relevant to TCDD-induced developmental toxicity.

5.2.3.4.3. ***Neurobehavior in rats.*** A considerable number of neurobehavioral endpoints have been evaluated following perinatal exposure to either TCDD and coplanar PCBs that are Ah receptor agonists, or to ortho-substituted PCBs that do not interact with the Ah receptor. Interest in the latter, for the purposes of this section, arises from the fact that mixtures to which children have been exposed in utero and via lactation typically contain Ah receptor agonists and non-Ah receptor agonists. Therefore, it is important from a mechanistic point of view to determine whether the effects of Ah receptor agonists can be distinguished from the effects of structurally similar non-Ah receptor agonists. It is plausible that some effects of TCDD on neurobehavior in rodents could be Ah receptor mediated because this protein has been detected in the developing neuroepithelium of the mouse fetus (Abbott et al., 1995) and in neuronal tissue of the adult rat brain (Kainu et al., 1995).

Two hypotheses have been advanced: (1) TCDD and TCDD-like PCB congeners do not produce behavioral impairment at biologically relevant doses (Rice et al., 1998; Rice, 1999) and (2) the effects of TCDD and TCDD-like PCB congeners on learning and memory might be distinguishable from effects of ortho-substituted PCB congeners that are not Ah receptor agonists (Schantz et al., 1996; Rice et al., 1999). These hypotheses have not been fully resolved. To the extent that effects of individual ortho-substituted PCB congeners on neurobehavior depend on reductions in thyroid hormone concentrations during the perinatal period (Collins et al., 1980; Ness et al., 1993), it is important to note that TCDD and coplanar PCBs do not reduce thyroid hormone concentrations to the same extent as the ortho-substituted PCBs (Seo et al., 1995). Difficulty in resolving these hypotheses also occurs because different laboratories, using the same testing methods, have not always obtained similar results. In addition, different testing paradigms that appear, at least superficially, to test similar phenomena can arrive at discordant conclusions. Where the results of testing by different methods are not in agreement, the differences are not easy to resolve, in part because the relative sensitivities of the different measures are not always clear.

Despite these difficulties, in utero and lactational exposure to TCDD-like Ah receptor agonists have affected endpoints that measure learning and memory, discrimination reversal learning, transitional behavior, avoidance behavior, neurotransmitter function, and locomotor activity. Perinatal exposure to Ah receptor agonists have inhibited long-term potentiation (LTP)

in the visual cortex, but not in the hippocampus evaluated in vitro (Altmann et al., 1995, 1998). In some cases, effects observed with Ah receptor agonists are similar to those of ortho-substituted PCB congeners (Schantz et al., 1995, 1996, 1997; Seo et al., 1999). Therefore, the available data obtained following in utero and lactational exposure of rats to these compounds tend to support the notion that TCDD and coplanar PCBs can affect neurobehavioral endpoints by a variety of mechanisms, only one of which is Ah receptor mediated. The results of neurobehavioral tests following perinatal exposure to TCDD and various PCBs are summarized below.

5.2.3.4.3.1. ***Spatial learning*****.** Female rats were administered 3,3',4,4'-TCB (PCB 77, 2 and 8 mg/kg/day), 3,3',4,4',5-PCB (PCB 126, 0.25 and 1 μg/kg/day), and TCDD (0.25 and 1 μg/kg/day) by gavage on gestational days 10-16 (Schantz et al., 1996). Beginning on postnatal day 80, spatial learning was evaluated in male and female offspring by using the radial arm maze. While no effects on overt toxicity were found, it was observed that the exposed rats made fewer errors than controls. This result was different from that of a previous study in which exposure to the ortho-substituted PCBs 2,4,4'-TCB (PCB 28), 2,3,4,4',5-PCB (PCB 118), and 2,2',4,4',5,5'-HCB (PCB 153) had no effect on the number of errors (Schantz et al., 1995).

The ability of in utero and lactational TCDD exposure to reduce the number of errors made by male rat offspring in the radial arm maze test were confirmed, even at a reduced exposure level (0.1 μg/kg/day) on gestational days 10-16 (Seo et al., 1999). In addition, no significant decreases in the error rate were found in female rats. However, further statistical analysis of the data suggested that the affected male rats were using a response strategy whereby they tended to enter adjacent arms of the maze. Because of this strategy, there might not be an effect of TCDD on working memory. The lack of an effect of TCDD on the Morris Water Maze test supports this interpretation (Seo et al., 1999). However, the test for adjacent arm selection behavior, which detects the use of a response strategy, had not been significant in the original study at the higher level of TCDD exposure (Schantz et al., 1996).

The low-dose TCDD exposure decreased latency in male rats in the radial arm maze test (Seo et al., 1999). This suggests an apparent feminization of this parameter similar to that caused by PCB 153 (Schantz et al., 1995). In addition, there may be other similarities between TCDD and at least some of the ortho-substituted PCBs, because a similar evaluation of 2,2',3,5',6-PCB (PCB 95) demonstrated an exposure-associated decrease in the error rate of male rat offspring (Schantz et al., 1997). Similar to the original result with the low-exposure dose of TCDD (Seo et al., 1999), the test for use of a response strategy was negative with PCB 95, but unlike the results with TCDD and PCB 153, there was no gender-related decrease in latency. In contrast to the decrease in the error rate that was caused by the perinatal exposure of Sprague-Dawley rats to

PCB 77, PCB 95, PCB 126, and TCDD (Schantz et al., 1996), there was no effect of perinatal exposure to PCB 77 or the diortho- substituted 2,2',4,4'-TCB (PCB 47) on the error rate of male Wistar rats that were tested on a similar radial arm maze (Weinand-Harer et al., 1997).

The male and female rat offspring that were exposed to the ortho-substituted PCB 28, PCB 118, and PCB 153 and tested on the radial arm maze were subsequently evaluated for delayed spatial alternation on the T-maze beginning after postnatal day 135 (Schantz et al., 1995). Exposed females learned this task more slowly than exposed males, and all compounds tested caused a decrease in the number of correct responses. There was no effect on the number of correct responses in exposed male offspring, but their latency to enter the maze was decreased compared with that of control male offspring. This effect on latency again suggests a more female-like pattern of response in male offspring exposed to the ortho-substituted PCBs, even though distinct gender differences remained for the delayed spatial alternation response. In contrast, in utero and lactational exposure to the coplanar PCBs produced no effect on the errors made by male or female offspring, or in their latency in the T-maze test (Schantz et al., 1996; Seo et al., 1999). In addition, another group also found that delayed spatial alternation was unaffected in both male and female Long Evans rat offspring exposed to PCB 126 and tested in an operant chamber setting (Rice, 1999). In this case, even prolonged dietary exposure of female rats to PCB 126, which began 7 weeks before mating to an unexposed male and continued until the offspring were weaned, caused no treatment-related differences in performance (Rice, 1999). However, the impression that delayed spatial alternation is selectively affected by the ortho-substitited PCBs is again offset by the results with PCB 95. Unlike the other ortho-substituted PCBs, PCB 95 did not affect the response (Schantz et al., 1997). Differences between the activities of PCB 95 and PCB 126 have also been found on parameters relevant to neurological function in vitro (Wong et al., 1997). Because effects of the triortho-substituted PCB 95 on delayed spatial alternation are similar to those of PCB 126, a coplanar PCB, but different from those of other ortho-substituted PCBs it remains possible that this effect of PCB 126 is non-Ah receptor mediated. However, not all ortho-chlorinated PCBs are equivalent (Schantz et al., 1995; Schantz et al., 1997), suggesting the existence of structural selectivity in the mechanism.

5.2.3.4.3.2. ***Visual discrimination reversal learning*****.** No effect was observed when the T-maze was used to assess spatial discrimination reversal learning following in utero and lactational exposure of male and female rat offspring to maternal doses of 0.1 μg TCDD/kg/day on gestational days 10-16 (Seo et al., 1999). Visual discrimination reversal learning was tested by placing electric light stimuli onto the cross-arms of the same T-maze used to evaluate spatial discrimination reversal learning. Male and female rat offspring were exposed to maternal doses of 0.1 μg TCDD/kg/day administered on gestation days 10-16 (Seo et al., 1999). When evaluated

beginning at approximately 100 days of age, the exposed offspring performed similar to controls during the original learning phase of the trial. However, TCDD-exposed offspring were slower to reach the testing criterion of 10 correct trials in a 12-trial session. This effect occurred equally in males and females and was most evident during the first and second reversal period. In the following reversal periods, no further differences were evident between the TCDD and vehicle exposure groups. Similarly, PCB 118 and PCB 126 were reported to impair visual discrimination learning in male rat offspring evaluated in an operant chamber (Holene et al., 1995). However, the authors of this study used more than one male offspring per litter, and they appear to have evaluated all rats from the same litter as if they were independent observations. Therefore, the results of this study have been considered to be uninterpretable on statistical grounds (Rice and Hayward, 1998; Rice, 1999), based on the criteria established by Holson and Pearce (1992).

One study using mixtures evaluated visual discrimination learning in the offspring of female rats exposed to Clophen A30 (32 mg total PCBs/kg diet) or a normal diet for 60 days prior to mating, and through pregnancy (Lilienthal et al., 1991). After birth some offspring exposed to each diet were cross-fostered to dams exposed to the other diet. When male and female offspring were evaluated at 120 to 180 days of age, there was no effect of PCB exposure during the acquisition phase of the paradigm (visual discrimination learning tested on a jumping stand). However, performance in all PCB-exposed groups was inferior during the retention phase, relative to their performance at the end of the acquisition phase. Because the effect was more pronounced in the prenatal-only and prenatal + lactational exposure groups, compared with the lactational-only exposure group, the results indicate that prenatal-only exposure to PCBs is all that is required to alter visual discrimination learning.

5.2.3.4.3.3. ***Transitional behavior*****.** Female Long Evans rats were exposed to PCB 126 (0.25 and 1 μg/kg/day) via dietary supplementation that began 35 days prior to mating, and continued through pregnancy and lactation (Rice and Hayward, 1999). After postnatal day 400, transitional behavior was tested in male and female offspring by using a concurrent random interval-random interval reinforcement schedule in an operant chamber. In this test offspring of both sexes apportioned their responses less accurately than control offspring with respect to the pattern of scheduled reinforcements on the two levers. However, the treated rats perceived the reward offered by the reinforcements similarly to the control rats, because testing by a progressive ratio reinforcement schedule resulted in no treatment-related differences in the relative strength of the reinforcing event (Rice and Hayward, 1999). No treatment-related differences had previously been found in the same rats tested on postnatal day 220 by using a multiple fixed interval-fixed ratio reinforcement schedule (Rice and Hayward, 1998). Therefore, the results obtained on the

concurrent random interval-random interval schedule of reinforcement may indicate a selective effect of PCB exposure on adaptive ability in the offspring (Rice and Hayward, 1999).

5.2.3.4.3.4. ***Behavioral responses to CNS drugs*.** Haloperidol-induced catalepsy was evaluated in male Wistar and Long Evans rat offspring exposed to the diortho-substituted PCB 47 (1 mg/kg/day) or the coplanar PCB 77 (1 mg/kg/day) from days 7 to 18 of gestation (Weinand-Harer et al., 1997; Hany et al., 1999). At 100 and 180 days of age, catalepsy was induced in the male offspring by the dopaminergic antagonist haloperidol. Developmental exposure to PCB 77, but not to PCB 47, caused an increase in the time required for the affected rat to move its paw after the paw had been placed into certain positions by the experimenter. The effects of similar exposure to PCB 77 on dopaminergic function have also been tested in Long Evans rats by evaluating their ability to discriminate between the dopaminergic agonist apomorphine and saline (Lilienthal et al., 1997). As a positive control, the antithyroid drug propylthiouracil (PTU) given to adult control animals just prior to testing blocked their ability to discriminate between apomorphine and saline, whereas no effect was found on this discrimination in rats exposed to PCB 77 in utero and via lactation. However, the administration of buspirone to the adult animals just prior to testing blocked the ability of vehicle-exposed rats to recognize apomorphine much more than it blocked this ability in the PCB 77-exposed offspring, or PTU-dosed groups. As buspirone is a mixed serotonin receptor agonist and partial dopamine receptor antagonist, the authors suggested that perinatal exposure to PCB 77 may produce long-lasting effects on the interaction between dopaminergic and serotonergic processes in the CNS (Lilienthal et al., 1997).

Since PCB 77 was effective in prolonging haloperidol-induced catalepsy, whereas PCB 47 was not, it is interesting that perinatal exposure to coplanar PCBs and ortho-substituted PCBs also produce opposite effects on dopamine synthesis in the brain (Seegal et al., 1990, 1997). Perinatal exposure to ortho-substituted PCB congeners decreases dopamine synthesis in adulthood, whereas perinatal exposure to coplanar PCBs causes persistent elevations in brain dopamine and metabolite concentrations (Seegal et al., 1997). An increase in endogenous brain dopamine concentrations could be related to the ability of PCB 126 to alter the recognition of exogenous apomorphine. Dopaminergic function is one area where the effects of coplanar and ortho-substituted PCB congeners may be distinguishable. However, only a few PCB congeners have been evaluated.

Female Long Evans rats were exposed to PCB 126 (0.25 and 1.0 μg/kg/day) by dietary supplementation that began 35 days prior to mating and continued through pregnancy and nursing (Bushnell et al., 1999). After postnatal day 112, a chlordiazepoxide (CDP, 0, 3, 5, and 8 mg/kg) challenge test was used to evaluate neurobehavior. In control offspring all doses of CDP reduced performance. This result suggested that the control offspring were affected by an

increase in the visual threshold. Rats exposed in utero and via lactation to the low dose of PCB 126 were unaffected by CDP, whereas those exposed to the high dose exhibited less of a decrement in their performance than did the control offspring. Since additional test results demonstrated that PCB 126 exposure did not cause deficits in attention, the altered performance of these rats after the administration of CDP suggests that perinatal exposure to PCB 126 may affect γ-aminobutyric acid (GABA)-mediated pathways in the CNS during development (Bushnell and Rice, 1999).

5.2.3.4.3.5. ***Passive avoidance behavior*****.** Male Wistar rats were exposed to the coplanar PCB 77 or the diortho-substituted PCB 47 on gestational days 7 to 18. Passive avoidance behavior was tested on a step-down platform when the rats were 220 days old (Weinand-Harer et al., 1997). The latency of male rat offspring to step onto a grid that had previously given them an electric shock was used to evaluate the effects of perinatal PCB exposure. Latency was decreased by both PCBs, compared with control rats, up to 24 hours after the initial shock. However, only the effect of PCB 77 was significant when evaluated at a single time (5 min, 4 hours, and 24 hours). A similar paradigm was used to evaluate the effects of perinatal exposure to PCB 77, PCB 47, and a combination of both PCBs in Long Evans rats on postnatal day 85 (Hany et al., 1999). Under these conditions the most significant effect observed was a decreased latency in the PCB 77 and combined exposure groups at the 5-minute time. No significant effect was found when rats were exposed to PCB 47 only. These results suggest that differences in passive avoidance behavior may exist following perinatal exposure to non-ortho- and ortho-substituted PCBs, but only one congener of each type has been tested.

5.2.3.4.3.6. ***Open field locomotor activity*****.** When open field activity was tested in male offspring on postnatal day 25, rats exposed to PCB 57 in utero and via lactation had a significantly higher activity level than rats similarly exposed to PCB 77. However, there were no significant differences between the PCB-exposed groups and the unexposed control group (Weinand-Harer et al., 1997). When tested on postnatal day 340, offspring exposed to PCB 47, PCB 77, and a combination of both PCBs were hyperactive when compared with controls (Hany et al., 1999).

Locomotor activity has also been tested in an operant chamber setting in rats exposed to PCBs only during lactation. Female DA/OLA/HSD female rats were mated to Lewis male rats, and the pregnant dams were administered vehicle, 2,2',4,4',5,5'-HCB (PCB 153, 5 mg/kg), or PCB 126 (2 μg/kg) (Holene et al., 1998). Dosing of the female rats was accomplished on every second day from postnatal days 3 to 13. PCB-exposed, 112-day-old male rats were found to be hyperactive during both the fixed interval and extinction components of the reinforcement

schedule. In addition, the PCB 153-exposed offspring displayed a behavior pattern similar to that of spontaneous hypertensive (SHR) rats, which are used as an animal model of attention-deficit hyperactivity disorder (ADHD) in children. With the results of only one congener of each type being tested, the SHR-like pattern of activity appeared to be selective for the ortho-substituted PCB. However, with both congeners, the activity level was increased by exposure solely during the postnatal period. In contrast to all results that show that in utero and/or lactational PCB exposure causes hyperactivity, perinatal exposure to PCB 95 caused hypoactivity in offspring (Schantz et al., 1997).

5.2.3.4.4. ***Neurobehavior in monkeys.*** Schantz and Bowman (1989) and Bowman et al. (1989b) have conducted a series of studies on the long-term behavioral effects of perinatal TCDD exposure in monkeys. Because these were the first studies to evaluate the behavioral teratology of TCDD, monkeys exposed to TCDD via the mother during gestation and lactation were screened on a broad selection of behavioral tests at various stages of development (Bowman et al., 1989b). At the doses studied (5 or 25 ppt in the maternal diet), TCDD did not affect reflex development, visual exploration, locomotor activity, or fine motor control in any consistent manner (Bowman et al., 1989a). However, the perinatal TCDD exposure did produce a specific, replicable deficit in cognitive function (Schantz and Bowman, 1989). TCDD-exposed offspring were impaired on object learning, but were unimpaired on spatial learning. TCDD exposure also produced changes in the social interactions of mother-infant dyads (Schantz et al., 1986). TCDD-exposed infants spent more time in close physical contact with their mothers. The pattern of effects was similar to that seen in lead-exposed infants and suggested that mothers were providing increased care to the TCDD-exposed infants (Schantz et al., 1986).

5.2.3.4.5. ***Neurobehavior in humans.*** The intellectual and behavioral development of Yu-Cheng children transplacentally exposed to PCBs, CDFs, and PCQs was studied through 1985 by Rogan et al. (1988). In Yu-Cheng children matched to unexposed children of similar age, area of residence, and socioeconomic status, there was a clinical impression of developmental or psychomotor delay in 12 (10%) Yu-Cheng children compared with 3 (3%) control children and of a speech problem in 8 (7%) Yu-Cheng children versus 3 (3%) control children. Also, except for verbal IQ on the Wechsler Intelligence Scale for Children, Yu-Cheng children scored lower than control children on three developmental and cognitive tests (Rogan et al., 1988). Neurobehavioral data on Yu-Cheng children obtained after 1985 shows that the intellectual development of these children continues to lag somewhat behind that of matched control children. In addition, Yu-Cheng children are rated by their parents and teachers as having a higher activity level; more health, habit, and behavioral problems; and a temperamental

clustering closer to that of a "difficult child." It is concluded that in humans, transplacental exposure to halogenated aromatic hydrocarbons can affect CNS function postnatally. However, which congeners, TCDD-like versus non-TCDD-like, are responsible for the neurotoxicity is unknown.

Further research on the mechanism of these postnatal neurobehavioral effects, dose-response relationships, and reversibility of the alterations is needed before the role of TCDD-like congeners versus non-TCDD-like congeners in causing this toxicity can be understood. Mechanisms that respond uniquely to TCDD-like congeners may not necessarily be involved, as three lightly chlorinated, ortho-substituted PCB congeners, 2,4,4'-TCB, 2,2',4,4'-TCB, and 2,2',5,5'-TCB, have been detected in monkey brain following dietary exposure to Aroclor 1016 and appear to be responsible for decreasing dopamine concentrations in the caudate, putamen, substantia nigra, and hypothalamus of these animals (Seegal et al., 1990). These nonplanar PCB congeners are believed to cause these effects by acting through a mechanism that does not involve the Ah receptor. On the other hand, the results presented for mice and monkeys suggest that TCDD-like congeners could be involved in producing the observed postnatal neurobehavioral effects in humans.

5.2.3.5. *Thermoregulation*

In adult rats TCDD-induced reductions in body temperature are associated with reduced serum thyroxin levels and a decrease in basal metabolism (Potter et al., 1983, 1986). More recently the offspring of rats exposed in utero and via lactation to a maternal diet that contained Aroclor 1254 were affected by decreased body core temperature, reduced metabolic rate, and marked reductions in serum thyroxin up to an age of 14 days (Seo et al., 1995). As part of a larger study, male rats that had been exposed to vehicle or a single maternal dose of 1 μg/kg of TCDD on gestational day 15 were castrated (for reasons unrelated to the study of thermoregulation) at approximately 8 months of age (Gordon et al., 1995). When evaluated at 15.4 to 17.7 months of age, TCDD-exposed animals exhibited significantly lower core body temperatures than controls when the ambient temperature was varied between 10° and 28°C. However, the metabolic rate was not affected by TCDD, which indicates that the effector regulating body core temperature during cold exposure was unaffected. In addition, in utero and lactational TCDD exposure had no effect on evaporative heat loss or on skin blood flow when the rats were anesthetized so that this parameter could be measured. These results suggest that perinatal exposure to TCDD can decrease core temperature set point and cause a reduction in the regulated body temperature.

In a subsequent study pregnant Long Evans rats were administered a single maternal dose of vehicle or 1 μg TCDD/kg on gestational day 15, and their male offspring were implanted with

transmitters to monitor core temperature and motor activity (Gordon et al., 1998). At various ages these TCDD-exposed male rats were affected by a nocturnal hypothermia that was accompanied by decreased motor activity. These effects were especially pronounced at 7 and 11 months of age, did not occur at 3 months of age, and were reduced at 16 months of age. In addition, TCDD-exposed animals exhibited a greater febrile response compared with vehicle-exposed control rats when challenged with lipopolysaccharide (LPS) to induce fever. However, when 8-month-old rats were placed in a temperature gradient and allowed to select their own most favored ambient temperature, vehicle- and TCDD-exposed offspring selected the same ambient temperatures. This suggests that hypothalamic thermoregulatory centers were not permanently altered and that there was not a change in body temperature set point.

Similar alterations in thermoregulation have been produced in hamsters exposed to TCDD in utero and via lactation. When monitored by radiotelemetry, like the rats cited above, these offspring exhibited a persistent hypothermia in spite of normal metabolic responses to cold exposure (Gordon et al., 1996). In addition, there was no effect of TCDD exposure on the selection of an ambient temperature when hamsters were placed in a temperature gradient for 22 hours. These results are important because the adult hamster has an unusually high resistance to the lethal and thyrotoxic effects of TCDD. However, the rat and hamster have approximately the same sensitivity to perinatal TCDD-induced reproductive dysfunction and thermoregulatory dysfunction. The mechanisms for these responses have not yet been determined.

5.2.3.6. *Auditory Function and Thyroid Hormones*

Long Evans rats were exposed to daily maternal doses of 0, 1, 4, and 8 mg Aroclor 1254/kg/day administered from gestational day 6 to weaning. Low-frequency auditory thresholds evaluated in these male and female offspring beginning on postnatal day 85 were increased at the two largest levels of PCB exposure (Goldey et al., 1995a). This effect was statistically significant at 1 kHz, but not at 4 kHz or higher test frequencies. Since similar low-frequency hearing loss can be produced by perinatal exposure to the antithyroid drug propylthiouracil (PTU), the effect of Aroclor 1254 is believed to be associated with neonatal hypothyroidism (Goldey et al., 1995b). Indeed, there were dramatic decreases in total and free plasma thyroxin (T4) concentrations at all doses of Aroclor 1254 and at all times evaluated between postnatal days 7-42 (Goldey et al., 1995a, 1998). Plasma total and free triiodothyronine (T3) concentrations were decreased only by the largest two exposure levels of Aroclor 1254, and statistically significant effects were observed only on postnatal days 21 and 28, with no decrease on postnatal day 42.

Perinatal exposure to a daily maternal dose of 1 μg/kg/day of 3,3'4,4',5-PCB (PCB 126) administered to the dam for 7 weeks prior to breeding and throughout breeding, gestation, and

lactation to weaning decreased the auditory threshold in Long-Evans rat offspring to 0.5 and 1 kHz (Crofton et al., 1999). However, the 0.25 μg PCB 126/kg/day maternal dose did not affect the auditory threshold in exposed offspring. Thus, it is plausible that AhR agonists within the Aroclor 1254 PCB mixture caused the hearing loss.

While the daily maternal dose of 1 mg Aroclor 1254/kg/day did not significantly increase the auditory threshold to 1 kHz, it did cause alterations in brain stem auditory-evoked responses in exposed male and female offspring that were evaluated at 1 year of age (Herr et al., 1996). This result is consistent with the hypothesis that developmental exposure to Aroclor 1254 can damage the peripheral auditory system. It is believed by the authors that this apparently irreversible damage might occur at the level of the cochlea and/or auditory nerve. This result is important because offspring exposed to a maternally administered level of 1 mg Aroclor 1254/kg/day were affected by less substantial reductions in plasma thyroxin concentration than were those exposed to 4 mg/kg/day or 8 mg/kg/day doses of Aroclor 1254, which increased the auditory threshold (Goldey et al., 1995a; Goldey and Crofton, 1998). Thus, it is possible that less of a thyroid deficit during development could result in hearing loss. In support of the relationship between the chemical-induced auditory deficit and thyroid hormone status, the auditory deficit was partially alleviated by daily doses of thyroxin given to the Aroclor 1254-exposed pups from postnatal day 4 to postnatal day 21 (Goldey and Crofton, 1998).

Even as early as gestational day 20 brain thyroxin levels in the forebrain and cerebellum of fetal rats can be depressed after maternal exposure to Aroclor 1254 (Morse et al., 1996). However, in late-gestation fetuses, induction of the brain type II thyroxin 5'-deiodinase results in compensation for the decrease in thyroxin levels so that brain triiodothyronine levels are maintained. Similar alterations occur after exposure to the non-ortho-substituted PCB congeners 3,3'4,4'-TCB (PCB 77) and 3,3',4,4',5,5'-HCB (PCB 169) that are Ah receptor agonists (Morse et al., 1993). The authors suggest that increases in deiodinase activity could be indicative of a local hypothyroidism occurring in the brains of fetal and neonatal rats exposed to these PCBs.

In utero and lactational exposure to a daily maternal dose of 0.1 μg TCDD/kg/day administered on gestational days 10-16 can produce a statistically significant decrease in plasma thyroxin concentration in female offspring evaluated on postnatal day 21 (Seo et al., 1995). However, this reduction in plasma thyroxin concentration in Sprague-Dawley rat offspring was less than those associated with no effect on auditory threshold in Long Evans rat offspring (Goldey et al., 1995a). Therefore, it has not been demonstrated that perinatal exposure to TCDD will decrease plasma thyroxin concentrations enough to evoke an increase in the auditory threshold. It may turn out that TCDD doses larger than those already tested may be required to cause these effects. While it is possible that prenatal TCDD exposure might produce a functional hypothyroidism prior to birth or that mechanisms other than perinatal hypothyroxinemia may

play a role in producing the hearing loss, it is also possible that PCBs and/or their metabolites could affect auditory functional development by decreasing plasma thyroxin concentrations via non-Ah receptor-related mechanisms (Brouwer et al., 1995). Paradoxically, Aroclor 1254 and a single maternal dose of 50 ng TCDD/kg administered to Long-Evans rats on day 15 of gestation can accelerate eye opening (Goldey et al., 1995a; Gray et al., 1997a). This effect of Arochlor 1254 is exacerbated by thyroxin replacement in the pups (Goldey and Crofton, 1998), whereas hypothyroidism is typically associated with a delay in this developmental landmark (Comer et al., 1982; Goldey et al., 1995b). This suggests that some developmental effects of Aroclor 1254 can resemble those of hyperthyroidism, rather than hypothyroidism. Additional mechanistic work on the ability of Ah receptor agonists to induce hypothyroidism early in development, and their ability to decrease auditory function and cause postnatal hearing loss, appears to be required.

5.2.3.7. *Night Vision*

Pregnant Long Evans rats were exposed to the ortho-chlorinated 2,2',4,4'-tetrachloro-biphenyl (PCB 47) and/or the coplanar 3,3',4,4'-tetrachlorobiphenyl (PCB 77) on days 7-18 of gestation. Daily doses 1.5 mg PCB 47/kg/day, 1.5 mg PCB 77/kg/day, a combination of 1.0 mg PCB 47/kg/day + 0.5 mg PCB 77/kg/day, or an equivalent volume of vehicle were administered subcutaneously to each dam (Kremer et al., 1999). The effects of PCB exposure on visual processes were then assessed in male and female offspring at 200 days of age. The scotopic b-wave, maximum potential, and oscillatory potentials were recorded on the electroretinogram after the rats were adapted to the dark. Perinatal exposure to PCB 77 reduced the amplitudes of these potentials in female offspring in adulthood, but not their male littermates. Exposure to PCB 47 alone was without effect; however, many of the decreases that resulted from PCB 77 appeared to be alleviated after simultaneous exposure to PCB 47. While this suggests that functional antagonism between these ortho-substituted and coplanar PCBs can occur in the endpoints measured, it is also possible that this apparent antagonism resulted from the lower level of PCB 77 administered in the combination. These results indicate that in utero and lactational exposure to PCB 77, but not PCB 47 exposure, can produce long-lasting effects on night vision in female rat offspring (Kremer et al., 1999). Interestingly, the susceptibility to this effect was congener-specific, suggesting that the effect may be Ah receptor mediated. In addition, it was gender dependent.

5.2.4. Cross-Species Comparison of Effect Levels

TCDD exposure levels that cause a variety of developmental effects in different species are summarized for fish in Table 5-5, birds in Table 5-6, and mammals in Table 5-7. Fertilized lake trout eggs and Japanese medaka eggs were exposed to different waterborne concentrations

of ^{3}H-TCDD. Estimates of the amount of TCDD in these eggs were then made from measurement of the TCDD-derived radioactivity within them. Fertilized rainbow trout, chicken, ring-necked pheasant, and eastern bluebird eggs were injected directly with the indicated doses of TCDD. Thus, the doses of TCDD given in Tables 5-5 and 5-6 for all fish and bird species represent TCDD egg burdens where a significant portion of the dose may be present within the yolk of the egg rather than the developing embryo.

Mammalian embryo/fetuses, on the other hand, were exposed via administration of TCDD to the pregnant female. Therefore, the doses given in Table 5-7 are maternal TCDD doses, where a significant portion of the dose may be retained by the mother and never actually reach the embryo/fetus. In some studies, pregnant rats and rhesus monkeys were exposed to TCDD on a chronic or subchronic basis, respectively. The doses given in Table 5-7 for these particular studies represent the calculated maternal body burdens at the time of conception. In rats, the duration of chronic exposure was much longer than the whole body elimination half-life for TCDD in rats. Therefore, the body burden of TCDD given for the rat is 92.8% of the calculated steady-state body burden. In rhesus monkeys, the half-life for whole body elimination of TCDD is longer than the duration of exposure prior to conception. Therefore, the steady-state body burdens that would be expected for rhesus monkeys exposed to the different levels of dietary TCDD intake are approximately three times greater than the maternal body burdens estimated at the time of conception (Table 5-7).

In both rats and rhesus monkeys, the maternal body burdens are calculated using a one-compartment open model, assuming 86.1% bioavailability for TCDD. The bioavailability used for TCDD was determined in rats (Rose et al., 1976). As no estimate for TCDD bioavailability has been reported in rhesus monkeys, the same 86.1% value was used. The whole body elimination half-life used for TCDD in the rat is 23.7 days (Rose et al., 1976).

McNulty et al. (1982) estimated a half-life of approximately 1 year for TCDD elimination from adipose tissue in the rhesus monkey, and for calculation of the body burdens estimated in Table 5-7, this half-life was rounded to 400 days for whole body elimination. The maternal body burden given for chronic exposure in the rat was calculated from the data of Murray et al. (1979). The maternal body burden given for subchronic exposure in the rhesus monkey was calculated from data obtained from Dr. R. E. Bowman (personal communication), which included the daily dietary TCDD exposure level for each pregnant female used in the studies reported by Bowman et al. (1989a,b) and Schantz and Bowman (1989). Dr. Bowman's results indicate that the range of TCDD half-lives in these monkeys was 200 to 600 days, which is consistent with the results of McNulty et al. (1982). The body burdens estimated for rhesus monkeys used in these studies are averages based on the average daily TCDD consumption of all pregnant females used at a particular level of maternal TCDD exposure.

As summarized in Table 5-5, lake trout and rainbow trout sac fry and Japanese medaka embryos are similarly affected by a spectrum of lesions that includes hemorrhage, edema, collapse of the yolk sac, cessation of blood flow, and embryo mortality. Estimates of the NOAEL and LOAEL are given in Table 5-5 for the appearance of these lesions in Japanese medaka embryos and for embryo mortality in the two trout species. Although fertilized lake trout eggs and Japanese medaka eggs were exposed to various TCDD concentrations dissolved in static water, and fertilized rainbow trout eggs were injected directly with TCDD, the egg doses given in Table 5-5 represent the concentration of TCDD within the eggs themselves. Therefore, the different NOAELs and LOAELs for developmental toxicity in different fish species probably represent species differences in susceptibility to TCDD-induced developmental toxicity rather than differences in method of TCDD exposure. Of the three fish species, lake trout sac fry are the most sensitive to TCDD-induced mortality. However, based on the LOAELs shown in Table 5-5, the difference in susceptibility between fish species may be less than tenfold.

Based on the LOAELs shown in Table 5-6, the sensitivity of different bird species to TCDD-induced embryo mortality varies by more than fortyfold. The chicken embryo is more susceptible to TCDD-induced mortality than are embryos of the ring-necked pheasant and eastern bluebird. In addition, chicken embryos are highly sensitive to the formation of TCDD-induced structural defects in the heart and aortic arch. The incidence of cardiac malformations in the chicken embryo is increased at an egg exposure level as low as 9 ng TCDD/kg egg. However, such cardiac malformations have not been found in any other bird species that has been examined.

Table 5-7 summarizes the levels of TCDD exposure that cause certain structural malformations, functional alterations, and prenatal mortality in the embryo/fetus of different mammalian species. Based on the LOAELs given for rats and monkeys in Table 5-7, functional

alterations in learning behavior and the male reproductive system occur at lower TCDD doses than those required to produce structural malformations. Maternal doses of TCDD between 19 and 160 ng/kg decreased object learning in monkeys, accelerated eye opening, produced adverse effects on the male reproductive system, and altered sexual behavior in rats. Developmental toxicity to the female reproductive tract in rats occurred at TCDD doses between 200 and 800 ng/kg. Although TCDD-induced developmental toxicity has been extensively studied in mice and rats, the LOAELs in Table 5-7 indicate that the embryo/fetus of rodent species is generally not as sensitive to TCDD-induced prenatal mortality as is the embryo/fetus of the rhesus monkey. The sensitivity of the embryo/fetus to TCDD-induced prenatal mortality in different mammalian species varies approximately 240-fold. This is in contrast to the 1,000- to 5,000-fold variation in the LD_{50} of TCDD when adult animals of these same species are exposed. The agreement between studies with respect to the LOAEL in Table 5-7 for prenatal mortality in rats and monkeys is particularly striking. The 500 ng/kg dose of TCDD on gestational days 6 to 15 that caused prenatal mortality in rats (Sparschu et al., 1971) agrees with the maternal TCDD body burden of 270 ng/kg calculated from the chronic exposure of rats by Murray et al. (1979) to within a factor of 2. Similarly, the TCDD dose of 111 ng/kg that was given to rhesus monkeys nine times during the first trimester of pregnancy (McNulty, 1984) agrees with the maternal body burden of 97 ng/kg that increased prenatal mortality in rhesus monkeys following subchronic dietary exposure (Schantz and Bowman, 1989).

5.3. REPRODUCTIVE TOXICITY

5.3.1. Female

5.3.1.1. *Reproductive Function/Fertility*

TCDD and its approximate isostereomers have been shown to affect female reproductive endpoints in a variety of animal studies. Among the effects reported are reduced fertility, reduced litter size, and effects on the female gonads and menstrual/estrous cycle. These studies are reviewed below. Other TCDD effects on pregnancy maintenance, embryo/fetotoxicity, and postnatal development are covered in Section 5.2 of this chapter.

5.3.1.1.1. ***Rats.*** The study by Murray et al. (1979) employed a multigenerational approach, examining the reproductive effects of exposure of male and female rats over three generations to relatively low levels of TCDD (0, 0.001, 0.01, and 0.1 μg/kg/day). There was variation in the fertility index in both the control and the exposed groups, and a lower than desirable number of impregnated animals in the exposed groups. Nevertheless, the results showed exposure-related effects on fertility, an increased time between first cohabitation and delivery, and a decrease in litter size. The effects on fertility and litter size were observed at 0.1 μg/kg/day in the F_0

generation and at 0.01 μg/kg/day in the F_1 and F_2 generations. Additionally, in a 13-week exposure to 1 to 2 μg/kg/day of TCDD in nonpregnant female rats, Kociba et al. (1976) reported anovulation and signs of ovarian dysfunction, as well as suppression of the estrous cycle. However, at exposures of 0.001 to 0.01 μg/kg/day in a 2-year study, Kociba et al. (1978) reported no effects on the female reproductive system.

5.3.1.1.2. ***Monkeys.*** Allen and colleagues reported on the effects of TCDD on reproduction in the monkey (Allen et al., 1977, 1979; Barsotti et al., 1979; Schantz et al., 1979). In a series of studies, female rhesus monkeys were fed 50 or 500 ppt TCDD for ~9 months. Females exposed to 500 ppt showed obvious clinical signs of TCDD toxicity and lost weight throughout the study. Five of the eight monkeys died within 1 year after exposure was initiated. Following 7 months of exposure to 500 ppt TCDD, seven of the eight females were bred to unexposed males. The remaining monkey showed such severe signs of TCDD toxicity that she was not bred due to her debilitated state. Of the seven females that were evaluated for their reproductive capabilities, only three were able to conceive and, of these, only one was able to carry her infant to term (Barsotti et al., 1979). When females exposed to 50 ppt TCDD in the diet were bred at 7 months, two of eight females did not conceive and four of six that did conceive could not carry their pregnancies to term. As one monkey delivered a stillborn infant, only one conception resulted in a live birth (Schantz et al., 1979). As described in an abstracted summary, these results at 50 and 500 ppt TCDD are compared with a group of monkeys given a dietary exposure to PBB (0.3 ppm, Firemaster FF-1) in which seven of seven exposed females were able to conceive, five gave birth to live, normal infants, and one gave birth to a stillborn infant (Allen et al., 1979). Although the effects at 500 ppt TCDD may be associated with significant maternal toxicity, this would not appear to be the case at the lower dose. After administration of 50 ppt TCDD, no overt effects on maternal health were observed, but the ability to conceive and maintain pregnancy was reduced (Allen et al., 1979).

In a similar series of experiments, female rhesus monkeys were fed diets that contained 0, 5, and 25 ppt TCDD (Bowman et al., 1989a; Schantz and Bowman, 1989). Reproductive function was not altered in the 5 ppt group, as seven of eight females mated to unexposed males after 7 months of dietary exposure to TCDD were able to conceive. Six of these females gave birth to viable infants at term and one gave birth to a stillborn infant. This was not significantly different from the results of the control group, which was fed a normal diet that contained no TCDD. All seven of the monkeys in this control group were able to conceive and give birth to viable infants. The 25 ppt dietary exposure level, however, did affect reproductive function. Only one of the eight females in this group that was mated gave birth to a viable infant. As in the 50 ppt group from earlier studies, there were no serious health problems exhibited by any females

exposed to 0, 5, or 25 ppt TCDD. Therefore, the results in the 25 and 50 ppt groups suggest that maternal exposure to TCDD before and during pregnancy can result in fetomortality without producing overt toxic effects in the mother.

McNulty (1984) examined the effect of a TCDD exposure during the first trimester of pregnancy (gestational age 25 to 40 days) in the rhesus monkey. At a total dose of 1 μg/kg given in nine divided doses, three of four pregnancies ended in abortion and two of these abortions occurred in animals that displayed no maternal toxicity. At a total dose of 0.2 μg/kg, one of four pregnancies ended in abortion. This did not appear to be different from the control population, but the low number of animals per group did not permit statistical analysis. McNulty (1984) also administered single 1 μg/kg doses of TCDD on gestational days 25, 30, 35, or 40. The number of animals per group was limited to three, but it appeared that the most sensitive periods were the earlier periods, days 25 and 30, and that both maternal toxicity and fetotoxicity were reduced when TCDD was given on later gestational days. For all days at which a single 1 μg TCDD/kg dose was given (gestational day 25, 30, 35, or 40), 10 of 12 pregnancies terminated in abortion. Thus, of 16 monkeys given 1 μg TCDD/kg in single or divided doses between days 25 and 40 of pregnancy, only three normal births occurred (McNulty, 1984, 1985).

5.3.1.2. *Ovarian Function*

Signs of ovarian dysfunction in rats and monkeys such as anovulation and suppression of the estrous cycle had been reported previously (Kociba et al., 1976; Barsotti et al., 1979; Allen et al., 1979), and Li et al. (1995a,b) recently extended these studies. In their initial study (Li et al., 1995a), adult female rats were given a single oral dose of 10 μg TCDD/kg BW and observed for changes in estrous cyclicity and ovulation. The number of ova ovulated per female and the number of females ovulating were decreased by 75%, and the estrous cycle was also altered, with a significant increase in the time spent in diestrus and a decrease in proestrus and estrus. However, these findings were clouded by the fact that the exposure caused a body weight loss in the females. A subsequent dose-response study in immature hypophysectomized/eCG-primed females provided support that the effects on ovulation were dose-dependent (Li et al., 1995b). However, the effects were only statistically significant at exposure levels that also caused a significant loss in body weight over the experimental period.

5.3.1.3. *Reproductive Capability of Ah Receptor Knockout Mice*

Reproductive success is adversely affected in some Ah receptor null mouse lines (in the absence of TCDD exposure). Ah receptor null female mice (Fernandez-Salguero et al., 1995) become pregnant at similar rates and implant similar numbers of embryos as control females. However, these Ah receptor null dams experience increased prenatal loss of conceptuses and

difficulty in surviving the stress of lactation, and their pups show poor survival during lactation and shortly after weaning (Abbott et al., 1999c). In contrast, offspring from a different Ah receptor null mouse line (Schmidt et al., 1996) exhibit low neonatal mortality. Possible reasons for this and other phenotypic differences between offspring of these two Ah receptor null mouse lines is unclear (Schmidt et al., 1996).

5.3.1.4. *Endometriosis*

5.3.1.4.1. *Humans*

Endometriosis is characterized by endometrial cell growth outside the uterus and can be associated with infertility and pain. Of increasing interest is the initial report that women with endometriosis in Germany are more likely to have elevated concentrations of PCBs in their blood (Gerhard and Runnebaum, 1992). While this report did not provide sufficient methodological detail (reviewed in Ahlborg et al., 1995), Koninckx and coworkers (1994) reported that Belgium also has a high incidence of endometriosis and that TCDD concentrations in breast milk in Belgian women are among the highest in the world. Similarly, a larger number of women in Israel with endometriosis were found to have measurable blood levels of TCDD when compared to age-matched control women that had tubal infertility but no endometriosis (Mayani et al., 1997). More recently in Belgian women, high serum TCDD-like toxic equivalent concentrations (TEQs) were associated with a greater risk for endometriosis (Pauwels et al., 1999), but no association was found between endometriosis and total serum PCB concentrations in this study. This suggests that only TCDD-like PCBs may be capable of producing the response in women.

A recent study has demonstrated the occurrence of certain TCDD-induced biochemical changes that facilitate the ectopic growth of human endometrial tissue (Bruner-Tran et al., 1999). When the human tissue is exposed to TCDD *in vitro* and implanted into immunologically impaired nude mice, TCDD exposure inhibits the ability of progesterone to decrease the expression of matrix metalloproteinase enzymes. This effect, which is associated with a TCDD-induced decrease in the ability of human endometrial organ cultures to produce TGF-β_2, enhances ectopic growth of the endometrial lesions. These results begin to provide a biochemical basis for the ability of TCDD exposure to facilitate the expression of endometriosis in women, and they strengthen the association between elevated exposure to TCDD-like AhR agonists and the increased incidence and severity of this disease.

5.3.1.4.2. *Monkeys*

An association between TCDD exposure and endometriosis has found some experimental support in studies using the rhesus monkey. However, the association between PCB exposure

and endometriosis in monkeys is less clear. Rier and coworkers chronically exposed rhesus monkeys to TCDD in their diet for 4 years and then maintained the monkeys for an additional 10 years. These monkeys were then compared to similar unexposed animals in the same colony (Rier et al., 1993; Rier et al., 1995). In monkeys exposed to dietary levels of 5 ppt and 25 ppt TCDD, the incidence of endometriosis was 43% and 71%, respectively, whereas the incidence in control monkeys was 33%. Moreover, the severity of endometriosis was TCDD dose-dependent. Monkeys in the studies by Rier and coworkers appeared to be quite sensitive to TCDD-induced increases in the incidence and severity of endometriosis. It has been calculated that the female monkeys exposed to 5 ppt TCDD in the diet for 4 years had accumulated a TCDD body burden of 69 ng/kg (DeVito et al., 1995). However, another study found no association between the incidence and severity of endometriosis and exposure to Aroclor 1254 when rhesus monkeys were exposed for up to 6 years. Unlike the Rier studies, these monkeys were not held for evaluation a long time after exposure (Arnold et al., 1996). Interestingly, both the Rier and the Arnold studies reported a similar high background incidence (33% -37%) of endometriosis in unexposed monkeys. When taken together the results of these studies indicate that it may take some time for a TCDD-induced increase in endometriosis to become manifest above the background level, that sensitivity to halogen aromatic hydrocarbon-induced increases in endometriosis may be more readily detected when TCDD equivalent concentrations (TEQs) rather than total PCB concentrations are considered, and that the effect, if produced by PCBs at all in monkeys, could be PCB congener-specific. In this last sense, the results in monkeys correspond to those recently obtained by Pauwels et al. (1999) in women, which also suggest that the effect on endometriosis is congener specific for those halogenated aromatic congeners with AhR agonist activity.

5.3.1.4.3. ***Rats and mice.*** An animal model has been developed in the rat and mouse to evaluate the effects of TCDD exposure on the development of endometriosis (Cummings et al., 1995, 1996). While rodents do not spontaneously develop endometriosis, the surgical implantation of uterine tissue at ectopic sites in the abdominal cavity is a way of mimicking aspects of the disease. The formation of clear vesicles, fibrosis, inflammation, and adhesions are common to the disease in primates and to the rodent model of endometriosis (Cummings et al., 1996). Female rats and mice were administered 0, 3, or 10 μg TCDD/kg 3 weeks before, at the time of, and at 3, 6, and 9 weeks after surgery to induce endometriosis (Cummings et al., 1996). At 3, 6, 9, and 12 weeks following surgery, there were dose-dependent increases in lesion diameter in both species if all time points were pooled. In addition, rats showed a decrease in body weight and ovarian weight at 9 and 12 weeks, accompanied by an increase in the time spent in vaginal estrus, and histology of the ovary at 12 weeks indicated ovulatory arrest. These effects on body

weight and the ovary were not observed in the mouse, but the mouse seemed more susceptible to the TCDD-increase in lesion diameter than the rat at 9 and 12 weeks postsurgery.

Additional studies done to assess the effects of TCDD in the mouse model of endometriosis used slightly different methodology and resulted in different results. In these studies mice were first subjected to the surgery to induce endometriosis and then were exposed chronically to daily doses of 0, 10, 50, or 100 ng TCDD/kg for 28 days. When the effects of TCDD exposure on the endometriosis lesions were assessed 2 days after the last dose, it was found that there was a dose-dependent decrease in lesion diameter (Yang et al., 1997). In addition, uterine tissue implant survival and growth was decreased in ovariectomized mice and restored by estrogen replacement (Foster et al., 1997). Exposure to TCDD inhibited the ability of estrogen replacement to promote implant survival and growth, suggesting that TCDD acts as an antiestrogenic compound in this form of the model. The authors of this study noted the difference between their results and those of Cummings et al., and they suggested that when TCDD is administered prior to the induction of endometriosis in ovary-intact mice, immune suppression facilitates the growth of the endometriosis implants, or that factors of ovarian origin other than steroids may play a role in the establishment, maintenance, and growth of endometriosis. In contrast, when TCDD is administered after surgically induced endometriosis is established, the antiestrogenic effects of TCDD inhibit lesion growth. In spite of these suggestions, it seems possible that insufficient time is allowed when this model is used for the severity of surgically-induced endometriosis to be increased by TCDD exposure subsequent to the initial inhibition.

Unlike TCDD, the Ah receptor agonists 3,3',4,4',5-PCB (PCB 126), 1,3,6,8-tetrachlorodibenzo-*p*-dioxin, and 2,3,4,7,8-pentachlorodibenzofuran were not able to alter lesion diameter or lesion weight in the mouse model (Johnson et al., 1997). This is reminiscent of the ability of TCDD, but not Aroclor 1254, to increase the incidence of endometriosis in rhesus monkeys. Interestingly, the dose-response relationship for TCDD in the mouse model was U-shaped, with low doses promoting endometriosis and larger doses resulting in a decreased response. Therefore, the effects of Ah receptor agonists on endometriosis may depend on a complex interplay between immune suppression and antiestrogenicity.

5.3.1.5. *Mammary Gland*

5.3.1.5.1. ***Postnatal mammary gland development.*** The mammary gland of weanling rats and mice is a system of branching ducts that terminate in actively growing terminal end buds (TEBs). Elongation of the mammary ducts and penetration of the epithelium into the surrounding adipose stroma results from the rapid cellular proliferation of the TEBs (Williams et al., 1983). The density of TEBs (number of TEB/mm^2) increases steadily after birth until it reaches a maximum

value in the rat on postnatal day 21 (Russo et al., 1978). This is accompanied by a concomitant increase in the total area of the mammary gland. After postnatal day 21 numerous lateral buds develop along the growing ducts as further growth of the gland occurs. During this time septation and cleavage in the TEBs and lateral ducts result in the formation of 3-5 smaller buds per structure, the alveolar buds (ABs) (Russo and Russo, 1978). With the initiation of estrus cycling (postnatal days 35-42), alveoli form from the ABs, and until cessation of mammary growth occurs, these branched structures increase progressively in number with each successive estrus cycle resulting in the formation of lobules. TEBs that do not further differentiate in this manner regress into finger-shaped structures called terminal ducts (TDs).

5.3.1.5.2. ***Effects of postnatal TCDD exposure in vivo*.** Female rats that were orally administered daily doses of 2.5 μg TCDD/kg or vehicle on postnatal days 24, 26, 28, and 30 were affected by decreased cellular proliferation within their mammary glands and by decreased mammary gland development (Brown et al., 1995). When evaluated 18 hours after the last TCDD dose, body weight in the treated rats was slightly but not significantly reduced. However, the combined uterine-ovarian weights were less than half, and mammary gland size was only 61% that of vehicle-treated control rats. TCDD treatment caused a statistically significant 59% reduction in the number of TEBs without significantly affecting the numbers of ABs, lobules, and TDs. Therefore, the postnatal TCDD exposure-induced inhibition of mammary growth is accompanied by a selective size reduction within the most rapidly dividing portion of the mammary ducts, the TEBs. While TCDD exposure did not decrease the percentage of TEB cells that are proliferating (PCNA labeling index) or percentage of TEB cells in S-phase, it decreased these parameters in TDs and lobules. Consistent with the decrease in the number of TEBs in TCDD- treated rats, the total numbers of PCNA-labeled and S-phase cells were decreased (even though percentages were not) compared with the values obtained in vehicle-exposed control rats. In addition, TCDD exposure decreased the total numbers of PCNA-labeled and S-phase cells in TDs and lobules. These results are consistent with the finding that early postnatal TCDD exposure in the rat causes an inhibition of mammary epithelial cell proliferation, but the mechanism for this effect remains to be determined. It may be a consequence of the antiestrogenic properties of TCDD (Harris et al., 1990; Safe et al., 1991).

5.3.1.5.3. ***Expression of Ah receptor and effects of the Ah receptor null mutation.*** Mammary glands from estrous cycling C57BL/6J mice express high levels of Ah receptor mRNA and protein (Hushka et al., 1998). Lower or undetectable levels of the Ah receptor mRNA and protein were found during late pregnancy and during mammary gland involution immediately after the cessation of nursing. Transgenic female mice heterozygous for the Ah receptor null

mutation were mated with transgenic heterozygous males. Comparative analysis of mammary gland development in 6- to 8-week-old female Ah receptor wild-type and Ah receptor null littermates demonstrated that there was a 50% reduction in TEBs and an increase in TDs in the Ah receptor null females. In most Ah receptor null females the ductal architecture, branching patterns, and overall organization of specific cell types in the mammary epithelium did not appear to be altered. However, a small percentage of mammary glands from Ah receptor null females exhibited little or no branching. These findings support the conclusion that Ah receptor-dependent processes may play a role in TEB development even in the absence of endogenous ligand. However, as indicated below, the effects of the Ah receptor null mutation and Ah receptor activation by exogenous ligand in the mouse turn out to be similar rather than opposite.

5.3.1.5.4. ***Response of organ-cultured mammary gland to exogenous ligand.*** Nulliparous C57BL/6J mice were primed with 15 daily injections of estradiol and progesterone (Hushka et al., 1998). Mammary glands were removed 24 hours after the last priming and cultured in the presence of 0.1% DMSO or 1 to 100 nM 2,3,7,8-TCDF for 5 days and prepared for histology and immunohistochemistry. Lobule size after culturing was suppressed by TCDF in a dose-related manner, such that lobules in mammary glands exposed to the largest dose of TCDF were less than one-half the size of vehicle-exposed lobules. The ^{3}H-thymidine labeling index was also reduced in the TCDF-exposed lobules. Therefore, the growth and development of TEBs into lobules appeared to be suppressed by TCDF, but the effects of TCDF on TEB number after organ culture were not reported, and therefore it is not known whether TCDD exposure caused the expected increase in the number of TEBs. Overall, these results are consistent with the effects of TCDD on mammary growth and development that were previously mentioned for the rat. In addition, they suggest that toxicity results from direct effects of TCDF on the mammary gland.

5.3.1.5.5. ***Effects of prenatal TCDD exposure.*** Pregnant rats were orally administered 1 μg TCDD/kg or vehicle on gestational day 15 (Brown et al., 1998). Mammary development was evaluated in female offspring at 21 and 50 days of age. While body weight of the TCDD-exposed female offspring, compared with that of vehicle-exposed female offspring, was reduced at both time points, liver weight was reduced only on postnatal day 50. TCDD exposure delayed the time of vaginal opening and caused a disruption in the estrus cycle. However, uterus weight and mammary gland size were unaffected by in utero and lactational TCDD exposure. Nevertheless, the number of TEBs was increased in the mammary glands of TCDD-exposed female offspring, and there was a corresponding decrease in the number of lobules. Cellular proliferation (BrdU labeling index) was not affected by TCDD exposure in TDs at either time

point, but the results indicate that the differentiation pathway from TEBs to lobules was inhibited.

When the carcinogen DMBA is administered to 50- to 60-day-old female rats, the differentiation pathway of the mammary gland epithelium is disrupted (Russo and Russo, 1978). Between 14 and 21 days post-DMBA inoculation, TEBs increase markedly in size and do not differentiate into lobules. Instead, these TEB-derived larger structures, termed intraductal proliferations (IDPs), may progress along an alternate pathway to form microtumors that have the characteristics of rat mammary adenocarcinomas. These structures are derived exclusively from TEBs. In utero and lactational exposure to a single maternal dose of 1 μg TCDD/kg administered on gestational day 15 increased the number of TEBs in 50-day-old female offspring (Brown et al., 1998). In addition, these glands were rendered more susceptible to the formation of DMBA-induced mammary tumors. While neither epidemiological data nor occupational studies provide clear support for an association between TCDD and the occurrence of breast cancer in women, it is interesting to note that prenatal and postnatal exposure to TCDD can have opposite effects in laboratory animals. Postnatal exposure to TCDD decreased the incidence of DMBA-induced mammary tumors in female rats (Holcomb et al., 1994). This latter effect was believed to be due to the antiestrogenic properties of TCDD. The mechanism whereby in utero and lactational TCDD exposure alters TEB differentiation and promotes DMBA-induced mammary tumorigenesis is not yet known.

5.3.1.5. Summary. The primary effects of TCDD on female reproduction appear to be decreased fertility, inability to maintain pregnancy for the full gestational period, and in the rat, decreased litter size. It is likely that ovarian dysfunction and alterations in normal estrous cyclicity also result from TCDD exposure. The growing body of data also indicate that TCDD exposure may lead to or favor the appearance of endometriosis. Koninckx et al. (1994) have noted that Belgium has a high incidence of endometriosis and that TCDD concentrations in breast milk in Belgium women are among the highest in the world, and a similar relationship between measurable blood levels of TCDD and endometriosis has been reported in women in Israel (Mayani et al., 1997). Mammary gland development in rats and mice can be adversely affected by in utero and lactational TCDD exposure potentially leading to the formation of tumors. Effects of TCDD exposure on the formation of mammary gland tumors can depend on the life-stage at which exposure occurs. Continued attention to these and other effects on the female reproductive system, especially in the nonpregnant state, will be important to determining the potential female reproductive toxicity of TCDD.

5.3.1.6. *Alterations in Hormone Levels*

The potential for TCDD to alter circulating female hormone levels has been examined, but only to a very limited extent. In monkeys fed a diet that contained 500 ppt TCDD for ~9 months, the length of the menstrual cycle, as well as the intensity and duration of menstruation, were not appreciably affected by TCDD exposure (Barsotti et al., 1979). However, there was a decrease in serum estradiol and progesterone concentration in five of the eight exposed monkeys, and in two of these animals the reduced steroid concentrations were consistent with anovulatory menstrual cycles. In summary form, Allen et al. (1979) described the effects of dietary exposure of female monkeys to 50 ppt TCDD. After 6 months of exposure to this lower dietary level of TCDD, there was no effect on serum estradiol and progesterone concentrations in these monkeys. Thus, the presence of these hormonal alterations is dependent on the level of dietary TCDD exposure.

5.3.1.7. *Antiestrogenic Action*

5.3.1.7.1. ***In vivo.*** Estrogens are necessary for normal uterine development and for maintenance of the adult uterus. The cyclic production of estrogens partially regulates the cyclic production of FSH and LH that results in the estrous cycling of female mammals. In addition, estrogens are necessary for the maintenance of pregnancy. Any effect that causes a decrease in circulating or target cell estrogen levels can alter normal hormonal balance and action.

Early experimental results in rats and monkeys indicated that TCDD may have an antiestrogenic action. Following administration of 1 μg TCDD/kg/day to rats for 13 weeks, Kociba et al. (1976) reported morphologic changes in the ovaries and uterus that were interpreted as being due to a suppression or inhibition of the estrous cycle. Rhesus monkeys exposed to 500 ppt of TCDD in the diet for 6 months developed hormonal irregularities in their estrous cycles that were associated with reduced conception rates as well as a high incidence of early spontaneous abortions (Allen et al., 1977; Barsotti et al., 1979).

In rhesus monkeys, the severity of the TCDD-associated reproductive alterations was correlated with decreased plasma levels of estrogen and progesterone (Barsotti et al., 1979). Thus, one possible mechanism for these effects would be increased metabolism of estrogen and progesterone due to induction by TCDD of hepatic microsomal enzymes and/or a decrease in the rate at which these steroids are synthesized. On the other hand, serum concentrations of 17β-estradiol are not significantly affected when TCDD is administered to pregnant rats (Shiverick and Muther, 1983). Thus, an alternative mechanism for TCDD-associated reproductive dysfunction could involve effects of TCDD on gonadal tissue itself, such as a decrease in its responsiveness to estrogen. In support of this latter mechanism, the administration of TCDD to CD-1 mice results in a decreased number of cytosolic and nuclear estrogen receptors in

hepatocytes and uterine cells. Although TCDD treatment induces hepatic cytochrome P-450 levels in these animals, it has no effect on serum concentrations of 17β-estradiol (DeVito et al., 1992). This indicates that the antiestrogenic effect of TCDD in CD-1 mice is not caused by a decrease in circulating levels of estrogen.

Effects of estrogen on the uterus include a cyclic increase in uterine weight, increased activity of the enzyme peroxidase, and an increase in the tissue concentration of progesterone receptors. Antiestrogenic effects of TCDD administration to female rats include a decrease in uterine weight, decrease in uterine peroxidase activity, and a decrease in the concentration of progesterone receptors in the uterus (Safe et al., 1991). In addition, when TCDD and 17β-estradiol are coadministered to the same female rat, the antiestrogenic action of TCDD diminishes or prevents 17β-estradiol-induced increases in uterine weight, peroxidase activity, progesterone receptor concentration, and expression of EGF receptor mRNA (Astroff et al., 1990; Safe et al., 1991). Similarly, in mice TCDD administration decreases uterine weight and antagonizes the ability of 17β-estradiol to increase uterine weight (Gallo et al., 1986).

The ability of TCDD to antagonize the effects of exogenously administered estrogen in the rat is dependent on the age of the animal. In 21-day-old rats, TCDD does not affect 17β-estradiol-induced increases in uterine weight or progesterone receptor concentration. On the other hand, in 28-day-old intact rats and 70-day-old ovariectomized rats, both of these 17β-estradiol-mediated responses are attenuated by TCDD (Safe et al., 1991). Previously, it had been reported that TCDD administration does not alter the dose-dependent increase in uterine weight due to exogenously administered estrone in sexually immature rats (Shiverick and Muther, 1982). The later work by Safe et al. (1991) suggests that this apparent lack of an antiestrogenic effect of TCDD may have been due to the young age of the rats used.

5.3.1.7.2. ***In vitro.*** Both TCDD and progesterone can affect a decrease in the nuclear estrogen receptor concentration in rat uterine strips (Romkes and Safe, 1988). However, the effect of progesterone is inhibited by actinomycin D, cycloheximide, and puromycin, whereas the effect of TCDD is inhibited only by actinomycin D. The reasons that the TCDD-induced decrease in nuclear estrogen receptors is blocked by a transcription inhibitor, but not by protein synthesis inhibitors, are not understood. However, these results indicate that TCDD and progesterone decrease the nuclear estrogen receptor concentration by different mechanisms. In addition, the antiestrogenic actions of TCDD can be demonstrated in cell culture, and two prominent mechanisms could potentially be involved. They are (1) increased metabolism of estrogen due to Ah receptor-mediated enzyme induction and (2) a downregulation of estrogen receptors within the target cell.

In MCF-7 cells, which are estrogen-responsive cells derived from a human breast adenocarcinoma, antiestrogenic effects caused by the addition of TCDD to the culture medium include a reduction of the 17β-estradiol-induced secretion of a 160 kDa protein, 52 kDa protein, and 34 kDa protein (Biegel and Safe, 1990). These last two proteins are believed to be procathepsin D and cathepsin D, respectively. In addition, treatment of MCF-7 cells with TCDD suppresses the 17β-estradiol-enhanced secretion of tPA and inhibits estrogen-dependent postconfluent cell proliferation (Gierthy et al., 1987; Gierthy and Lincoln, 1988). Thus, cultured MCF-7 cells have several estrogen-dependent responses that are inhibited by TCDD; this characteristic makes them a useful model system for studying the antiestrogenic actions of dioxin.

In cultured MCF-7 cells, TCDD treatment induces aryl hydrocarbon hydroxylase (AHH) activity, the hallmark response of Ah receptor binding, and increases hydroxylation of 17β-estradiol at the C-2, C-4, C-6α, and C-15α, positions (Spink et al., 1990). It turns out that the particular cytochrome P-450 that catalyzes the C-2, C-15α, and C-6α hydroxylations of 17β-estradiol is cytochrome P-4501A1, which is identical to AHH (Spink et al., 1992). TCDD treatment also results in reduced levels of occupied nuclear estrogen receptors (Harris et al., 1990). These results indicate, in MCF-7 cells, that the antiestrogenic effect of TCDD could result from (1) an increased metabolism of estrogens due to Ah receptor-mediated enzyme induction and/or (2) a decreased number of estrogen receptors in the nucleus. Safe and his colleagues have published TCDD-concentration-response information for both the TCDD-induced decrease in occupied nuclear estrogen receptors (Harris et al., 1989) and the induction of AHH and EROD activities in MCF-7 cells (Harris et al., 1990). In addition, they have reported that TCDD causes a decreased number of cytosolic and nuclear estrogen receptors in Hepa 1c1c7 cells, which are a mouse hepatoma cell line (Zacharewski et al., 1991).

Independent analysis of the data suggests that the EC_{50} values for these effects are not dissimilar enough to distinguish between the proposed mechanisms. Instead, it appears as though TCDD induces the enzymes AHH and EROD over the same concentration range that it causes a decreased concentration of occupied nuclear estrogen receptors in MCF-7 cells. In Hepa 1c1c7 cells, the lowest concentration used was 10 pM. Although exposure to 10 pM TCDD resulted in a statistically significant downregulation of estrogen receptors, Israel and Whitlock (1983) reported that this concentration is the approximate EC_{50} for the induction of cytochrome P-4501A1 mRNA and enzyme activity in these cells. Therefore, in Hepa 1c1c7 cells as well as in MCF-7 cells, it would appear that the TCDD concentrations required to produce enzyme induction and reduction in occupied nuclear estrogen receptor levels are not dissimilar enough to distinguish between the two proposed mechanisms.

More recently, Safe and his colleagues have used an analog of TCDD, MCDF, which inhibits the 17β-estradiol-induced secretion of the 34, 52, and 160 kDa proteins and downregulates estrogen receptors in MCF-7 cells. These effects occurred at concentrations of MCDF at which there is no detectable induction of EROD activity (Zacharewski et al., 1992). In addition, it has been stated that the downregulation of estrogen receptors in Hepa 1c1c7 cells can be detected as early as 1 hour after exposure of the cell cultures to 10 nM TCDD (Zacharewski et al., 1991). This time is slightly less than the 2 hours that was required for Israel and Whitlock (1983) to detect an increase in cytochrome P-4501A1 mRNA levels after exposure of Hepa 1c1c7 cells to 10 pM TCDD. After exposure of Hepa 1c1c7 cells to a maximally inducing concentration of 1 nM TCDD, however, there are significant increases in the cellular concentration of cytochrome P-4501A1 mRNA after 1 hour, whereas the induction of AHH activity takes slightly longer (Israel and Whitlock, 1983).

Gierthy et al. (1987) reported that exposure of MCF-7 cells to 1 nM TCDD caused suppression of the 17β-estradiol-induced secretion of tPA. This effect of TCDD, however, occurred in the absence of any measurable decrease in the whole cell concentration of estrogen receptors, even though the cultures were pretreated with serum-free medium to reduce cell proliferation and maximize the cellular content of estrogen receptors. Gierthy's group pretreated their cultures with serum-free medium, which was done to reduce cell proliferation and maximize the cellular content of estrogen receptors. The disparity between this result of Gierthy et al. (1987), which suggests no effect of TCDD on the estrogen receptor content of MCF-7 cells, and the results of Safe and his colleagues to the contrary in this same cell line remains largely unexplained. Overall, it appears as though no obvious distinction between the two proposed mechanisms can be made at the present time. Therefore, it seems that the antiestrogenic effect of TCDD results from both an increased metabolism of estrogen and a decreased number of estrogen receptors. It is important to note that TCDD does not compete with radiolabeled estrogens or progesterone for binding to estrogen or progesterone receptors and that these steroids do not bind to the Ah receptor or compete with radiolabeled TCDD for binding (Romkes et al., 1987; Romkes and Safe, 1988).

5.3.1.7.3. *Evidence for an Ah receptor mechanism*

5.3.1.7.3.1. *Ah receptor mutants*. Although the precise cellular mechanism by which TCDD produces its antiestrogenic effect is subject to a discordance between two primary schools of thought, there is agreement that the response is mediated by the Ah receptor. Thus, the antiestrogenic effects of TCDD in cultured cells appear to involve an Ah receptor-mediated alteration in the transcription of genes. This is indicated by studies using wild-type Hepa 1c1c7 cells and mutant Hepa 1c1c7 cells in culture (Zacharewski et al., 1991). In wild-type cells,

TCDD reduces the number of nuclear estrogen receptors, and this response can be inhibited by cycloheximide and actinomycin D. However, in class 1 mutants, which have relatively low Ah receptor levels, TCDD has only a small effect. Similarly, in class 2 mutants, which have a defect in the accumulation of transcriptionally active nuclear Ah receptors, there was no effect of TCDD on the number of nuclear estrogen receptors. Taken together, these results indicate that the downregulation of estrogen receptors in Hepa 1c1c7 cells involves an Ah receptor-mediated effect on gene transcription. As previously noted, TCDD induces cytochrome P-4501A1 mRNA transcription and enzyme activity in Hepa 1c1c7 cells (Israel and Whitlock, 1983). This effect is also Ah receptor mediated (Nebert and Gielen, 1972).

5.3.1.7.3.2. ***Structure-activity relationships in vivo.*** The relative potencies of halogenated aromatic hydrocarbon congeners as inhibitors of uterine peroxidase activity in the rat are similar to their relative Ah receptor-binding affinities (Astroff and Safe, 1990). Only limited relative potency information is available for the reduction of hepatic and uterine estrogen receptor concentrations per se by these substances in rats. TCDD and 1,2,3,7,8-PeCDD both exhibit high affinity for the Ah receptor. At an 80 μg/kg dose of either of these two substances, hepatic estrogen receptor concentrations are reduced 42% and 41%, whereas uterine estrogen receptor concentrations are reduced 53% and 49% by TCDD and 1,2,3,7,8-PeCDD, respectively. On the other hand, 1,3,7,8-TCDD and 1,2,4,7,8-PeCDD bind less avidly to the Ah receptor. At a 400 μg/kg dose of either of these two substances, hepatic estrogen receptor concentrations are reduced 36% and 40%, whereas uterine estrogen receptor concentrations are reduced 21% and 24% by 1,3,7,8-TCDD and 1,2,4,7,8-PeCDD, respectively (Romkes et al., 1987). As the potency of these congeners for reducing estrogen receptor concentrations correlates with their Ah receptor-binding affinities, these in vivo results provide evidence that the antiestrogenic effect of TCDD is mediated by the Ah receptor.

5.3.1.7.3.3. ***Genetic evidence.*** Consistent with the interpretation based on structure-activity relationships, there is a greater reduction in the number of hepatic estrogen receptors when Ah^bAh^b C57BL/6 mice are exposed to TCDD than when Ah^dAh^d DBA/2 mice are similarly exposed (Lin et al., 1991). To date, however, the antiestrogenic effects have not been studied in the progeny of test crosses between Ah^bAh^b and Ah^dAh^d mouse strains that respectively produce Ah receptors with high- or low-binding affinity for TCDD. Therefore, the potential segregation of the antiestrogenic effects of TCDD with the Ah locus has not been verified by the results of genetic crosses.

5.3.1.7.3.4. ***Structure-activity relationships in vitro.*** The Ah receptor is detectable in MCF-7 cells, and AHH as well as EROD activities are both inducible in these cells (Harris et al., 1989). The relative abilities of TCDD and other CDD, CDF, and PCB congeners to suppress 17β-estradiol-induced secretion of tPA by MCF-7 cells are consistent with the structure-activity relationships for other Ah receptor-mediated responses (Gierthy et al., 1987). In addition, the rank order of potency for several Ah receptor agonists in reducing nuclear estrogen receptors in MCF-7 cells is TCDD > 2,3,4,7,8-PeCDD > 2,3,7,8-TCDF > 1,2,3,7,9-PeCDD > 1,3,6,8-TCDF (Harris et al., 1990). The rank order of potency for these substances is consistent with their relative activities as Ah receptor agonists. These results in vitro support a role for the Ah receptor in the antiestrogenic actions of TCDD.

5.3.2. Male

5.3.2.1. *Reproductive Function/Fertility*

TCDD and related compounds decrease testis and accessory sex organ weights, cause abnormal testicular morphology, decrease spermatogenesis, and reduce fertility when given to adult animals in doses sufficient to reduce feed intake and/or body weight. Certain of these effects have been reported in chickens, rhesus monkeys, rats, guinea pigs, and mice treated with overtly toxic doses of TCDD, TCDD-like congeners, or toxic fat that was discovered later to contain TCDD (Allen and Lalich, 1962; Allen and Carstens, 1967; Khera and Ruddick, 1973; Kociba et al., 1976; van Miller et al., 1977; McConnell et al., 1978; Moore et al., 1985; Chahoud et al., 1989; Morrisey and Schwetz, 1989). In testis of these different species, TCDD effects on spermatogenesis are characterized by loss of germ cells, the appearance of degenerating spermatocytes and mature spermatozoa within the lumens of seminiferous tubules, and a reduction in the number of tubules containing mature spermatozoa (Allen and Lalich, 1962; Allen and Carstens, 1967; McConnell et al., 1978; Chahoud et al., 1989). The lowest cumulative dose of TCDD to decrease spermatogenesis in the rat was 1 μg/kg/day administered 5 days a week for 13 weeks (Kociba et al., 1976). With this dosage regimen, which resulted in a TCDD body burden of approximately 20 μg/kg at the end of the dosing period (Rose et al., 1976), body weights and feed consumption of the rats also were significantly depressed. A similar 13-week dosing study using adult male mice found that 3 and 30 mg 3,3',4,4'-TCAOB/kg/day caused reductions in epididymal sperm number (van Birgelen et al., 1999). In adult male Sprague-Dawley rats a single dose of 25 μg TCDD/kg decreased epididymal sperm numbers, whereas testicular Leydig cell volume was decreased at 12.5 μg TCDD/kg (Johnson et al., 1992). By comparison, daily sperm production was not affected, even by 50 μg TCDD/kg. Thus, the suppression of spermatogenesis and reduction in epididymal sperm number are not highly sensitive effects when Ah receptor agonists are administered to adult animals.

In contrast, daily sperm production assessed on postnatal day 90 was significantly decreased in weanling Sprague-Dawley rats administered 1 μg TCDD/kg on postnatal day 21 (el-Sabeawy et al., 1998). In addition, testis histology revealed that a dose of 10 μg TCDD/kg caused a decrease in seminiferous tubule diameter compared with that in vehicle-dosed control rats. The spermatogonial population normally located in the basal area of the tubules was absent in the TCDD-treated rats. However, these effects on testis histology were not found at TCDD doses less than 10 μg TCDD/kg. Motility studies were performed on epididymal sperm, and dose-related decreases in sperm curvilinear velocity and beat cross frequency were found over the dose range from 0.1-5.0 μg TCDD/kg. Average path and straight line velocity were significantly decreased at 5 μg TCDD/kg (el-Sabeawy et al., 1998).

Effects of TCDD administration to 21-day-old rats on epidermal growth factor receptor-, protein tyrosine kinase-, protein kinase A-, protein kinase C-, mitogen-activated protein 2 kinase, and c-Src tyrosine kinase-mediated pathways in the testis were also examined (el-Sabeawy et al., 1998). Dose-related increases in the activity of c-Src kinase were found on postnatal days 34 and 90 over the dose range from 0.1-5.0 μg TCDD/kg. In addition, the administration of multiple doses of the c-Src kinase inhibitor geldanamycin over the time period from postnatal days 21-90 blocked the effects of TCDD on testis weight and daily sperm production. The authors conclude that these results provide evidence for the involvement of epidermal growth factor and Src kinasesignaling pathways in the mechanism by which TCDD disrupts testicular development and subsequently affects testis function.

5.3.2.2. *Alterations in Hormone Levels*

The effects of TCDD on the male reproductive system are believed to be due in part to an androgenic deficiency. This deficiency is characterized in adult rats by decreased plasma testosterone and DHT concentrations, unaltered plasma LH concentrations, and unchanged plasma clearance of androgens and LH (Moore et al., 1985, 1989; Mebus et al., 1987; Moore and Peterson, 1988; Bookstaff et al., 1990a). The ED_{50} of TCDD for producing this effect in adult male rats on day 7 after dosing is 15 μg/kg (Moore et al., 1985), and it can be detected within 1 day of treatment. As described in the following sections, the cause of the androgenic deficiency is decreased testicular responsiveness to LH and increased pituitary responsiveness to feedback inhibition by androgens and estrogens (Moore et al., 1989, 1991; Bookstaff et al., 1990a,b; Kleeman et al., 1990).

5.3.2.3. *Target Organ Responsiveness*

5.3.2.3.1. ***Inhibition of testicular steroidogenesis.*** Testicular steroidogenesis occurs within Leydig cells and is regulated primarily by plasma LH concentrations (Payne et al., 1985; Hall,

1988). Binding of LH to the LH receptor causes cAMP and possibly other second messengers to be formed (Cooke et al., 1989). In response, cholesterol is rapidly transported to the initial enzyme in the testosterone biosynthetic pathway, a cholesterol side-chain cleavage enzyme, which is a cytochrome P-450 (cytochrome P-450_{scc}) located on the inner side of the inner mitochondrial membrane that converts cholesterol to pregnenolone. The mobilization of free cholesterol rather than its conversion to pregnenolone and other metabolites is generally considered to be the rate-limiting step in testicular steroidogenesis. TCDD inhibits testosterone biosynthesis, predominantly if not exclusively by inhibiting the mobilization of free cholesterol that acts as a substrate for cytochrome P-450_{scc} (Moore et al., 1991). Thus, in the testes of TCDD-treated rats, cholesterol is provided to the cytochrome P-450_{scc} enzyme at too slow a rate to maintain androgenic homeostasis, even when the plasma LH concentration characteristic of "normal" androgen levels is present.

Leydig cell volume was significantly reduced 4 weeks after a single intraperitoneal injection of TCDD (Johnson et al., 1994). The effect was dose related and observed at the lowest dose tested, 12.5 μg TCDD/kg BW. This reduction in total cell volume resulted from both a reduced number of cells and a reduced size of individual cells. Wilker et al. (1995) were able to establish that this effect of TCDD can be prevented by hCG.

5.3.2.3.2. ***Altered regulation of pituitary LH secretion.*** In TCDD-treated male rats, the expected increase in plasma LH concentration that would facilitate testicular compensation for the decreased plasma androgens does not occur (Moore et al., 1989; Ruangwises et al., 1991). The failure of the plasma LH concentration to rise appropriately is not caused by an increase in the plasma clearance of LH or by a decrease in the maximal rate of pituitary LH synthesis or secretion (Bookstaff et al., 1990a,b). Rather, TCDD alters the feedback regulation of LH secretion in male rats by increasing the potency of testosterone and its metabolites (DHT and 17β-estradiol) as inhibitors of LH secretion. The ED_{50} of TCDD for enhancing the testosterone-mediated inhibition of LH secretion 7 days after treatment is the same as its ED_{50} for causing the androgenic deficiency (15 μg/kg). Also, both responses are detected within 1 day of TCDD dosing and are fully developed after 7 days when the ED_{50}s were determined.

Decreased plasma androgen concentrations normally result in compensatory increases in both the number of pituitary gonadotropin-releasing hormone (GnRH) receptors and the responsiveness of the pituitary to GnRH. TCDD treatment prevents the increases in GnRH receptor number and responsiveness that would be expected in the light of the decreased plasma androgen concentrations (Bookstaff et al., 1990b). The pituitary is thus a target organ for TCDD because its responsiveness to hormones secreted by the testis (testosterone) and hypothalamus (GnRH) is altered by TCDD.

If the plasma LH concentrations in TCDD-treated rats did increase appropriately in response to decreased plasma androgens, it is expected that plasma androgens would return to normal levels (Kleeman et al., 1990). This is because the testes of TCDD-treated rats are capable of synthesizing more testosterone than is needed to maintain androgen concentrations in the physiological range, although this would require significantly elevated levels of LH in TCDD-treated rats. The fact that there is a testicular reserve capacity to provide for sufficient amounts of androgen synthesis, even when compromised, underscores the importance of the effects of TCDD on pituitary LH secretion in producing the effects of TCDD on plasma androgen concentrations.

5.3.2.3.3. ***Differential responsiveness of androgen target organs.*** The dose-related reductions in plasma testosterone and DHT concentrations in intact adult rats are accompanied by similar dose-related reductions (ED_{50} 15 μg TCDD/kg) in seminal vesicle and ventral prostate weights measured 7 days after dosing (Moore et al., 1985). In contrast, TCDD has no effect on accessory sex organ weights (or plasma androgen concentrations) in castrated adult rats implanted with either testosterone- or DHT-containing capsules (Moore and Peterson, 1988; Bookstaff et al., 1990a,b). As trophic responsiveness of the seminal vesicles and ventral prostate to testosterone and DHT are unaffected by postpubertal TCDD treatment, it follows that TCDD can increase responsiveness of the pituitary to androgens without affecting responsiveness of the accessory sex organs to androgens.

5.3.2.3.4. ***Relative sensitivity.*** The male reproductive system in rats is ~100 times more susceptible to TCDD toxicity when exposure occurs perinatally (ED_{50} for the most sensitive effects, 0.16 μg/kg) rather than in adulthood (ED_{50} for the most sensitive effects, 15 μg/kg). To illustrate this sensitivity, a single maternal TCDD dose as low as 0.064 μg/kg given on day 15 of gestation significantly decreases epididymis and cauda epididymis weights, cauda epididymal sperm numbers, and daily sperm production in male offspring at various stages of sexual development. Decreases in ventral prostate weights in 32-day-old male offspring and in older males, increases in the number of mounts preceding ejaculation, and increases in intromission latency also are produced by maternal TCDD doses as low as 0.064 μg/kg. The 0.064 μg TCDD/kg dose is not maternally toxic and produces no signs of overt toxicity in male or female offspring. Other effects of perinatal exposure on the male reproductive system were detected at a maternal TCDD dose of 0.16 μg/kg or higher (Mably et al., 1991, 1992a,b,c). On the other hand, when exposure occurs in adulthood, relatively large doses in the overtly toxic range are required to cause decreases in spermatogenesis and in ventral prostate and caput epididymis weight (Kociba et al., 1976; Moore et al., 1985). Kociba et al. (1976) reported that accessory sex organ

weights and spermatogenesis are decreased in rats following exposure to 1 μg TCDD/kg/day, 5 days per week for 13 weeks. Using the parameters for TCDD half-life and bioavailability in the rat determined by Rose et al. (1976), this dosage regimen results in a TCDD body burden of approximately 20 μg/kg at the end of the dosing period.

In adult rats, the most sensitive toxic responses to TCDD have been observed following long-term, low-level exposure. In a three-generation reproduction study, Murray et al. (1979) reported that dietary administration of TCDD at doses as low as 0.01 μg/kg/day significantly affected reproductive capacity in female rats, with no effects seen at 0.001 μg/kg/day (NOAEL). The same NOAEL was found in a 2-year chronic toxicity and oncogenicity study in which an increased incidence of certain types of neoplasms was altered among rats given TCDD doses of 0.01 or 0.1 μg/kg/day (Kociba et al., 1978). Based on the pharmacokinetics of TCDD in the rat (Rose et al., 1976), the steady-state body burden of TCDD in these rats that were chronically dosed (>90 days) with either 0.01 or 0.001 μg TCDD/kg/day is approximately 0.29 μg/kg (LOAEL) and 0.029 μg/kg (NOAEL), respectively. Yet, Mably et al. (1991, 1992a,b,c) found that a single TCDD dose of 0.064 μg/kg given on day 15 of gestation produces a number of statistically significant effects on the reproductive system of male rat offspring. Because 0.064 μg TCDD/kg was the lowest dose tested, a NOAEL for developmental male reproductive toxicity, which is defined as the lowest dose used that has no statistically significant effect, could not be determined by Mably et al. (1991, 1992a,b,c). It is concluded that developmental effects on spermatogenesis occur at a maternal TCDD dose that is lower than any previously shown to produce toxicity in rats.

5.4. SUMMARY

This chapter has focused on the variety of effects that dioxin and dioxin-like agents can have on human reproductive health and development. The review is not exhaustive, and emphasis has been placed on the more recent reports. These have been put into context with previous reviews of the literature applicable in risk assessment (Kimmel, 1987) to develop a profile of the potential for dioxin and dioxin-like agents to cause reproductive or developmental toxicity based on the available literature. A portion of this report has been previously published (Peterson et al., 1993).

5.4.1. Human

The literature base with regard to potential human effects is detailed in Chapter 7. In general, there is no epidemiological evidence that makes a direct association between exposure to TCDD or TCDD-related agents and effects on human reproduction or development. However, the evidence that has been accumulated is suggestive of such an effect, at least with respect to

developmental toxicity. All four manifestations of developmental toxicity (reduced viability, structural alterations, growth retardation, and functional alterations) have been observed to some degree following presumed exposure to TCDD-related agents. The incidents at Yusho and Yu-Cheng resulted in increased perinatal mortality and low birthweight in infants born to women who had been exposed. Rocker bottom heal was observed in Yusho infants, and functional abnormalities have been reported in Yu-Cheng children.

Of particular interest is the ectodermal origin of many of the organs and tissues that are affected in the human. An ectodermal dysplasia syndrome has been clearly associated with the Yusho and Yu-Cheng episodes, involving hyperpigmentation, deformation of the fingernails and toenails, conjunctivitis, gingival hyperplasia, and abnormalities of the teeth. The developmental effects that can be associated with the nervous system are also consistent with this pattern because the nervous system is of ectodermal origin.

5.4.2. Experimental Animal

In developing a toxicological profile, it is rare to have sufficient data from human studies for quantitative analysis. Consequently, the risk assessment most often relies on data from experimental animal studies. For dioxin and the dioxin-related agents, the experimental animal database is fairly extensive with respect to reproductive and developmental toxicity. Dioxin exposure has been observed to result in both male and female reproductive effects, as well as effects on development. These latter effects are among the most responsive health endpoints to dioxin exposure. In general, the prenatal and developing postnatal animal is more sensitive to the effects of dioxin than the adult.

5.4.2.1. Developmental Toxicity

Dioxin exposure results in a wide variety of developmental effects and these are observed in three different vertebrate classes and in several species within each class. All four of the manifestations of developmental toxicity have been observed following exposure to dioxin, including reduced viability, structural alterations, growth retardation, and functional alterations. As summarized previously (Peterson et al., 1993), increased prenatal mortality (rat and monkey), functional alterations in learning and sexual behavior (rat and monkey), and changes in the development of the reproductive system (rat) occur at the lowest exposure levels.

Dioxin exposure results in reduced prenatal or postnatal viability in virtually every species in which it has been tested. Previously, increased prenatal mortality appeared to be observed only at exposures that also resulted in maternal toxicity. However, the studies of Olson and McGarrigle (1991) in the hamster and Schantz et al. (1989) in the monkey were suggestive that this was not the case in all species. Although the data from these two studies were limited,

prenatal death was observed in cases where no maternal toxicity was evident. In the rat, Peterson's laboratory (Bjerke et al.,1994a,b; Roman et al., 1995) reported increased prenatal death following a single exposure to TCDD during gestation that did not cause maternal toxicity, and Gray et al. (1995a) observed a decrease in postnatal survival under a similar exposure regimen. While identifying the presence or absence of maternal toxicity may be instructive as to the specific origin of the reduced prenatal viability, it does not alter the fact that pre- and postnatal death were observed. In either case, the Agency considers these effects as being indicators of developmental toxicity in response to the exposure (U.S. EPA, 1991).

Some of the most striking findings regarding dioxin exposure relate to the effects on the developing reproductive system. The findings are even more impressive with the understanding that only a single, low-level exposure during gestation is required to initiate these developmental alterations. Mably et al. (1992a,b,c) originally reported that a single exposure of the Holtzman maternal animal to as low as 0.064 μg/kg could alter normal sexual development in the male offspring. More recently, these findings have been further defined (Bjerke et al., 1994; Gray et al., 1995; Roman et al., 1995), as well as extended to females and another strain and species (Gray et al., 1995). In general, the findings of these later studies have produced qualitatively similar results that define a significant effect of dioxin on the developing reproductive system.

In the developing male, dioxin exposure during the prenatal and lactational periods results in the delay of the onset of puberty as measured by age at preputial separation. There is a reduction in testis weight, sperm parameters, and sex accessory gland weights. In the mature male exposed during the prenatal and lactational periods, there is an alteration of normal sexual behavior and reproductive function. Males exposed to TCDD during gestation are demasculinized. Feminization and a reduction in the number of implants in females mated with exposed males have also been reported, although these effects have not been consistently found. These effects do not appear to be related to reductions in circulating androgens, which were shown in the most recent studies to be normal. Most of these effects occur in a dose-related fashion, some occurring at 0.05 μg/kg and 0.064 μg/kg, the lowest TCDD doses tested (Mably et al., 1992c; Gray et al., 1997a).

In the developing female, Gray and Ostby (1995) have demonstrated altered sexual differentiation in both the Long Evans and Holtzman rat. The effects observed depended on the timing of exposure. Exposure during early organogenesis altered cyclicity, reduced ovarian weight, and shortened reproductive life span. Exposure later in organogenesis resulted in slightly lowered ovarian weight, structural alterations of the genitalia, and a slight delay in puberty. However, cyclicity and fertility were not affected with the later exposure. The most sensitive dose-dependent effects of TCDD in the female rat were structural alterations of the genitalia that occurred at 0.20 μg/kg (Gray et al., 1997b).

Structural malformations, particularly cleft palate and hydronephrosis, occur in mice. While these are not the most sensitive developmental endpoints, the findings indicate that exposure during the critical period of organogenesis can affect the processes involved in normal tissue formation. The TCDD-sensitive events appear to require the Ah receptor. Mouse strains that produce Ah receptors with relatively high affinity for TCDD respond to lower doses than strains with relatively low-affinity receptors. Moreover, congeners with a greater affinity for the Ah receptor are more developmentally toxic than those with a lower affinity.

5.4.2.2. Adult Female Reproductive Toxicity

The primary effects of TCDD on female reproduction appear to be decreased fertility, inability to maintain pregnancy for the full gestational period, and in the rat, decreased litter size. In some studies, signs of ovarian dysfunction such as anovulation and suppression of the estrous cycle have been reported (Kociba et al., 1976; Barsotti et al., 1979; Allen et al., 1979; Li et al., 1995a,b). Rier et al. (1993) reported TCDD-associated endometriosis in the monkey, and similar effects have now been reproduced in rats and mice (Cummings et al., 1996). Unfortunately, the amount of attention given to the female reproductive system, especially in the nonpregnant state, has been limited. Additional studies on the female reproductive system will be important to determining the potential female reproductive toxicity of TCDD.

5.4.2.3. Adult Male Reproductive Toxicity

TCDD and related compounds decrease testis and accessory sex organ weights, cause abnormal testicular morphology, decrease spermatogenesis, and reduce fertility when given to adult animals in doses sufficient to reduce feed intake and/or body weight. In the testis of these different species, TCDD effects on spermatogenesis are characterized by loss of germ cells, the appearance of degenerating spermatocytes and mature spermatozoa within the lumens of seminiferous tubules, and a reduction in the number of tubules containing mature spermatozoa (Allen and Lalich, 1962; Allen and Carstens, 1967; McConnell et al., 1978; Chahoud et al., 1989). This suppression of spermatogenesis is not a highly sensitive effect when TCDD is administered to postweanling animals, as an exposure of 1 μg/kg/day over a period of weeks appears to be required to result in these effects.

The effects of TCDD on the male reproductive system when exposure occurs in adulthood are believed to be due in part to an androgenic deficiency. This deficiency is characterized in adult rats by decreased plasma testosterone and DHT concentrations, unaltered plasma LH concentrations, and unchanged plasma clearance of androgens and LH (Moore et al., 1985, 1989; Mebus et al., 1987; Moore and Peterson, 1988; Bookstaff et al., 1990a). The cause of the androgenic deficiency is decreased testicular responsiveness to LH and increased pituitary

responsiveness to feedback inhibition by androgens and estrogens (Moore et al., 1989, 1991; Bookstaff et al., 1990a,b; Kleeman et al., 1990).

5.4.3. Conclusion

TCDD and related compounds have reproductive and developmental toxicity potential. It is assumed that the responses observed in animal studies are indicative of the potential for reproductive and developmental toxicity in humans. This is an established assumption in the risk assessment process for developmental toxicity (U.S. EPA, 1991). It is supported by the number of animal species and strains in which effects have been observed. The limited human data are consistent with an effect following exposure to TCDD or TCDD-like agents.

Many of the effects have been shown to be dose-response related. The effects on perinatal viability and male reproductive development are among the most sensitive effects reported, occurring at a single prenatal exposure range of as little as 0.05-0.075 μg/kg. In these studies, this was the lowest exposure level tested; thus a NOAEL has not been established for these endpoints.

In general, the structure-activity results are consistent with an Ah receptor-mediated mechanism for many of the developmental effects that are observed. The structure-activity relationship in laboratory mammals appears to be similar to that for Ah receptor binding. This is especially the case with cleft palate in the mouse. However, a direct relationship with Ah receptor binding is less clear for other effects, including those involving the nervous system.

Table 5-1. Relationship between maternal toxicity and prenatal mortality in laboratory mammals exposed to TCDD during gestation

Species/strain	Daily TCDD dose (μg/kg/day)	Cumulative TCDD dose (μg/kg)	Overt maternal toxicity[a]	Percent prenatal mortality[b]	Reference
Monkey/rhesus		0[c]	-	25	McNulty, 1984
		0.2	-	25	
		1	+[d]	81	
		5	+[d]	100	
Guinea pig/Hartley		0[e]	-	-	Olson and McGarrigle, 1991
		0.15	-	-	
		1.5	+	+	
Rabbit/New Zealand	0[f]	0	-	7	Giavini et al., 1982b
	0.1	1	-	12	
	0.25	2.5	+	42	
	0.5	5	+	22	
	1	10	+	100	
Rat/Wistar	0[f]	0	-	3	Khera and Ruddick, 1973
	0.125	1.25	-	1	
	0.25	2.5	-	2	
	0.5	5	-	9	
	1	10	±	8	
	1	10	+	36[g]	
	2	20	+	53[g]	
	4	40	+	100[g]	
Rat/Sprague-Dawley	0[f]	0	-	25	Sparschu et al., 1971
	0.03	0.3	-	21	
	0.125	1.25	-	15	
	0.5	5	+	41[g]	
	2	20	+	95[g]	
	8	80	+	100[g]	
Hamster/Golden Syrian		0[h]	-	-	Olson and McGarrigle, 1991
		1.5	-	-	
		3	-	-	
		6	-	-	
		18	-	58	
Mouse/CD-1	0[i]	0	-	7	Courtney, 1976
	25	250	-	6	
	50	500	-	13	
	100	1,000	-	14	
	200	2,000	+	87	
	400	4,000	+	97	

[a]Decreased body weight gain or marked edema compared with vehicle dosed controls. A (+) or (-) indicates the presence or absence of an effect.
[b]Percentage of absorptions plus late gestational deaths relative to all implantations. A (+) or (-) indicates the presence or absence of an effect.
[c]TCDD administered in single or divided doses between gestational days 20 and 40.
[d]Effects include thickening and reddening of the eyelids, weight loss, dryness and granularity of the skin, loss of hair, and in some cases anemia, purpura, and bleeding from the nose and mouth.
[e]Single dose of TCDD administered on gestational day 14.
[f]TCDD administered daily on days 6 to 15 of gestation.
[g]Significant at $p<0.05$.
[h]Single dose of TCDD administered on gestational days 7 or 9.
[i]TCDD administered daily on days 7 to 16 of gestation.

Source: Couture et al., 1990a.

Table 5-2. Developmental toxicity following gestational exposure to 2,3,7,8-TCDD

Species/Strain	Daily dose[a]	Treatment days[b]	Sacrifice day[b]	Maternal effects[c]	Embryo/fetal effects[c]	Reference
Mice/C57BL/6N	0, 1, or 3 μg/kg	10, 10-13	18	NR	Increase in cleft palate and hydronephrosis	Moore et al., 1973
Mice/C57BL/6N	0, 12, 17, or 22 μg/kg	10	18	Increase in liver-to-body weight ratio	Increase in cleft palate and hydronephrosis	Weber et al., 1985
Mice/C57BL/6N	0, 3, or 12 μg/kg	11, 10-13	18	Increase in liver-to-body weight ratio	Increase in cleft palate and hydronephrosis	Birnbaum et al., 1985
Mice/C57BL/6N	0 or 3 μg/kg	10-13	18	Increase in liver-to-body weight ratio	Increase in hydronephrosis	Birnbaum et al., 1986
Mice/C57BL/6N	0, 6, 9, 12, 15, or 18 μg/kg	10, 12	18	Increase in liver-to-body weight ratio and weight gain	Increase in cleft palate and hydronephrosis	Birnbaum et al., 1989
Mice/C57BL/6J	0 or 3 μg/kg (subcutaneous)	6-15	18	Increase in liver-to-body weight ratio	Increase in cleft palate and kidney anomaly	Courtney and Moore, 1971
Mice/C57BL/6J	20 μg/kg	10	17	Increase in liver-to-body weight ratio	Increase in cleft palate, hydronephrosis, and fetal body weight	Haake et al., 1987
Mice/C57BL/6J	0, 0.5, 1, 2, or 4 μg/kg	6-15	18	Increase in liver-to-body weight ratio	Increase in cleft palate, hydronephrosis, and fetal body weight	Silkworth et al., 1989
Mice/NMR	0.3, 3, 4, 5, or 9 μg/kg	6-15	18	NR	Increase in cleft palate and fetal mortality; decrease in fetal body weight	Neubert and Dillman, 1972
Mice/CF-1	0, 0.001, 0.01, 0.1, or 1.3 μg/kg	6-15	NR	None	Increase in cleft palate and hydronephrosis	Smith et al., 1976
Mice/DBA	0 or 3 μg/kg (subcutaneous)	6-15	18	Increase in liver-to-body weight ratio	Increase in cleft palate and kidney anomaly	Courtney and Moore, 1971
Mice/DBA	0, 0.5, 2, 4, or 8 μg/kg	6-15	18	Increase in liver-to-body weight ratio; decrease in thymus-to-body weight ratio	Increase in cleft palate and hydronephrosis	Silkworth et al., 1989

Table 5-2. Developmental toxicity following gestational exposure to 2,3,7,8-TCDD (continued)

Species/Strain	Daily dose[a]	Treatment days[b]	Sacrifice day[b]	Maternal effects[c]	Embryo/fetal effects[c]	Reference
Mice/CD-1	0, 1, or 3 μg/kg (subcutaneous)	6-15	17	None	Increase in cleft palate and kidney anomaly	Courtney and Moore, 1971
Mice/CD-1	0, 25, 50, 100, 200, or 400 μg/kg	6-15	17	Increase in liver-to-body weight ratio	Increase in cleft palate, hydronephrosis, and fetal mortality	Courtney, 1976
Rats/CD	0 or 0.5 μg/kg 2 μg/kg (subcutaneous)	6-15 9-10 or 13-14	20	None at 0.5 μg/kg NR at 2 μg/kg	Increase in kidney anomaly	Courtney and Moore, 1971
Rats/Sprague-Dawley	0, 0.125, 0.5, or 2 μg/kg	0-2	20	Decrease in weight gain	Decrease in fetal body weight	Giavini et al., 1982a
Rats/Sprague-Dawley	0.03, 0.125, 0.5, 2, or 8 μg/kg	6-15	21	Decrease in weight gain; toxicity	Increase in fetal mortality, resorptions, edema, and gastrointestinal hemorrhage	Sparschu et al., 1971
Rats/Wistar	0, 0.125, 0.25, 0.5, 1, 2, 4, 8, or 16 μg/kg	5-14	21	Toxicity	Increase in fetal mortality, edema and gastrointestinal hemorrhage; decrease in fetal weight	Khera and Ruddick, 1973
Guinea pigs/Hartley	0, 0.15, or 1.5 μg/kg	14	58	Increase in mortality; toxicity	Increase in fetal mortality	Olson and McGarrigle, 1990
Hamsters/Golden Syrian	0, 1.5, 3, 6, or 18 μg/kg	7, 9	15	Increase in liver-to-body weight ratio	Increase in fetal mortality, hydronephrosis, and renal congestion; decrease in thymus size	Olson and McGarrigle, 1990
Rabbits/New Zealand	0, 0.1, 0.25, 0.5, or 1 μg/kg	6-15	28	Decrease in weight gain; toxicity	Increase in fetal mortality and resorptions; extra ribs	Giavini et al. 1982b

Table 5-2. Developmental toxicity following gestational exposure to 2,3,7,8-TCDD (continued)

Species/Strain	Daily dose[a]	Treatment days[b]	Sacrifice day[b]	Maternal effects[c]	Embryo/fetal effects[c]	Reference
Monkeys/rhesus	0, 5, 25, 50, or 500 ppt 7 months before and during pregnancy	Chronic	--	Increase in mortality; toxicity	Increase in fetal mortality	Allen et al., 1979; Bowman et al., 1989
Monkeys/rhesus	0, 0.2[d], 1[d], 1[e], or 5[d] µg/kg	20-40	--	Increase in mortality; toxicity	Increase in fetal mortality	McNulty, 1985

[a]Oral exposure unless otherwise noted.
[b]All days adjusted to reflect plug day—gestation day 0.
[c]Effects reported are only those that were statistically significant.
[d]Cumulative dose divided into nine oral doses administered between days 20 and 40 of gestation; two to four monkeys/dose.
[e]Three animals given single oral dose, on either gestation days 25, 30, 35, or 40; 12 monkeys total.
NR = Not reported.

Source: Couture et al., 1990a.

Table 5-3. TCDD responsiveness of palatal shelves from the mouse, rat, and human in organ culture

Species	Molar concentration of TCDD		
	Induction of epithelial proliferation and prevention of epithelial-to-mesenchyme transformation		
	LOEL	EC_{100}	Cytotoxicity
Mouse	1×10^{-13}	5×10^{-11}	1×10^{-10}
Rat[a]	1×10^{-10}	1×10^{-8}	1×10^{-7}
Human[b]	5×10^{-11}	1×10^{-8}	1×10^{-7}

[a]At the highest concentration tested, 60% of the palatal shelves failed to undergo programmed cell death.
[b]One of four shelves responded by failing to undergo programmed cell death at 5×10^{-11} M.

Source: Birnbaum, 1991.

Table 5-4. Relative teratogenic potency of halogenated aromatic hydrocarbon congeners in C57BL/6 mice

Congener	Relative potency (ED_{50} TCDD/ED_{50} congener)	
	Cleft palate	Hydronephrosis
2,3,7,8-TCDD	1.000	1.000
2,3,7,8-TBDD	0.235	0.444
2,3,7,8-TBDF	0.100	0.333
2,3,4,7,8-PeCDF	0.095	0.057
2,3,7,8-TCDF	0.049	0.021
1,2,3,7,8-PeCDF	0.026	0.074
1,2,3,4,7,8-HxCDF	0.010	0.049
2,3,4,7,8-PeBDF	0.005	0.009
1,2,3,7,8-PeBDF	0.004	0.018
2,3,4,5,3′,4′-HxCB	0.0000287	0.0000894

Source: Weber et al., 1985; Birnbaum et al., 1987a,b, 1991.

Table 5-5. Cross-species comparison of NOAELs and LOAELs for TCDD developmental toxicity in fish

Species	Effect	Exposure	Egg dose	Effect level	Reference
Lake trout	Sac fry mortality	Static waterborne	34 ng/kg	NOAEL	Walker et al., 1991
Japanese medaka	Lesions[a]	Static waterborne	<100 ng/kg	NOAEL	Wisk and Cooper, 1990a
Rainbow trout	Sac fry mortality	Single injection	194 ng/kg	NOAEL	Walker et al., 1992
Lake trout	Sac fry mortality Sac fry mortality	Static waterborne Static waterborne	40 ng/kg 55 ng/kg	LOAEL LOAEL	Spitsbergen et al., 1991 Walker et al., 1991
Rainbow trout	Sac fry mortality	Single injection	291 ng/kg	LOAEL	Walker et al., 1992
Japanese medaka	Lesions[a]	Static waterborne	300 ng/kg	LOAEL	Wisk and Cooper, 1990a

[a]Consist of a spectrum of effects including hemorrhage in various areas, pericardial edema, collapse of the yolk sphere, cessation of blood flow throughout the animal, and embryo mortality.

Table 5-6. Cross-species comparison of NOAELs and LOAELs for TCDD developmental toxicity in birds

Species	Effect	Exposure	Egg dose	Effect level	Reference
Ring-necked pheasant	Embryo mortality	Single injection	100 ng/kg	NOAEL	Nosek et al., 1993
Eastern bluebird	Embryo mortality	Single injection	1,000 ng/kg	NOAEL	Thiel et al., 1988 Martin et al., 1989
Chicken	Cardiac malformations	Single injection	9 ng/kg[a]	LOAEL	Cheung et al., 1981a,b
Chicken	Embryo mortality	Single injection	240 ng/kg	LD_{50}	Allred and Strange, 1977
Ring-necked pheasant	Embryo mortality	Single injection	1,000 ng/kg	LOAEL	Nosek et al., 1993
Ring-necked pheasant	Embryo mortality	Single injection	1,354 ng/kg[b]	LD_{50}	Nosek et al., 1993
Ring-necked pheasant	Embryo mortality	Single injection	2,182 ng/kg[c]	LD_{50}	Nosek et al., 1993
Eastern bluebird	Embryo mortality	Single injection	10,000 ng/kg	LOAEL	Thiel et al., 1988

[a]Chi-square analysis of the data in Table 1 of Cheung et al. (1981b) demonstrated that the incidence of cardiac malformations in all embryos examined at dose levels of 1.6 pmol/egg or greater are significantly ($p<0.05$) increased compared to the incidence in the control group designated "all examined." Assuming a 55 g egg weight, 1.6 pmol/egg corresponds to a TCDD egg burden of 9 ng/kg.
[b]Injected into the egg albumin.
[c]Injected into the egg yolk.

Table 5-7. Cross-species comparison of NOAELs and LOAELs for TCDD developmental toxicity in mammals

Species	Effect	Exposure	Maternal dose	Effect level	Reference
Monkey	Prenatal mortality	Multiple dose	22 ng/kg, 9×, gd 20-40	NOAEL	McNulty, 1984
Rat	Prenatal mortality	1 ng/kg/day	27 ng/kg[a], chronic	NOAEL	Murray et al., 1979
Rat	Prenatal mortality	Multiple dose	30 ng/kg/day, gd 6-15	NOAEL	Sparschu et al., 1971
Mouse	Hydronephrosis	Multiple dose	100 ng/kg/day, gd 6-15	NOAEL	Smith et al., 1976
Mouse	Cleft palate	Multiple dose	300 ng/kg/day, gd 6-15	NOAEL	Neubert and Dillman, 1972
Monkey	Object learning	0.126 ng/kg/day	19 ng/kg[a], subchronic	LOAEL	Schantz and Bowman, 1989
Rat	Accelerated eye opening	Single	50 ng/kg, gd 15	LOAEL	Gray et al., 1997a
Rat	Reduced ejaculated sperm numbers	Single	50 ng/kg, gd 15	LOAEL	Gray et al., 1997a
Rat	Reduced ventral prostate weight	Single	64 ng/kg, gd 15	LOAEL	Mably et al., 1992a
Rat	Reduced cauda epididymal sperm numbers	Single	64 ng/kg, gd 15	LOAEL	Mably et al., 1992c
Rat	Partial feminization of sexual behavior (male)	Single	160 ng/kg, gd 15	LOAEL	Mably et al., 1992b
Rat	Vaginal thread malformation	Single	200 ng/kg, gd 15	LOAEL	Gray et al., 1997b
Rat	Hypospadias (female)	Single	200 ng/kg, gd 15	LOAEL	Gray et al., 1997b
Rat	Cleft phallus (female)	Single	800 ng/kg, gd 15	LOAEL	Gray et al., 1997b
Rat	Partial demascu-linization of sexual behavior (male)	Single	64 ng/kg, gd 15	LOAEL	Mably et al., 1992b
Monkey	Prenatal mortality	0.642 ng/kg/day Multiple dose	97 ng/kg[a], subchronic 111 ng/kg, 9×, gd 20-40	LOAEL LOAEL	Schantz and Bowman, 1989 McNulty, 1984
Rabbit	Extra ribs	Multiple dose	100 ng/kg/day, gd 6-15	LOAEL	Giavini et al., 1982b

Table 5-7. Cross-species comparison of NOAELs and LOAELs for TCDD developmental toxicity in mammals (continued)

Species	Effect	Exposure	Maternal dose	Effect level	Reference
Rat	Fetal growth	Multiple dose	125 ng/kg/day, gd 6-15	LOAEL	Sparschu et al., 1971
Rabbit	Prenatal mortality	Multiple dose	250 ng/kg/day, gd 6-15	LOAEL	Giavini et al., 1982b
Rat	Prenatal mortality	10 ng/kg/day Multiple dose	270 ng/kg[a], chronic 500 ng/kg/day, gd 6-15	LOAEL LOAEL	Murray et al., 1979 Sparschu et al., 1971
Mouse	Hydronephrosis	Multiple dose	500 ng/kg/day, gd 6-15	LOAEL	Silkworth et al., 1989
Guinea pig	Prenatal mortality	Single dose	1,500 ng/kg, gd 14	LOAEL	Olson and McGarrigle, 1992
Hamster	Thymic hypoplasia	Single dose	1,500 ng/kg, gd 7 or 9	LOAEL	Olson and McGarrigle, 1992
Mouse	Cleft palate	Multiple dose	3,000 ng/kg/day, gd 6-15	LOAEL	Courtney and Moore, 1971
Hamster	Prenatal mortality	Single dose	18,000 ng/kg/day, gd 7 or 9	LOAEL	Olson et al., 1990
Mouse	Prenatal mortality	Single dose	24,000 ng/kg/day, gd 6	LOAEL	Couture et al., 1990b

[a]Maternal body burdens of TCDD at the time of conception were calculated by assuming a one-compartment open model and half-life for whole body TCDD elimination of 400 days in the monkey (McNulty et al., 1982) and 23.7 days in the rat (Rose et al., 1976). A bioavailabilty of 86.1 percent was used in the monkey and rat (Rose et al., 1976). The daily dietary exposure levels in rhesus monkeys were approxiately 5 and 25 ppt at the NOAEL and LOAEL doses, respectively. Rhesus monkeys were exposed to these levels of TCDD for 7 months prior to conception. At this time (0.525 half-lives) the cumulative amount of TCDD in rhesus monkeys was 30.5 percent of the calculated steady-state level. Rats were exposed to the indicated daily doses of TCDD for a period of 90 days (3.8 half-lives) prior to conception. At this time the cumulative amount of TCDD in rats was 92.8 percent of the calculated steady-state level.
gd=gestational day.

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6. CARCINOGENICITY OF TCDD IN ANIMALS

6.1. INTRODUCTION

Additional scientific information on the use of animal cancer data for estimating human risks from 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has become available since the 1988 health risk assessment for dioxin. Much of the data on tumor incidence in experimental animals available in 1988 demonstrated that TCDD is a carcinogen at multiple sites in both sexes of rats and mice. Some of the cancers occurred following particularly low doses. Since 1988, TCDD has been shown to be a carcinogen in hamsters, and some of the tumor incidence data in rat liver have been reevaluated.

There is considerable evidence that TCDD does not damage DNA directly through the formation of DNA adducts. Mechanisms have been proposed that support the possibility that TCDD might be indirectly genotoxic, either through the induction of oxidative stress or by altering the DNA-damaging potential of some endogenous compounds, including estrogens. In addition, there have been numerous reports on TCDD-induced modifications of growth factor signaling pathways and cytokines in experimental animals and cell systems. Some of the altered systems include those for epidermal growth factor, transforming growth factor alpha, estrogen, glucocorticoids, tumor necrosis factor-alpha, interleukin 1-beta, plasminogen inactivating factor-2, and gastrin. Many of these pathways are involved in cell proliferation and differentiation and provide plausible avenues for researching the mechanisms responsible for the carcinogenic actions of TCDD. These effects are consistent with the generally accepted conclusion that TCDD acts as a "tumor promoter" in multistage models for chemical carcinogenesis and is virtually devoid of initiating activity in these models. It is important to note that "tumor promotion" is an operational and not a mechanistic term and that multiple mechanisms of tumor promotion are likely. Each of these mechanisms may be fundamentally different from the others.

There is a scientific consensus that most, if not all, of the biochemical and toxic effects of TCDD require an initial interaction with its cognate receptor, the aryl hydrocarbon (Ah). The properties of the Ah receptor (AhR) and the mechanisms whereby this receptor regulates gene expression are described in more detail in other chapters. However, formation of the AhR-TCDD complex is only the first of many steps involved in the production of a biochemical and toxic effect. Although there is considerable knowledge of details regarding activation of expression of the TCDD-inducible cytochrome P450 1A1 by the AhR, we still know very little about many components of AhR-mediated responses and their relationship to the development of adverse responses such as cancer. It is clear, however, that tissue- and cell-specific factors other than the AhR must be involved in determining tissue responses once TCDD binds the AhR.

Evaluation of dose-response is one of the more important issues that affect dioxin risk assessments. The focus of this controversy centers on the shape of the dose-response curve, particularly at low doses, and whether the effects of dioxin may exhibit operational thresholds. It now appears that for some responses there is a proportional relationship between receptor occupancy and response, which is evidenced by a linear relationship between target dose and effect over a wide dose range. However, different dose-response relationships are seen for different responses, so it is probably inappropriate to use a single surrogate marker to estimate dioxin's risks. Furthermore, these data reveal there is no unifying dose-response relationship for all AhR-mediated events. A more detailed evaluation of dose-response relationships for TCDD-modulated responses is described in Chapter 8.

Another controversial area in risk assessment is whether experimental animal models are appropriate for estimating human risks. There has been increasing evidence that biochemical and toxic responses resulting from human exposure to TCDD and its structural analogues appear to be similar to responses in experimental animals. However, it may be possible that humans are sensitive or resistant to some responses. There also is increasing awareness that interindividual variations in human responses to dioxin are a complicating factor in risk assessment, as it appears that there are individuals who are responsive and nonresponsive to numerous environmental chemicals, including TCDD.

Much of the controversy surrounding dioxin risk assessment reflects the selection of mathematical models: threshold, linear multistage, or others. We now know considerably more about the mode of action of dioxin, and this knowledge has allowed the construction of biologically based models that may reduce some of the uncertainty in current risk estimates.

These approaches and advances in our understanding of the mechanisms of tumor promotion and dose-response relationships will be discussed in more detail in Chapter 8, Dose-Response Modeling for 2,3,7,8 TCDD.

6.2. ANIMAL BIOASSAYS FOR CANCER

Long-term studies for carcinogenicity of TCDD have been conducted in several species (van Miller et al., 1977; Kociba et al., 1978; NTP, 1982a; Rao et al., 1988; Johnson et al., 1992). All studies have produced positive results. It is clear that TCDD is a multi-site carcinogen in both sexes of rats and mice (U.S. EPA, 1985; Huff et al., 1991; Zeise et al., 1990, IARC 1997). It is a carcinogen in the hamster (Rao et al., 1988), which is considered the most resistant species to the acute toxic effects of TCDD, and a preliminary report indicates that TCDD is also carcinogenic in fish (Johnson et al., 1992). The important studies are summarized in Table 6-1, including information on species, sex, and tumor site.

The 2-year rodent bioassays conducted by Dow Chemical (Kociba et al., 1978) and the National Toxicology Program (NTP, 1982a) studies are the most comprehensive to date and most relevant to risk characterization, and are described in the following paragraphs.

6.2.1. Kociba Study

The most cited cancer bioassay for TCDD was published by Kociba et al. (1978). It was a lifetime feeding study of male and female Sprague-Dawley rats using doses of 0, 1, 10, and 100 ng/kg/day. There were 50 males and 50 females in each group. Data derived from these studies have been used as the basis for many risk assessments for TCDD.

The most significant finding was an increase in hepatocellular hyperplastic nodules and hepatocellular carcinomas in female rats. The incidence of hepatocellular carcinomas was significantly elevated above the control incidence at the 100 ng/kg/day dose, whereas increased incidence of hyperplastic nodules was evident in the 10 ng/kg/day dose group.

There have been two reevaluations of slides of liver sections from the Kociba study (Squire, 1980; Sauer, 1990; Goodman and Sauer, 1992). The Squire review was requested by EPA as an independent review of the slides. The Sauer review was carried out using refined criteria for the diagnosis of proliferative hepatocellular lesions (Maronpot et al., 1986, 1989). Liver tumor incidences for the three evaluations are compared in Table 6-2. Although there are some quantitative differences between the evaluations, the lowest detectable effect for liver tumor incidence is consistently observed at 10 ng/kg/day.

In the 10 ng/kg/day dose group, significant increases in the incidence of hyperplastic nodules of the liver were observed in female rats (18/50 in the Kociba evaluation, 27/50 in the Squire evaluation). Two females (2/50) had hepatocellular carcinomas. In the 1990 reevaluation (Sauer, 1990; Goodman and Sauer, 1992), nine females (9/50) were identified with hepatocellular adenomas and none with carcinomas; thus only one-third of the previously observed “tumors” were identified when using the refined diagnostic criteria.

In addition to nodules in the liver, increased incidence of stratified squamous cell carcinoma of the tongue and nasal turbinates/hard palate, and keratinizing squamous cell carcinoma of the lung were also observed in female rats in the 100 ng/kg/day dose group. One possible cause for the induction of lung tumors in the Kociba feeding study may have been the inhalation of dosed feed into the lungs. However the promotion of lung tumors has been observed in mice treated systemically by i.p. injections of TCDD (Beebe et al 1995). In addition the induction of hyperplastic and metaplastic lesions in rats has been observed following chronic oral gavage treatment with TCDD (Tritscher et al 2000). More recently chronic oral exposure to HCDD resulted in the induction of lung tumors in treated female rats (Rozman 2000). These

data indicate that the induction of lung tumors in the Kociba was most likely primarily the result of systemic chronic dietary exposure to TCDD rather than due to a localized inhaled exposure.

There was no detectable increase in liver tumor incidences in male rats in any of the dose groups (Table 6-1). The mechanism responsible for dioxin-mediated sex specificity for hepatocarcinogenesis in rats is not clear, but may involve ovarian hormones (Lucier et al., 1991). This is discussed in Section 6.3 on tumor promotion.

Although there was no increase in liver tumors in male rats in this study, in the 100 ng/kg/day group there was an increased incidence of stratified squamous cell carcinoma of the hard palate/nasal turbinate, stratified squamous cell carcinoma of the tongue, and adenoma of the adrenal cortex.

Kociba et al. (1978) had reported that chemically related increases in preneoplastic or neoplastic lesions were not found in the 1 ng/kg/day dose group. However, Squire identified two male rats in the 1 ng/kg/day dose group with squamous cell carcinoma of the nasal turbinates/hard palate, and one of these male rats had a squamous cell carcinoma of the tongue. These are both rare tumors in Sprague-Dawley rats, and these sites are targets for TCDD, implying that 1 ng/kg/day may not represent a no-observed-effect level (NOEL). However, no dose-response relationships were evident for tumors at these sites (Huff et al., 1991)

One of the more interesting findings in the Kociba bioassay was a TCDD-induced reduction in the incidence of spontaneous tumors including pituitary adenoma, benign tumor of the uterus, benign mammary neoplasm and mammary carcinoma in female rats, and acinar adenoma of the pancreas and adrenal pheochromocytoma in male rats. For example, carcinomas of the mammary gland occurred in 8 of 86 control female rats, whereas the incidence was 0/49 in the 1 ng/kg/day dose group. However, the incidence of mammary gland carcinomas in the medium- and high-dose groups was similar to that of control rats, suggesting that protection against breast cancer might be a low-dose effect. A relationship between body-weight reduction and spontaneous cancer incidence in rodents has been observed across numerous studies (Rao et al., 1987). This suggest that the reduction in the incidence of the spontaneous tumors by TCDD is likely related to the TCDD-induced reduction in body-weight gain. These findings, coupled with the sex specificity of TCDD-induced liver tumors in rats, highlight that the carcinogenic actions of TCDD may involve a complex interaction of hormonal factors. Moreover, it appears likely that tissue- and cell-specific factors modulate TCDD/hormone actions relevant to cancer.

There is considerable controversy concerning the possibility that TCDD-induced liver tumors are a consequence of cytotoxicity. Goodman and Sauer (1992) have extended the reevaluation of the Kociba slides to include liver toxicity data and have reported a correlation between the presence of overt hepatotoxicity and the development of hepatocellular neoplasms in female rats. With the exception of two tumors in controls and one each in the low- and

mid-dose groups, all liver tumors occurred in livers showing clear signs of toxicity. However, male rat livers exhibit cytotoxicity in response to high TCDD doses, yet they do not develop liver tumors. Moreover, both intact and ovariectomized female rats exhibit liver toxicity in response to TCDD, yet TCDD is a more potent promoter in intact but not ovariectomized rats (Lucier et al., 1991). Therefore, if cytotoxicity is playing a role in liver tumorigenesis, other factors must also be involved. Also, there is little information on the role of cytotoxicity in TCDD-mediated cancer at other sites such as the lung and thyroid.

6.2.2. NTP Study

The NTP study was conducted using Osborne-Mendel rats and B6C3F1 mice (NTP, 1982a). Groups of 50 male rats, 50 female rats, and 50 male mice received TCDD as a suspension in corn oil:acteone (9:1) by gavage twice each week (Tuesday and Friday) to achieve doses of 0, 10, 50, or 500 ng TCDD/kg/week for 2 years; groups of 50 female mice were treated similarly to achieve doses of 0, 40, 200, or 2,000 ng/kg/week. These exposures correspond to daily averaged doses of 1.4, 7.1, or 71 ng/kg/day for rats and male mice and to doses of 5.7, 28.6, or 286 ng/kg/day for female mice, so the doses were comparable to those used in the Kociba feeding study. There were no statistically significant dose-related decreases in survival in any sex-species group.

Tumor data in the NTP bioassay are summarized in Tables 6-3 and 6-4. TCDD-induced malignant liver tumors occurred in the high-dose female rats and in male and female mice. These can be considered to result from TCDD exposure because they are relatively uncommon lesions in control Osborne-Mendel rats (male, 1/208; female, 3/208), are seen in female rats and mice of both sexes, and their increasing incidence with increasing dose is statistically significant (Cochran-Armitage trend test, p=0.004). Because liver tumors were increased in both sexes of mice, this effect is not female-specific as was observed in rats. Interestingly, liver tumor incidences were decreased in female rats in both the NTP and Kociba low doses (not statistically significant compared with controls). For example, the combined control incidence data were 11/161 (7%) compared with 4/99 (4%) in the low-dose group.

The incidences of thyroid gland (follicular cell) tumors were increased in all three dose groups in male rats. Because the responses in the two highest dose groups are highly significant, the statistically significant elevation of incidence in the lowest dose group (Fisher exact p-value=0.042) is considered to be caused by exposure to TCDD. Thus, for this study the lowest-observed-effect level (LOEL) is 1.4 ng/kg/day and a NOEL was not achieved within the specified dose range, suggesting that thyroid tumor incidence may be the most sensitive site for TCDD-mediated carcinogenesis. Because 71 ng/kg/day is above the maximum tolerated dose

(MTD) (Huff et al., 1991), thyroid tumors occur at doses more than 50 times lower than the MTD.

TCDD-induced neoplasms of the adrenal gland were observed in the 7.1 ng/kg/day/dose group in male rats and in high-dose female rats. Fibrosarcomas of the subcutaneous tissue were significantly elevated in high-dose female mice and female rats. One additional tumor type, lymphoma, was seen in high-dose female mice. Lung tumors were elevated in high-dose female mice; the increase was not statistically significant when compared with concurrent controls, but the increase was dose related (Cochran-Armitage trend test, p=0.004).

Therefore, TCDD is a multisite complete carcinogen (Huff, 1992) and induced neoplasms in rats and mice of both sexes. As was observed in the Kociba study (Kociba et al., 1978), liver tumors were observed with greater frequency in treated female rats, but in male rats the thyroid appears to be the most sensitive (increased tumor incidence at doses as low as 1.4 ng/kg/day).

6.2.3. Syrian Golden Hamster

Groups of 10 to 24 male Syrian Golden hamsters were given two to six intraperitoneal or subcutaneous injections of TCDD over a 4-week period at doses of 0, 50, or 100 µg TCDD/kg in dioxane (Rao et al., 1988). The experiments were terminated after 12 to 13 months. The 100 µg/kg groups (total dose of 600 µg/kg) from both injection routes developed squamous cell carcinomas of the skin in the facial region: 4/18 (22%) from the intraperitoneal injection and 3/14 (21%) from the subcutaneous injection. The lesions were large (1.5 to 3 cm) with extensive necrosis, and some metastasized to the lung. The earliest neoplasms were detectable 8 months after the initial injection. Similar lesions were not seen in hamsters receiving two intraperitoneal injections of 100 µg/kg TCDD or six subcutaneous injections of dioxane vehicle, and none have been reported over the past 10 years in this laboratory. An extensive study by Pour et al. (1976) identified only 1 skin papilloma in 533 control Syrian hamsters. This report demonstrates that the hamster, a nonresponsive species for acute toxic effects, is susceptible to the carcinogenic actions of TCDD at doses well below the MTD.

6.2.4. B6C3 and B6C Mice

In a study by Della Porta et al. (1987), TCDD was administered intraperitoneally in corn oil at doses of 0, 1, 30, and 60 µg/kg to groups of 89 to 186 B6C3 and B6C mice of both sexes once weekly for 5 weeks starting at day 10 of life, and the animals were observed until 78 weeks of age. Histopathological observations were limited to the liver, kidney, and organs with apparent or suspected pathological changes. Thymic lymphomas were induced at the 60 µg/kg level in both sexes of both hybrids and at 30 µg/kg in all but female B6C3 mice. Neoplasms of

the liver occurred in male B6C3 mice at 30 µg/kg and female B6C3 mice at 60 µg/kg. In a separate experiment, groups of 42 to 50 B6C3 mice were exposed to 0, 2.5, and 5.0 µg/kg TCDD in corn oil by gavage once weekly for 52 weeks starting at 6 weeks of age. The study was stopped at 110 weeks. Increased incidences of liver tumors were related to TCDD exposure at both dose levels.

6.2.5. Fish

A preliminary study, reported in abstract form only, examined the carcinogenicity of TCDD in medaka (*Oryzias latipes*) immersed in 2,3,7,8 TCDD-treated water for 28 days, followed by immersion in clean water for up to 8 months (Johnson et al., 1992). Exposure to 33.9 ppq TCDD led to an increase in tumors at multiple sites including gills, thyroid, and swim bladder. Total body burden of TCDD in these fish was 2 ppb (Johnson et al., 1992).

6.2.6. Carcinogenicity of Related Compounds

A mixture of two isomers of hexachlorodibenzo-*p*-dioxin (HCDD) (1,2,3,6,7,8 and 1,2,3,7,8,9) was given by gavage twice weekly for 2 years to Osborne-Mendel rats and B6C3F1 mice (NTP, 1980). The doses of HCDD were 0, 1.25, 2.5, or 5 µg/kg/week in rats and male mice. Doses for female mice were 0, 2.5, 5, and 10 µg/kg/week. There was no effect of administration of HCDD on survival of either sex of rats or mice (NTP, 1980). Results revealed that HCDD increased liver tumors in both sexes of rats and mice, although female rats seemed to be more sensitive than male rats (significant increases detected in female rats in the 1.25 µg/kg/week dose group, equivalent to 180 ng/kg/day). Therefore, HCDD is approximately 1/20 as potent a liver carcinogen as TCDD.

Dermal applications of the HCDD mixture described above (NTP, 1982b) were given to Swiss Webster mice for 104 weeks (three times per week). For the first 16 weeks, doses of 5 ng/application were used. Thereafter, doses of 10 ng/application were used. No HCDD-exposure-related carcinogenic responses were noted.

Dibenzo-*p*-dioxin given in the diet for 2 years at concentrations of 0, 5,000, and 10,000 ppm did not increase carcinogenic responses in Osborne-Mendel rats or B6C3F1 mice (NCI, 1979a). 2,7-Dichlorodibenzo-*p*-dioxin (DCDD) in the diet of Osborne-Mendel rats for 110 weeks or B6C3F1 mice for 90 weeks at levels of 0, 5,000, or 10,000 ppm did not increase neoplasms in male or female rats or in female mice. In male mice, increased incidences of lymphoma or hemangiosarcoma were observed in the low-dose group and neoplasms of the liver were observed in both dose groups (NCI, 1979b). The more highly chlorinated dibenzo-*p*-dioxins (CDDs) and dibenzofurans (CDFs) have not been studied in long-term animal

cancer bioassays. Many of the CDDs and CDFs bioaccumulate and exhibit toxicities similar to those of TCDD and are considered to be carcinogens (EPA Science Advisory Board, 1989).

There are no carcinogenicity data on individual congeners of coplanar (dioxin-like) polychlorinated biphenyls. However, laboratory studies found statistically significant increased incidences of liver tumors in rats ingesting Aroclor 1260 or Clophen A60. Significant increases in gastric cancer, leukemia, and lymphoma were found in rats ingesting Aroclor 1254. Partial lifetime studies found precancerous liver lesions in rats and mice ingesting PCB mixtures of high or low chlorine content. More recent studies have compared the carcinogenicity of several Aroclor mixtures (Mayes et al., 1998). The Aroclor 1254 mixture contains the highest level of dioxin-like coplanar PCBs of these mixtures. All Aroclors tested, 1016, 1242, 1254, and 1260, resulted in an increased incidence of liver neoplasms in female rats. However, only Aroclor 1260 at high doses was carcinogenic in males. In addition, Aroclor, 1242, 1254, and 1260 induced thyroid tumors in male rats. Analysis of liver levels of specific PCB congeners suggests that in males the induction of tumors is dependent on total PCB content, whereas the liver tumor incidence in females is dependent upon the total TCDD toxic equivalents level (TEQ) as a result of accumulation of dioxin-like PCBs from the Aroclor mixture (Silkworth et al., 1997).

With regard to studies of the carcinogenicity of dioxin-like compounds, including PCBs, the National Toxicology Program is currently conducting 2-year carcinogenicity bioassays of multiple dioxin-like compounds and mixtures in female Sprague-Dawley rats (van Birgelen et al., 1997). Compounds under study include TCDD 2,3,4,7,8-pentachlorodibenzofuran (PeCDF), 3,3',4,4',5-pentachlorobiphenyl (PCB 126, a coplanar dioxin-like PCB), 2,3',4,4'5 -pentachlorobiphenyl (a mono-ortho PCB, PCB 118), 2,2',4,4',5,5'-hexachlorobiphenyl (a non-dioxin-like PCB, PCB 153), a binary mixture of a non-dioxin-like (PCB 153) and a dioxin-like PCB (PCB 126), and a mixture of dioxin-like compounds (TCDD, PeCDF, and PCB126).

6.3. INITIATION/PROMOTION STUDIES

The multistage nature of chemical carcinogenesis is being defined by an increasing understanding of the discrete steps required to produce a genetically altered cell that is clonally expanded and ultimately progresses to a tumor (IARC, 1992; Barrett and Wiseman, 1987; Swenberg et al., 1987; Barrett, 1992) (Figure 6-1). Briefly, the process involves damage to a specific site on DNA, a round of cell replication to fix that damage into the genome, clonal expansion of the genetically altered cells (tumor promotion), and additional genetic damage and rounds of cell replication (tumor progression). Figure 6-1 schematizes the multistage nature of cancer. The birth and death rates of genetically altered cells compared with normal cells are the centerpiece of risk assessment models that recognize the multistage nature of chemical carcinogenesis (Moolgavkar and Knudson, 1981; Portier, 1987).

The roles of proto-oncogene activation and tumor suppression gene inactivation have provided clues in attempts to discern discrete steps in carcinogenesis. It is also clear that cell proliferation is an essential component of chemical carcinogenesis, for without it, DNA damage would not be fixed into the genome and clonal expansion of genetically altered cells would not occur.

Concurrent with our increased understanding of the mechanistic underpinnings of chemical carcinogenesis, multistage models have been developed to identify the particular stage or stages in which carcinogens act to increase tumor incidence.

There is a wealth of information on liver initiation/promotion protocols in the scientific literature (Pitot and Sirica, 1980; Farber, 1984; Pitot and Campbell, 1987). These protocols frequently employ a single initiating dose of a chemical that damages DNA, followed by enhancement of cell replication (partial hepatectomy or cytotoxicity) to fix that damage into the genome (initiation), and then chronic exposure to a chemical that produces clonal expansion of the genetically altered cells (promotion). Increased tumor incidence is produced by chemicals that act at either stage. It is important to note that "initiation" and "promotion" are operational and not mechanistic terms because both stages are likely to be composed of multiple steps, and the mechanisms are not mutually exclusive. Nevertheless, the protocols have provided valuable information in our attempts to understand chemical carcinogenesis. Detailed descriptions of initiation/promotion protocols in liver and skin are provided elsewhere (Pitot and Campbell, 1987; Dragan et al., 1991; Pitot et al., 1987; Farber, 1984; Slaga et al., 1982; Peraino et al., 1981; Ito et al., 1980).

6.3.1. TCDD Is Not a Direct Genotoxic Agent

There is substantial evidence that TCDD is not a direct genotoxic agent. Because "genotoxic" and "nongenotoxic" are controversial and often misused terms, it is prudent to describe accurately the scientific criteria used to call a chemical "genotoxic" or "nongenotoxic" (IARC, 1992). Some of the criteria for designating TCDD a nongenotoxic agent are that it does not bind covalently to DNA (does not form DNA adducts). Although one study detected radioactivity associated with crude DNA preparations after in vivo exposure, no study that has rigorously looked for TCDD-DNA adducts has been positive. TCDD is negative in short-term tests for genotoxicity and is a potent promoter and weak initiator in multistage models for chemical carcinogenesis. In a another study (Turteltaub et al., 1990) using accelerator mass spectrometry, DNA adducts were not detected in rodent tissue following exposure to TCDD. This method is extraordinarily sensitive, being capable of detecting one adduct in 10^{12} normal nucleotides. Randerath et al. (1988) were unable to detect TCDD-related DNA adducts by the sensitive ^{32}P postlabeling method (limit of detection of one adduct in 10^{9} normal nucleotides).

For comparison, approximately one adduct in 10^6 normal nucleotides is found in rodent tissues following carcinogenic doses of benzo(a)pyrene (7,8-diol-9,10 epoxide deoxyguanosine DNA adduct) or methylnitrosourea (O^6 methylguanine).

Another criterion for designating TCDD a "nongenotoxic carcinogen" is that numerous studies have demonstrated that TCDD is negative in the *Salmonella*/Ames test in the presence or absence of a mixed-function oxidase (MFO) activating system. These negative studies have encompassed 13 different bacterial strains with tests performed in 9 laboratories (Wassom et al., 1977; Kociba, 1984; IARC, 1982; Giri, 1987; Shu et al., 1987). Using its battery of tests for genetic toxicity, the NTP (1984) concluded that TCDD was nonmutagenic. Additionally, several scientific panels have stated that false negatives for TCDD genetic toxicity are highly unlikely (EPA Science Advisory Board, 1984). TCDD has been found to promote the transformation of C3H/10T1/2 cells; it was concluded that this response did not reflect TCDD's ability to directly damage DNA (Abernethy et al., 1985). In human populations accidentally or occupationally exposed to TCDD, there is no consistent evidence for increased frequencies of chromosomal aberrations in workers exposed to TCDD (Shu et al., 1987).

However, Yang et al. (1992) demonstrated that immortalized human keratinocytes cultured with TCDD were neoplastically transformed, as evidenced by tumorigenic activity of those cells in nude mice. This response is characteristic of genotoxic carcinogens and occurred at a low TCDD concentration (0.1 nM). For comparison, induction of CYP1A2 in these same cells was not detected until a dose of 3 nM was used (Yang et al., 1992).

6.3.2. Two-Stage Models of Liver Tumor Promotion by TCDD

TCDD is designated as a nongenotoxic carcinogen because it is negative in most assays for DNA damaging potential, a potent tumor promoter, and a weak initiator or noninitiator in two-stage models for liver (Pitot et al., 1980; Graham et al., 1988; Lucier et al., 1991; Clark et al., 1991a; Flodstrom and Ahlborg, 1991) and skin (Poland et al., 1982).

Pitot et al. (1980) were the first to report that TCDD was a potent liver tumor promoter in female rats. Animals were initiated with a single dose of diethylnitrosamine (DEN)(10 mg DEN/kg) 24 hours following a 2/3 hepatectomy, followed by chronic TCDD exposure (0.14 and 1.4 µg/kg subcutaneously once every 2 weeks for 7 months). When expressed as a daily averaged dose, these doses are equivalent to 10 and 100 ng TCDD/kg/day (the medium and high dose in the Kociba bioassay). Histological evaluation revealed that five of seven animals that had received DEN and 100 ng TCDD/kg/day had hepatocellular carcinomas. No liver tumors were evident in rats receiving DEN only, DEN/low-dose TCDD, or TCDD only (high or low dose). Altered hepatocellular foci (AHF) exhibiting altered expression of the marker enzymes glucose-6-phosphatase, canalicular ATPase, and gamma glutamyl transpeptidase were also

evaluated in this study. AHF are considered to represent preneoplastic lesions because increases in AHF are associated with liver cancer in rodents (Maronpot et al., 1989; Popp and Goldsworthy, 1989; Pitot et al., 1989; Williams, 1989). The AHF data were consistent with the tumor data in that a large proportion of the liver was occupied by AHF (43%) in animals initiated with DEN and the high dose of TCDD. A much smaller proportion of the liver was occupied by AHF in the other groups. This work provides strong evidence that TCDD is a potent tumor promoter in liver.

A second set of studies (Graham et al., 1988; Lucier et al., 1991; Clark et al., 1991a; Dragan et al., 1992) confirmed and extended Pitot's findings, including data suggesting a mechanistic basis for TCDD's tumor-promoting effects in rat liver. These DEN studies, using a necrogenic dose of DEN (200 mg/kg) as the initiator, have demonstrated that the effect of TCDDs on the promotion of AHF are reduced following ovariectomy. This finding is consistent with 2-year bioassays showing that TCDD is a hepatocarcinogen in female rats but not in male rats. In the tumor-promoting studies (Graham et al., 1988; Lucier et al., 1991), DEN was used as the initiating agent and TCDD (biweekly doses of 1.4 µg TCDD/kg, equivalent to 100 ng/kg/day for 30 weeks) was used as the promoter. There were four groups of intact female rats (controls, TCDD only, DEN only, and DEN/TCDD). The same four groups were used following ovariectomy. Data revealed that TCDD was a weaker liver tumor promoter in ovariectomized rats (Table 6-5). For example, there were 387 gamma glutamyl transpeptidase (GGT) positive AHF/cm^3 in intact rats compared with 80 in ovariectomized rats in the DEN/TCDD groups. Corresponding differences were evident in the proportion of liver occupied by GGT positive AHF: 0.37% in DEN/TCDD intact rats compared with 0.08% in DEN/TCDD ovariectomized rats. Few or no AHF were found in the control or TCDD-only groups. Placental glutathione S-transferase (PGST) is being used increasingly as a phenotypic marker of AHF (Ito et al., 1989), and results with this marker of preneoplasia were similar to those for GGT in that ovariectomy reduced the liver tumor-promoting actions of TCDD. The influence of ovariectomy on liver tumor incidence was evaluated in a parallel experiment using the same treatment groups in which TCDD was administered for 60 weeks. In the intact DEN/TCDD rats, liver tumor incidence was 13/37, with a total of 32 tumors compared with 7/39 (11 total tumors) in DEN/TCDD ovariectomized rats. Both hepatocellular adenomas and carcinomas were evident, along with a smaller incidence of hepatocholangiomas and hepatocholangiocarcinomas.

The mechanisms responsible for the protective effect of ovariectomy are not clear, but ovarian influences on liver TCDD retention do not seem to be involved; liver TCDD concentrations were ~20 ppb in both intact and ovariectomized rats (Lucier et al., 1991), which is similar to liver concentrations reported by Kociba et al. (1978) using the same dose of TCDD (100 ng/kg/day) but for 2 years rather than 60 weeks. One plausible mechanism may be related

to cell proliferation. Another possible mechanism for the influence of the ovaries is that TCDD induces cytochrome P4501A2, which could lead to DNA-reactive metabolites of 17-beta-estradiol, the naturally occurring estrogen. P4501A2 catalyzes the formation of catechol estrogens that are carcinogens in hamsters and are considered by some to be DNA-reactive precursors (Metzler, 1984; Li and Li, 1990, Yager and Liehr, 1996).

In addition to these initial studies, a large number of studies have addressed the effect of dioxins on the development of preneoplastic AHF in the rat liver. These studies are summarized in Tables 6-5, 6-6, and 6-7. These studies, while using different rat strains, different initiation protocols, and different dosing regimens, are consistent in showing that the induction of AHF by TCDD in the female Sprague-Dawley rat liver is dose-dependent (Maronpot et al., 1993; Teeguarden et al., 1999) (Table 6-8), exposure duration-dependent (Dragan et al., 1992; Walker et al., 2000; Teeguarden et al., 1999), and reversible after cessation of treatment (Dragan et al., 1992; Tritscher et al., 1995; Walker et al., 2000).

Other studies indicate that the capacity to induce the development of AHF in the liver by compounds structurally related to TCDD, such as the polychlorinated dibenzo-dioxins and polychlorinated dibenzo-furans, exhibits a rank-order potency similar to that for the induction of CYP1A1 activity (Flodstrom and Ahlborg, 1992; Waern et al., 1991; Schrenk et al., 1994). Although these data suggest that the potency of different dioxin-like compounds cannot be predicted solely on the basis of their potency for induction of CYP1A1, they provide evidence that liver tumor promotion likely requires an initial interaction with the AhR. Studies also demonstrate that the non-ortho-substituted (dioxin-like) polychlorinated biphenyls (PCBs) that induce the development of AHF exhibit a similar potency to that required to induce CYP1A1 activity (Hemming et al., 1995; van der Plas, 1999). Furthermore, when PCBs are administered in combination with TCDD, the effects on AHF development are additive, suggesting that tumor promotion by dioxins and dioxin-like PCBs likely acts through similar mechanisms.

6.3.3. Lung

Because the lung and respiratory tract seem to be target sites for TCDD carcinogenesis in humans (Fingerhut et al., 1991), it is of interest to evaluate whether TCDD is a tumor promoter in rodent lung. There are few published reports on the promotion of lung tumors in rats. Clark et al. used DEN as the initiating agent and TCDD (100 ng/kg/day for 60 weeks) as the promoting agent (Clark et al., 1991a) in both intact and ovariectomized rats. In contrast to liver tumor promotion, lung tumors were seen only in DEN/TCDD ovariectomized rats (4/37). No lung tumors were present in DEN/TCDD intact rats, in DEN only/TCDD only, or in control rats with or without ovariectomy. The background incidence of lung tumors in rats is very low, so the

lack of tumors in controls was not unexpected (Haseman et al., 1984). The four tumors in DEN/TCDD intact rats were two squamous cell carcinomas and two adenocarcinomas.

More recently, the induction of lung lesions was examined in DEN-initiated female rats exposed biweekly to 1,750 ng TCDD/kg for up to 61 weeks. Although there was no significant effect on the development of lung tumors, TCDD exposure was associated with an increase in alveo-bronchiolar metaplasia and bronchiolar hyperplasia (Tritscher et al., 1999).

There is only a single report of the effect of TCDD on promotion of lung tumors in mice (Beebe et al., 1995). Three weeks following a single initiating dose of 25 mg NDMA/kg, male Swiss mice were administered a single dose ranging from 0.05 µg up to 48 µg TCDD/kg, or were treated with 50 ng TCDD/kg per week for 20 weeks. The incidence of lung tumors (alveolar adenomas and carcinomas) in the initiated animals that received vehicle alone was 100%, but treatment with TCDD, either as a single dose of 1.6 µg/kg or as 50 ng/kg/week, resulted in a significant increase in tumor multiplicity. Single doses of TCDD greater than 1.6 µg/kg had no effect on tumor multiplicity, although the authors note that this may have been due to observed pulmonary toxicity.

The rodent tumorigenicity data provide clues to the complex hormonal interactions that produce site-specific carcinogenic actions of TCDD. Liver tumors are ovarian dependent, whereas the ovaries appear to protect against TCDD-mediated tumor promotion in lung. Therefore, the rat tumor data are of interest because recent epidemiologic studies (Chapter 7) have shown that TCDD exposure is associated with an increase in respiratory tract tumors.

6.3.4. Mouse Skin

Initiation/promotion studies on skin have demonstrated that TCDD is a potent tumor promoter in mouse skin as well as rat liver. Poland et al. (1982) administered a single dermal initiating dose of *N*-methyl-*N*-nitrosoguanidine (MNNG) to HRS/J hairless mice followed by twice-weekly doses of TCDD (3.75, 7.5, 15, or 30 ng) or TPA (1 or 3 µg) for 20 weeks. TCDD promoted the development of papillomas at all doses, and the response was dose dependent (100% of the animals in the high-dose TCDD group had tumors). Control animals or animals receiving only MNNG or TCDD exhibited a low incidence of tumors. These studies demonstrate that TCDD is at least two orders of magnitude more potent an agent than tetradecanoyl phorbol acetate (TPA) in mouse skin (Poland et al., 1982). On the basis of structure activity and genetic studies, it appears that the skin tumor-promoting actions of TCDD are AhR dependent. Moreover, tumorigenic responses segregate with the *hr* locus, and biochemical responses such as CYP1A1 induction can occur without carcinogenesis (Poland and Knutson, 1982; Poland et al., 1982).

Other studies have tested TCDD as an initiator and TPA as a promoter in CD-1 mice (DiGiovanni et al., 1977). Results revealed that TCDD had weak or no initiating activity in this system. To better understand the possible influence of TCDD-mediated induction of cytochrome P450 on the carcinogenicity of PAHs, TCDD was coadministered with benzo(a)pyrene or dimethylbenzanthracene to mice, followed by promotion with TPA (Cohen et al., 1979). Results revealed that TCDD decreased tumor incidence of both PAHs compared with controls. However, coadministration of TCDD with 3-methylcholanthrene to mice produced tumor incidences similar to those produced by 3-methylcholanthrene alone (Kouri et al., 1978). These results are consistent with the findings that TCDD induction of drug-metabolizing enzymes is associated with both metabolic activation deactivation of PAHs (Lucier et al., 1979).

The relative toxicity and tumor-promoting capacity of two CDFs (2,3,4,7,8-CDF and 1,2,3,4,7,8-CDF) have been investigated in hairless mice (Hebert et al., 1990). These studies used a treatment protocol similar to that of Poland et al. (1982), including the use of MNNG as the initiating agent and varying doses of TCDD, 2,3,4,7,8-CDF, or 1,2,3,4,7,8-CDF for 20 weeks. Proliferative lesions (squamous cell papilloma, squamous cell carcinoma, or hyperproliferative nodules) were quantified. Results demonstrated that 2,3,4,7,8-CDF was 0.2 to 0.4 times as potent as TCDD and that 1,2,3,4,7,8-CDF was 0.08 to 0.16 times as potent as TCDD. These data suggest that the tumor-promoting potencies of structural analogues of TCDD, like the promotion of liver tumors, reflect relative binding properties to the AhR as well as pharmacokinetic parameters.

Taken together, results on initiation/promotion protocols indicate that TCDD is an extraordinarily potent promoter of liver and skin tumors (Pitot et al., 1987), and the results provide strong evidence that the carcinogenic actions are AhR mediated. A summary of studies on tumor promotion by TCDD or the polychlorinated dibenzofurans is given in Table 6-6. Plausible mechanisms responsible for the tumor-promoting actions of TCDD and the impact of these mechanisms on dose-response relationships are presented in Section 6.4.

6.3.5. Transgenic Models

Studies on the effect of TCDD on tumor promotion in rat liver and mouse skin require the use of an exogenous initiating agent such as diethylnitrosamine or *N*-methyl-*N*-nitrosoguanidine. Recently transgenic models for classifying the mechanism of action of carcinogens have been used to examine the mechanism of carcinogenicity of TCDD in mice (Eastin et al., 1998). These are the Tg.AC transgenic mouse, which harbors an activated mouse v-Ha-ras oncogene, and the p53 +/- transgenic mouse models, which are heterozygous for the wild-type tumor suppressor p53. Dermal application of tumor promoters such as phorbol esters results in the development of epidermal papillomas in the Tg.AC. Topical application of

166 ng TCDD/kg in acetone three times per week for 24 weeks led to a significant increase in the incidence of squamous cell papillomas in both male Tg.AC mice (8/15 TCDD-treated vs. 1/15 controls) and female Tg.AC mice (10/15 TCDD-treated vs. 1/15 controls) (Eastin et al., 1998). Treatment of p53 +/- mice by gavage with 250 ng/kg (males) or 1,000 ng/kg (females) twice a week for 24 weeks did not result in any neoplastic lesions.

Subsequent studies showed that the induction of papillomas by dermal application of TCDD to hemizygous Tg.AC mice is dose dependent over a dose range of 0-760 ng TCDD/kg 3 times per week for 26 weeks, with the lowest observed effect occurring in the 17 ng/kg dose group (7.3 ng/kg/day) (van Birgelen et al., 1999, Dunson et al., 2000). In addition, the induction of skin papillomas in this model occurs when administration is at a site distant to the site of administration. Treatment of Tg.AC mice for 26 weeks by oral gavage with 0, 105, 450, or 1,250 ng TCDD/kg led to an increase in skin papillomas in the 1,250 ng/kg dose group only (5/20 TCDD-treated vs. 0/18 in controls) (van Birgelen et al., 1999). These data provide further support for the potent tumor-promoting action of TCDD.

6.4. MECHANISMS OF TCDD CARCINOGENICITY

6.4.1. Indirect DNA Damage

Although TCDD is negative in genetic toxicity tests, high doses of TCDD (50 to 100 µg/kg) induce single-strand breaks in Sprague-Dawley rats, presumably as a consequence of increased lipid peroxidation (Wahba et al., 1988, 1989). In addition, though TCDD may not be directly genotoxic, it has been suggested that it may be indirectly genotoxic through the formation of potentially DNA reactive oxygen species. This may result from cytochrome P450 induction by TCDD (Park et al., 1996), through the induction of oxidative stress (Slezak et al., 1999), or through the formation of catechol estrogens (Graham et al., 1988; Spink et al., 1992; Yager et al., 1996). Indeed, higher levels of oxidative DNA damage (8-OH-dG adducts) have been observed in chronically exposed female rats (Tritscher et al., 1996) and these TCDD-induced increases were not observed in ovariectomized rats. Other evidence to support this hypothesis includes the observation that mathematical modeling of the development of altered hepatocellular foci indicates that TCDD may have an effect on the initiation rate within the framework of a one-cell two-stage initiation-promotion model (Portier et al., 1996; Moolgavkar et al., 1996)(see Chapter 8). However, alternate two-cell models for tumor promotion do not suggest an effect on the initiation rate (Conolly et al., 1997).

6.4.2. Endocrine Disruption/Growth Dysregulation/Altered Signal Transduction

One of the characteristics of TCDD is that it is a potent growth dysregulator and alters the signaling of numerous hormonal systems. TCDD induces the expression of a large number

of genes involved in growth regulation, hormonal signaling and signal transduction, and hormone metabolism. In addition to these effects, which are presumably mediated through the AhR-ARNT heterodimer, there are also AhR-dependent effects on signaling pathways independent of activation of gene expression by the AhR-ARNT heterodimer that may be related to the mechanism of toxicity of TCDD. These effects are described in more detail in Chapter 2. Although many of the effects of TCDD have not been directly assessed for their role in the carcinogenicity of TCDD, it is likely that sex, species, and tissue specificity of dioxin carcinogenicity is due to a combination of these effects. Consequently, it is unlikely that a single mechanism is responsible for all the carcinogenic effects of TCDD in all tissues and species. However, it is now accepted by the scientific community that most, if not all, of TCDD's toxic and biochemical effects, including tumor promotion, are AhR dependent and that TCDD provides an example for evaluating the issues relevant to risk assessment for receptor-mediated carcinogens.

The list of biochemical effects produced by TCDD in humans, experimental animals, and cell systems is expanding. These effects include those that may alter normal cell regulatory processes, such as cell proliferation and differentiation, metabolic capacity, and hormonal pathways. Potentially the effects of TCDD on the endocrine system and tissue differentiation may play a role in susceptibility to carcinogenesis induced by other compounds, that is distinct from effects on metabolism of procarcinogens. Brown and co-workers showed that prenatal exposure of female rats to TCDD resulted in an increased susceptibility to DMBA-induced mammary adenocarcinomas. This was likely due to an increase in mammary gland terminal end buds as a result of prenatal exposure (Brown et al., 1998).

6.4.3. Cell Replication/Apoptosis and Tumor Promotion

One mechanism that has been proposed for the reduced tumor promotion capacity of TCDD in ovariectomized rats is the effect of TCDD on cell proliferation. TCDD did not stimulate cell proliferation rates in ovariectomized rats, whereas a mean increase of tenfold was apparent in intact rats receiving 100 ng TCDD/kg for 30 weeks (Table 6-5) (Lucier et al., 1991). There was considerable interindividual variation in both cell proliferation rates and enzyme-altered foci in the DEN/TCDD groups. Comparisons of the two data sets revealed a strong positive correlation between enzyme-altered foci and cell proliferation, although the importance of this finding is diminished by the fact that cell proliferation was quantified in nonlesioned hepatocytes. The mechanism whereby ovarian hormones and TCDD interact to produce cell proliferation in hepatocytes may involve growth factor pathways. Consistent with this idea, TCDD induced a loss of plasma membrane epidermal growth factor receptor (EGFR) in intact rats but not in ovariectomized rats (Sewall et al., 1993) EGF is thought to provide a

mitogenic stimulus in hepatocytes and to play a key role in hepatocarcinogenesis (Vickers and Lucier, 1991; Velu, 1990; Shi and Yager, 1989; Eckl et al., 1988). A schematic representation of a plausible mechanism for the role of estrogen in TCDD-mediated liver cancer in rats is given in Figure 6-2.

These observations of the ovarian hormone-dependent increase in hepatocyte replication following chronic exposure to TCDD (Lucier et al., 1991) parallel the observed sex-dependent induction of liver tumors in rats. This observation has led to the hypothesis that the induction of cell replication by TCDD may be a critical event in the mechanism of hepatocarcinogenesis. This hypothesis was supported by the observation that hepatocyte replication was dose-dependently increased after chronic exposure to TCDD (Maronpot et al., 1993)(Table 6-8).

Other studies, however, have failed to observe any effect of TCDD on nonfocal hepatocyte replication (Buchmann et al., 1994; Stinchcombe et al., 1995). More recently, it was shown that induction of hepatocyte replication is exposure-duration dependent and is only observed following 30 weeks of exposure to TCDD (Walker et al., 1998). Indeed, after 14 weeks of exposure, hepatocyte replication is lower in TCDD-treated animals than in controls. These data indicate that the induction of hepatocyte replication is not an early event in tumor promotion by TCDD and likely represents a secondary response to the induction of putatively preneoplastic AHF. However, data are insufficient to conclude that induction of hepatocyte replication is not involved in development of liver tumors.

Although cell replication is not seen after subchronic exposure to TCDD, it was observed that there was a suppression of hepatocyte apoptosis following TCDD treatment (Stinchcombe et al., 1995). The suppression of UV-inducible apoptosis by TCDD has also been observed in vitro (Worner et al., 1996), suggesting that this suppression may be an early event in tumor promotion. The suppression of apoptosis by TCDD in AHF may provide a growth advantage to these preneoplastic lesions, and therefore may be involved in the mechanism of hepatocarcinogenesis.

6.4.4. Thyroid Cancer–Proposed Mechanism of Action

TCDD causes a dose-related increase in thyroid follicular cell adenomas and carcinomas in rats and mice. One hypothesis for the induction of thyroid tumors involves the disruption of thyroid hormone homeostasis via induction of phase II enzymes UDP-glucuronosyltransferases (UGTs) (Hurley, 1998; Hill et al., 1998). Dioxin-like compounds induce the synthesis of UDP-glucuronosyltransferase-1 (UGT1) mRNA by an AhR-dependent transcriptional mechanism (Bock et al., 1998; Nebert et al., 1990). It is proposed that dioxin-like compounds increase the incidence of thyroid tumors through an extrathyroidal mechanism. Dioxin-like compounds induce hepatic UGT resulting in increased conjugation and elimination of thyroxine (T4),

leading to reduced serum T4 concentrations. T4 production is controlled by the thyroid stimulating hormone (TSH) which is under negative and positive regulation from the hypothalamus, pituitary, and thyroid by the thyrotrophin-releasing hormone (TRH), TSH, T4, and triiodothyronine (T3). Consequently, the reduced serum T4 concentrations would lead to a decrease in the negative feedback inhibition on the pituitary gland. This would then lead to a rise in the secreted TSH and stimulation of the thyroid. The persistent induction of UGT by dioxins and subsequent prolonged stimulation of the thyroid would result in thyroid follicular cell hyperplasia and hypertrophy of the thyroid, thereby increasing the risk of progression to neoplasia. In support of this hypothesis, Kohn et al. modeled the effect of TCDD on UGTS and thyroid hormones in female rats within the framework of a pharmacologically based-pharmacokinetic (PBPK) model (Kohn et al., 1996). This mathematical model described release and uptake of thyroid hormones, metabolism, TCDD induction of UGT1, regulation of TSH release from the pituitary by T4 and feedback on TRH and somatostatin which inhibits TSH release. The model successfully reproduced the observed effects of TCDD on serum T3, T4, and TSH, and UGT1 mRNA and enzyme activity, suggesting that this is a plausible mechanism for an indirect role of TCDD on the thyroid. This model is supported by the more recent experimental work of Schuur et al. which demonstrated the extrathyroidal effects of TCDD on thyroid hormone turnover (Schuur et al., 1997).

6.4.5. Mechanisms of Reduced Spontaneous Tumor Incidence

In the Kociba study, there was a significant reduction in the incidence of spontaneous benign tumors of the uterus, benign neoplasms of the mammary gland, mammary carcinomas, and pituitary adenomas in female rats, and pheochromocytoma of the adrenal gland and pancreatic adenomas in male rats. It is likely that the reduction in body weight gain as a result of TCDD exposure is responsible for the reduced incidence in these spontaneous lesions. Studies by the National Toxicology Program (Haseman and Johnson, 1996; Seilkop, 1995) indicate that chemical exposures resulting in a reduction of body weight by 10%-20% is correlated with a decrease in incidence of both mammary tumors and anterior pituitary tumors. This phenomenon may be related to a homeostatic growth suppression in reproductive organs during periods of reduced nutritional status. In addition, reduction in pancreatic adenomas (Kociba et al., 1978) has been observed in diet-restricted animals, and consequently, this reduction in incidence may be due to TCDD induced body weight reduction. The reduction in pheochromocytoma in male rats does not appear to be a consequence of changes in body weight, yet it exhibited a dose-dependent reduction in TCDD exposed males. The mechanism for the reduction in pheochromocytoma is unknown. The decrease in hormone-dependent cancers also may be related to the ability of TCDD to alter estrogen metabolism and/or its ability to act in some

tissues/cell systems as an antiestrogen. Increased estrogen metabolism may result from increased expression of CYP1 cytochromes P450, UGT, and GST. Decreased estrogen action could result from effects on the estrogen receptor (ER) levels or ER transcriptional function. TCDD may also induce the inactivation of estrogen in target cells by metabolism by TCDD inducible cytochromes CYP1A2, CYP1B1, or conjugating enzymes such as UGT1/GST without altering circulating estradiol concentrations.

6.5. BIOCHEMICAL RESPONSES

This section will summarize some of the changes produced by TCDD, including discussion of (1) possible relevance of the response to TCDD-mediated cancer, (2) whether the response is AhR mediated, (3) whether information is available on the role of transcriptional activation, (4) dose-response relationships, and (5) whether animal models are consistent with human responses. This chapter will not attempt to evaluate all of the biochemical and molecular responses to TCDD, but will focus on the ones that are either the most relevant to carcinogenic responses or have received the most study. The responses include induction of P4501A1 (CYP1A1), cytochrome P4501A2 (CYP1A2), EGFR, estrogen receptor (ER), and UDP-glucuronosyltransferase (UDPGT). Table 6-9 lists many of the biochemical changes affected by TCDD in in vivo and/or in vitro systems and some information on mechanisms of action.

6.5.1. Cytochrome P450

The most studied response to TCDD has been induction of cytochrome P450 isozymes (Whitlock, 1990; Silbergeld and Gasiewicz, 1989; Poland and Knutson, 1982). The first reports of P450 induction in vivo and in vitro appeared in 1973 (Lucier et al., 1973; Greig and DeMatteis, 1973; Poland and Glover, 1973), and hundreds of papers have been published on the subject since that time. These papers have dealt with various aspects of TCDD-mediated induction of P450, such as isozyme specificity, time course, structure-activity relationships, molecular mechanisms of transcriptional activation of the CYP1A1 gene, identification of transcriptional activating factors, tissue and cell specificity, and dose-response relationships. The molecular mechanisms responsible for enzyme induction are described elsewhere in this volume.

The mechanistic relationship of CYP1A1 and 1A2 induction to cancer or any other toxic endpoint following dioxin exposure has not yet been demonstrated, yet considerable controversy exists on this subject (Roberts, 1991). Because CYP1A1 catalyzes the metabolic activation of many chemicals, such as the PAHs, to DNA-reactive metabolites, it has been postulated that induction of CYP1A1 might enhance the carcinogenic actions from a given exposure level to

many PAHs. Recently it has been shown that benzo(a)pyrene is not carcinogenic in transgenic mice that are AhR deficient (Shimizu et al., 2000). The lack of carcinogenicity is presumably due to the lack of induction of CYP1A1 by B(a)P in these animals, supporting a proposed role for CYP1A1 in the carcinogenicity of B(a)P. Usually, however, preinduction of CYP1A1 diminishes the carcinogenic potency of PAHs such as 3-methylcholanthrene, benzo(a)pyrene, and 7,2-dimethylbenzanthracene if exposure to an inducing agent (such as TCDD) is short term (Parkinson and Hurwitz, 1991; Wattenberg, 1985; Cohen et al., 1979; Wattenberg, 1978; Miller et al., 1958). Induction also protects against the carcinogenic actions of aflatoxin, diethylnitrosamine, arylamines, and urethane. Protection occurs at numerous cancer sites, including liver and lung. Several lines of evidence support the idea that enzyme induction is the mechanism responsible for the protective effect. First, treatment of mice deficient in AhR with inducers does not protect against PAH-mediated cancer (Kouri et al., 1978). Second, the ability of inducing agents to protect against cancer is positively correlated with their potency as inducing agents (Wattenberg and Leong, 1970; Arcos et al., 1961). Third, the inducing agent must be administered at least 1 day prior to treatment, which allows sufficient time for the inducer to produce elevated levels of CYP1A1 (Parkinson et al., 1983; Wheatley, 1968).

The most probable mechanism for the protective effect of enzyme induction is that it leads to decreased concentrations of promutagenic DNA adducts in target tissues. These findings appear to contradict the knowledge that CYP1A1 is required for the metabolism of PAHs, aflatoxin, and several other carcinogens to DNA-reactive arene oxides (Guengerich, 1988; Levin et al., 1982; Conney, 1982). For example, the promutagenic DNA adduct of benzo(a)pyrene appears to be a 7,8-diol-9,10 epoxide metabolite adducted to deoxyguanosine, and formation of this metabolite requires two separate actions of CYP1A1. The contradiction can be resolved by analysis of all the metabolic pathways for chemical carcinogens whose potencies are decreased by pretreatment with inducing agents. In addition to CYP1A1-mediated increases in metabolic activation, CYP1A1 also converts PAHs to inactive metabolites (Thakker et al., 1985; Pelkonnen and Nebert, 1982). Moreover, induction of uridine diphosphoglucuronyltransferase also occurs concurrently with CYP1A1 induction (Lucier et al., 1986). This enzyme also detoxifies metabolites of PAHs and other carcinogens and facilitates their excretion from the body (Thakker et al., 1985; Nemoto and Gelboin, 1976). Therefore, it appears that TCDD-mediated enzyme induction increases the rate of detoxification of some carcinogens to a greater extent than it increases the rate of formation of DNA-damaging metabolites.

Increased frequency of sister chromatid exchanges was observed in lymphocytes of people exposed to pentachlorinated dibenzo-*p*-dioxins (PCDFs) in Taiwan when those lymphocytes were challenged with beta-naphthoflavone (Lundgren et al., 1986, 1988). This may

be because the PCDFs cause increased rates of metabolic activation of beta-naphthoflavone to DNA-reactive metabolites (Lundgren et al., 1987). These findings are consistent with the idea that TCDD's ability to induce drug-metabolizing enzymes (CYP1A1 and 1A2) may lead to an increased rate of formation of DNA-reactive metabolites of some carcinogens, most notably the PAHs and aromatic amines. However, there is evidence that the opposite effect occurs in some cases, because in vivo exposure to CYP1A1 inducers actually leads to a decrease in DNA adducts in target tissue following in vivo exposure to PAHs such as benzo(a)pyrene (Cohen et al., 1979; Parkinson and Hurwitz, 1991). It can reasonably be concluded that TCDD exposure may increase the rate of DNA adduct formation for some carcinogens but decreases the rate for others, and that predictions should not be made without experimental data on DNA adduct concentrations in control and TCDD-treated animals.

Although there is no clear mechanistic link between CYP1A1 induction and cancer, it is important to note that many CYP1A1 inducers are themselves carcinogens when encountered in chronic dosing regimens; therefore, the protective effect of inducing agents appears to be limited to short-term exposure. For example, benzo(a)pyrene, 3-methylcholanthrene, and TCDD are CYP1A1 inducers and multisite carcinogens (Vanden Heuvel and Lucier, 1993; Levin et al., 1982; Slaga et al., 1979; Sims and Glover, 1974).

The relationship of CYP1A2 induction to the carcinogenic actions of other compounds is less clear than it is for CYP1A1. For example, CYP1A2 catalyzes the formation of catechol estrogens from 17-beta-estradiol (Graham et al., 1988). The catechol estrogens are considered to be possible toxic metabolites because they could lead to increased free radical damage to cellular macromolecules such as DNA (Li and Li, 1990; Metzler, 1984; Yager and Liehr, 1996). This mechanism could be responsible, in part, for the findings that TCDD is a hepatocarcinogen in female rats but not male rats, and that ovariectomy protects against the hepatocarcinogenic actions of TCDD. Also consistent with the hepatocarcinogenicity data is the observation that CYP1A2 is induced in liver but not in extrahepatic organs, with the possible exception of the nasal mucosa (Goldstein and Linko, 1984). In contrast, CYP1A1 induction occurs in virtually every tissue of the body, which is consistent with the observation that the AhR is found in a wide variety of cell types.

In addition to the well-characterized induction of CYP1A1 and CYP1A2, TCDD also induces another cytochrome P450, CYP1B1, that has been identified in humans and rodents (Bhattacharyya et al., 1995; Savas et al., 1994; Sutter et al., 1994; Walker et al., 1995). CYP1B1 is expressed in a variety of human tissues and is inducible by TCDD in numerous human cell and rodent tissues including liver, lung, and kidney (Hayes et al., 1996, Sutter et al., 1994; Walker et al., 1995). CYP1B1 is active in the metabolism of numerous polycyclic aromatic hydrocarbons and arylamines (Otto et al., 1992; Shimada et al., 1996; Crofts et al., 1998) and can catalyze the

4-hydroxylation of 17-beta-estradiol in humans cells (Hayes et al., 1996). The potent carcinogenicity of 4-hydroxyestradiol in Syrian Golden hamsters (Liehr et al., 1986) and the observed elevation of 4-hydroxylase activity in human tumors (Liehr et al., 1996) suggest that the estradiol hydroxylase activity of CYP1B1 may play a critical role in tumorigenesis. This implication has been further extended to suggest that the induction of CYP1B1 in rat liver may play a role in the ovarian hormone-dependent hepatocarcinogenicity of TCDD (Yager et al., 1996). However, there are no reports in the literature that CYP1B1 in rodents has any significant estradiol hydroxylase activity, and therefore it is not clear if CYP1B1 is involved in the mechanism of hepatocarcinogenesis in rats.

CYP1B1 in both humans and rodents is active in the metabolism of PAHs and arylamines, and therefore, like CYP1A1, CYP1B1 may play a role in modulating the carcinogenicity of procarcinogens in both humans and experimental models. A recent report indicates that CYP1B1-dependent DMBA metabolism is required for the induction of DMBA-induced lymphomas in mice (Buters et al., 1999).

There are a number of studies on dose-response relationships for TCDD's effects on CYP1A1 and 1A2 (DeVito et al., 1991; Lin et al., 1991a; Kedderis et al., 1991; Harris et al., 1990a; Goldstein and Safe, 1989; Abraham et al., 1988; Lucier et al., 1986; Vecchi et al., 1983; Kitchin and Woods, 1979; Poland and Glover, 1973). These studies (Tritscher et al., 1992; Graham et al., 1988; Sloop and Lucier, 1987) include single and chronic dosing, time-course evaluations, and species comparisons. Dose-response relationships have been evaluated by quantitation of CYP1-dependent enzyme activities, quantitation of mRNA levels by Northern blot analysis, and quantitation of CYP1 protein by radioimmunoassay and immunolocalization in tissue sections. Dose-response modeling of these studies is described in detail in Chapter 8 of this document. Evaluations of various data sets for TCDD-mediated dose-response relationships have revealed some interesting information. One way of analyzing data for linearity or nonlinearity of dose-response for receptor-mediated events is the Hill equation (Hayashi and Sakamoto, 1986). A Hill coefficient of 1 suggests a linear relationship between exposure and dose throughout the experimental dose range, and would predict a proportional relationship between target tissue concentration of TCDD and biological response at all dose levels. This would imply that the response had no practical threshold or “no effect level.” Hill coefficients greater than 1 would indicate sublinearity in dose-response, whereas a Hill coefficient of less than 1 would indicate supralinearity for response in the low-dose region. Analyses of single-exposure and chronic exposure data for CYP1A1 and CYP1A2 induction in rat or mouse liver indicate a Hill coefficient of slightly greater than 1 for CYP1A1 and slightly less than 1 for CYP1A2 (Portier et al., 1992; Kohn et al., 1993). Although these analyses involve an extrapolation beyond the range of experimental data, they are consistent with the hypothesis that

there is no threshold for TCDD-mediated induction of CYP1A1 and 1A2. Time-course and dose-response analyses indicate that CYP1B1 is expressed at significantly lower levels than either CYP1A isozyme and is induced only at higher doses than those required for CYP1A1 or CYP1A2 (Santostefano et al., 1997; Walker et al., 1999). Furthermore, the Hill coefficient for CYP1B1 induction is greater than that for CYP1A1 (Walker et al., 1999). A more detailed analysis of dose-response relationships for cytochrome P450 induction and other dioxin-inducible responses can be found in Chapter 8 of this volume.

Immunological detection of induced CYP1A1 and 1A2 in liver sections obtained from rats exposed chronically to TCDD indicates hepatocyte heterogeneity in response to TCDD (Tritscher et al., 1992; Bars and Elcombe, 1991). For example, relatively low doses of TCDD (1 ng/kg/day) appear to maximally induce some cells around the centrilobular region. Increasing doses of TCDD increase the number of cells responding, rather than the amount of induction in responding cells. Like CYP1A1 and CYP1A2, CYP1B1 is also induced by TCDD in the rat liver in a centrilobular pattern of expression (Walker et al., 1997). It has been suggested that the heterogeneous pattern of expression may be due to differences in expression of the AhR across the acinus (Lindros et al., 1997) or to differences in binding affinity (Andersen et al., 1997). Alternatively, the observation that CYP1A2 is responsible for hepatic sequestration of TCDD (Diliberto et al., 1999) suggests that the heterogeneity in expression of the CYPs may be in part due to a heterogeneity in distribution of TCDD across the liver acinus. In support of this theory, the concentration of TCDD in periportal hepatocytes is higher than that seen in centrilobular hepatocytes (Santostefano et al., 1999). These data, which document cell differences in sensitivity to induction, complicate evaluation of dose-response relationships. For example, some hepatocytes appear to be maximally induced by low doses of TCDD, whereas other hepatocytes exhibit no detectable P450 induction response at the same doses. As discussed earlier, a mechanistic link between P450 induction and cancer has not been established. Evaluations of P450 induction and TCDD-mediated cell proliferation by immunocytochemical methods in rat liver reveal that cells expressing CYP1A1 and 1A2 are different from those exhibiting TCDD-mediated increases in DNA replication (Lucier et al., 1992).

Placentas from Taiwanese women exposed to rice oil contaminated with polychlorinated dibenzofurans have markedly elevated levels of CYP1A1 (Lucier et al., 1987; Wong et al., 1986). Comparison of these data with induction data in rat liver suggests that humans are at least as sensitive as rats to the enzyme-inductive actions of TCDD and its structural analogues (Lucier, 1991). Consistent with this contention, the in vitro EC_{50} for TCDD-mediated induction of CYP1A1-dependent enzyme activities is approximately 1.5 nM when using either rodent or human lymphocytes (Clark et al., 1992). Also, binding of TCDD to the AhR occurs with a higher affinity in rat cellular preparations compared with humans (Lorenzen and Okey, 1991;

Okey et al., 1989). This difference may be related to the greater lability of the human receptor during tissue preparation and cell fractionation procedures, or to an inherent property of the human AhR (Manchester et al., 1987). In any event, it does appear that humans contain a fully functional AhR (Cook and Greenlee, 1989), as evidenced by significant CYP1A1 induction in tissues from exposed humans, and this response occurs with sensitivity similar to that observed in experimental animals.

6.5.2. Epidermal Growth Factor Receptor

EGF is a potent mitogen and stimulates the generation of mitotic signals in both normal and neoplastic cells (Stoscheck and King, 1986; Carpenter and Cohen, 1979). Several lines of evidence suggest that the EGF receptor and its ligands, including transforming growth factor-alpha, possess diverse functions relevant to cell transformation and tumorigenesis (Velu, 1990; Marti et al., 1989; Mukku and Stancel, 1985). In fact, the mechanism of action for several tumor promoters, such as phenobarbital and the phorbol esters, is thought to involve the EGF receptor pathway (Stoscheck and King, 1986). A schematic representation of the proposed mechanism for EGF-stimulated mitogenesis is given in Figure 6-3.

Several studies have shown that TCDD decreases the binding capacity of the plasma membrane EGF receptor for its ligand without a change in K_d (Clark et al., 1991a; Lin et al., 1991a; Abbott and Birnbaum, 1990; Astroff et al., 1990; Sunahara et al., 1989; Stoscheck and King, 1986; Hudson et al., 1985; Madhukar et al., 1984). One study used a range of TCDD doses (3.5 to 125 ng/kg/day) for 30 weeks to evaluate the effects of TCDD exposure on EGF receptor in rat liver plasma membranes. There was a clear dose-response relationship for TCDD's effects on the total binding capacity of the EGF receptor, although TCDD did not produce a change in binding affinity of the receptor. The maximal effect was a threefold decrease in the concentration of plasma membrane EGF receptor; the ED_{50} was ~10 ng/kg/day based on administered dose and ~2 ppb TCDD based on liver TCDD concentration. These values are similar to the ED_{50} for induction of CYP1A1 and CYP1A2 for 30-week exposures. The dose-response data, like the data for CYP1A1 and CYP1A2 induction, were subjected to curve-fitting analyses using the Hill equation (Portier et al., 1992). This analysis indicated that a Hill coefficient of 1 provided the best fit, suggesting that there is a linear relationship between target tissue dose and response for effects on the EGF receptor. Although Hill analyses of dose-response data for TCDD's effects on the EGF receptor, CYP1A1 induction, and CYP1A2 induction are inconsistent with the idea of a threshold, the lowest dose used in these experiments was 100 pg/kg/day, so the possibility exists that dose-response relationships are different in the very low-dose region (1 to 10 pg/kg/day) encountered as background human exposures.

Dose-response data on EGFR were compared with dose-response relationships for TCDD-mediated increases in cell proliferation and growth of preneoplastic lesions within the framework of a two-stage model for hepatocarcinogenesis in rats (Lucier et al., 1992, Sewall et al., 1993, 1995a). Results indicate that cell proliferation and the growth of preneoplastic lesions are less sensitive responses to TCDD than is loss of plasma membrane EGF receptor. Therefore, the EGF receptor may be involved in the hepatocarcinogenic actions of TCDD, but dose-response relationships for this effect may be different from dose-response relationships for liver cancer in rats. These data reflect the knowledge that several steps and/or several genes are involved in the modulation of coordinated biological responses.

The mechanism by which TCDD alters EGF receptor-binding capacity is not fully understood, although TCDD does not appear to decrease EGF receptor mRNA (Lin et al., 1991a; Osborne et al., 1988). By using congenic mice deficient in the high-affinity AhR, TCDD's effects on the EGF receptor were shown to require the AhR (Lin et al., 1991a). In control animals, the EGF receptor is distributed on the surface of the plasma membrane and is composed of an external ligand-binding domain, a transmembrane domain, and an intercellular domain (Velu, 1990; Carpenter, 1987). Ligands for the EGF receptor (EGF or TGF-alpha) in the intracellular space bind the EGF receptor, producing a conformational change that stimulates the intercellular region to catalyze phosphorylation of the receptor itself as well as other proteins involved in cell regulation. The process results in internalization of the receptor, characterized by an increase in cytosolic EGFR coupled with a decrease in membrane-bound receptor. The effects of TCDD and CDFs on the number of binding sites for the plasma membrane EGF receptor are correlated with a concomitant decrease in EGF-stimulated autophosphorylation of the EGF receptor, indicating that TCDD produces a true functional change in the EGF receptor (Clark et al., 1991a; Sunahara et al., 1989; Nelson et al., 1988; Sunahara et al., 1988). Importantly, the addition of EGF to hepatocytes or several cell lines in culture produces a loss of plasma membrane EGF receptor coupled with a loss of EGF-stimulated autophosphorylation (Velu, 1990; Carpenter, 1987). Therefore, TCDD produces an EGF receptor-like response consistent with the idea that TCDD enhances the generation of cellular mitotic signals.

Although TCDD exposure mimics EGF actions in hepatocytes, TCDD itself does not appear to bind to the EGF receptor. The most plausible mechanism for effects on the EGF receptor involves the finding that TCDD induces production of TGF-alpha in hepatocytes as well as human keratinocytes (Choi et al., 1991). This response could alter control of normal growth patterns because TGF-alpha binds the EGF receptor with high affinity, leading to enhanced production of mitogenic signals. Alternatively, TCDD may affect EGF receptor transcription. In fact, TCDD has been shown to decrease uterine EGF receptor mRNA levels (Astroff et al., 1990). Receptor concentrations may also be altered by other events including posttranslational

glycosylation, increased lysosomal degradation, or alterations in signal transduction pathways such as protein kinases (Madhukar et al., 1988). It is also possible that TCDD alters phosphorylation of the EGF receptor by activation of protein kinase C, resulting in decreased binding capacity of the plasma membrane EGF receptor. This effect occurs following exposure to the tumor promoter TPA and is associated with decreased autophosphorylation rates and EGF receptor internalization (Beguinot et al., 1985; Cochet et al., 1984). In any event, TCDD-mediated alterations in EGF receptor pathways may, in part, be responsible for the tumor-promoting actions of TCDD by enhancement of mitotic signals.

The effects on the EGF receptor system may be mediated by estrogen action, and it has been postulated that the estrogen and EGF receptor pathways are integrated by "cross talk" mechanisms (Ignar-Trowbridge et al., 1992; Astroff et al., 1990). In vivo and in vitro studies have demonstrated that TCDD alters the ER (DeVito et al., 1992; Lin et al., 1991a; Clark et al., 1991a; Umbreit and Gallo, 1988; Romkes et al., 1987) and estrogens can, in turn, alter EGF receptor binding and cellular distribution (Vickers and Lucier, 1991; Vickers et al., 1989; Mukku and Stancel, 1985). Moreover, studies conducted within the framework of a two-stage model for hepatocarcinogenesis have demonstrated that TCDD-mediated decreases in plasma membrane EGF receptor are ovarian hormone dependent (Sewall et al., 1993). These studies concluded that ovarian hormones are essential to the tumor-promoting actions of TCDD because TCDD does not induce hepatocyte proliferation or stimulate the growth of preneoplastic lesions in ovariectomized rats (Section 6.3, Initiation/Promotion Studies).

Evidence indicates that TCDD and its structural analogues produce the same effects on the EGF receptor in human cells and tissues as observed in experimental animals. First, incubation of human keratinocytes with TCDD decreases plasma membrane EGF receptor, and this effect is associated with increased synthesis of TGF-alpha (Choi et al., 1991; Hudson et al., 1985). Second, placentas from humans exposed to rice oil contaminated with polychlorinated dibenzofurans exhibit markedly reduced EGF-stimulated autophosphorylation of the EGF receptor, and this effect occurred with similar sensitivity to that observed in rats (Lucier, 1991; Sunahara et al., 1989). The magnitude of the effect on autophosphorylation was positively correlated with decreased birth weight of the offspring.

6.5.3. UDP-Glucuronosyltransferases

Several studies have shown that TCDD induces synthesis of at least one isozyme of UDPGT (Lucier et al., 1973, 1974, 1986) by a mechanism that requires the AhR (Bock, 1991). The gene UGT-1 regulates synthesis of the UDPGT isozyme, which conjugates numerous substrates including 1-naphthol, p-nitrophenol, and thyroxine (Burchell et al., 1991). This gene contains a TCDD-responsive element that permits transcriptional activation following binding of

the TCDD-AhR complex. Other chemicals that bind the AhR, such as 3-methylcholanthrene and benzo(a)pyrene, also induce UGT-1 (Bock, 1991). UDPGTs are considered a deactivation pathway for numerous environmental chemicals and endogenous compounds, such as steroid hormones, by rendering them water soluble and excretable as a consequence of the catalytic addition of a glucuronide moiety (Tephly and Burchell, 1990). Therefore, induction of UDPGT may be responsible, in part, for the finding that pretreatment with TCDD leads to diminished DNA adducts for PAHs and decreased concentrations of some steroid hormones.

Conjugation of thyroxine by UGT-1 leads to deactivation and elimination of this thyroid hormone (Henry and Gasiewicz, 1987; Bastomsky, 1977). The decreased levels of thyroxine associated with UDPGT induction produce decreased feedback inhibition of the pituitary gland, which responds by secreting increased amounts of TSH (Sanders et al., 1988; Barter and Klaassen, 1992). Several studies have provided evidence that prolonged stimulation by TSH produces an oncogenic effect on the thyroid (Hill et al., 1989). Interestingly, rat liver EGF receptor may, in part, be regulated by thyroid hormones (Mukku, 1984). Increased incidence of thyroid tumors is the most sensitive endpoint in cancer bioassays, as evidenced by a statistically significant increase at a dose of 1.4 ng/kg/day. Consistent with this hypothesis, rodent studies have shown that TCDD and other inducers of hepatic UDPGT decrease thyroxine concentration in blood, which is associated with increased levels of thyroid-stimulating hormone (Barter and Klaassen, 1992; Henry and Gasiewicz, 1987).

Dose-response studies for TCDD's inductive effects on hepatic UDPGT in rats have demonstrated that the single dose ED50 is approximately 0.7 µg/kg, which is similar to the ED50 for CYP1A1 induction (Lucier et al., 1986). Furthermore, the shape of the dose-response curve for both responses is similar. Analysis of the expression of UGT1A1 in rodent liver showed that induction of UGT1A1 RNA was dose dependently increased following a single dose of TCDD (Vanden Heuvel et al., 1994). Further studies showed that chronic exposure of female rats to 0-125 ng TCDD/kg/day for 30 weeks led to a significant increase in UGT and subsequent alterations in thyroid function (Sewall et al., 1995b). A mathematical pharmacokinetic-pharmacodynamic model for TCDD (Kohn et al., 1993) was modified to include effects of TCDD on UGT and thyroid hormone levels (Kohn et al., 1996) (see Chapter 8). Model outcomes accurately predicted changes in thyroid hormone levels in TCDD-treated female rats and lend support to the hypothesis that induction of UGT, and subsequent persistent stimulation of the thyroid by TSH, may be involved in the promotion of thyroid tumorigenesis. It is noteworthy, however, that these data were obtained from female Sprague-Dawley rats and that the thyroid carcinogenicity of TCDD was observed in male but not female Osborne-Mendel rats. Furthermore, in the Kociba study chronic exposure to TCDD did not induce thyroid tumors in female Sprague-Dawley rats. Although gender-specific difference in carcinogenicity may be due

to higher circulating levels of TSH in male rats, the model predictions increase confidence in the hypothesis that the induction of UDPGT by TCDD is directly involved in the mechanism.

Because humans have the dioxin-responsive UDPGT (UGT-1) (Burchell et al., 1991) and TCDD induces UDPGT in human hepatocyte cell cultures, it is reasonable to assume that TCDD and its structural analogues would induce UDPGT in humans, although laboratory data are needed to validate this assumption.

6.5.4. Estrogen Receptor

Several lines of evidence have demonstrated that interactions of TCDD and estrogens are critical to some of the carcinogenic responses to TCDD. Although the precise mechanisms of those interactions have not been established, recent data indicate that TCDD effects on the ER and on estrogen metabolism are involved. The mechanisms for TCDD/estrogen interactions appear to be tissue specific. Of particular interest is the finding that TCDD increases liver tumor incidence in rats, and at the same time decreases tumor incidence in organs such as the mammary gland, uterus, and pituitary (Kociba et al., 1978). Therefore, TCDD/estrogen interactions will be examined separately for liver and other endocrine organs.

The liver contains a fully functional ER that possesses characteristics similar to those identified for ER in the mammary gland and uterus (Mastri and Lucier, 1983; Powell-Jones et al., 1981; Eisenfeld et al., 1976). For example, the liver exhibits high-affinity binding for 17-beta-estradiol and other potent estrogens, liver ER binding is specific for estrogens, the ligand receptor complex interacts reversibly with DNA, and this interaction leads to transcriptional activation of estrogen-responsive genes. Synthesis of hepatic ER, unlike ER in other target tissues, is under pituitary control (Lucier et al., 1981). Treatment of rats with a single dose of TCDD decreases binding capacity of the hepatic ER, and this effect is correlated with a decrease in ER protein (Zacharewski et al., 1991, 1992; Harris et al., 1990b; Romkes and Safe, 1988; Romkes et al., 1987). TCDD also decreases rat hepatic ER in chronic exposure experiments, with a threefold decrease evident following a dose of 100 ng/kg/day for 30 weeks (Clark et al., 1991b). TCDD also decreases hepatic ER binding in C57Bl6 mice, but a much higher dose is needed to produce this effect in congenic mice deficient in the high-affinity AhR, indicating that TCDD-mediated decreases in ER are dependent on the AhR (Lin et al., 1991b). Dose-response studies in mice demonstrate that the single-dose ED50 is ~0.7 µg TCDD/kg, similar to the ED50 for other biochemical end points such as CYP1A1 induction, loss of plasma membrane EGF receptor, and induction of UDPGT. The observation that TCDD decreases hepatic ER is in apparent contradiction to the finding that TCDD increases hepatocyte proliferation, because the ER is thought to produce mitogenic signals. However, quantitation of ER in control and TCDD-treated rats was done using preparations from liver homogenates. Immunolocalization

studies are needed so that the relationship of ER concentrations to cell proliferation in normal and preneoplastic cells can be more carefully evaluated.

In addition to effects on hepatic ER, TCDD may influence estrogen action in another way. CYP1A2 efficiently catalyzes the conversion of estrogens to catechol estrogens in liver (Graham et al., 1988; Dannan et al., 1986). CYP1A2 is not found in extrahepatic tissues, with the possible exception of the nasal cavity, so catechol estrogen formation would be expected to occur only in liver. Catechol estrogens have been postulated to possess macromolecule-damaging properties as a consequence of free radical generation (Li and Li, 1990; Metzler, 1984). Therefore, TCDD may increase the DNA-damaging capacity of estrogens in liver as a function of CYP1A2 induction. This effect may, in part, explain the carcinogenic actions of TCDD in female rat liver, and is consistent with the knowledge that ovariectomy protects against the hepatocarcinogenic actions of TCDD and that male rats do not appear to be susceptible to TCDD-induced liver tumors (Lucier et al., 1991; Kociba et al., 1978). It is important to note that cancer is more than a two-stage process, and the stage-specific actions of TCDD in multistage cancer models are not known, although TCDD-mediated cell proliferation and possible indirect genotoxic effects may be critical at more than one stage. A hypothetical mechanistic scheme for TCDD-mediated liver cancer is shown in Figure 6-2.

The finding that chronic TCDD exposure decreases tumor incidences in the pituitary, mammary gland, and uterus may also reflect TCDD's effects on ER and estrogen metabolism. As discussed above, TCDD decreases uterine ER concentrations in cytosolic and nuclear fractions of rats and mice, and these changes are associated with diminished estrogen action in both in vivo and in vitro studies. TCDD also increases estrogen metabolism, presumably as a consequence of CYP1A2 in liver and UDPGT induction in liver and extrahepatic tissues (Shiverick and Muther, 1982). Likewise, the addition of TCDD to a breast cancer cell line (MCF-7) results in increased estrogen degradation (Gierthy et al., 1988). However, there are only small effects on serum 17-beta estradiol levels following administration of TCDD to either rats or mice (Shiverick and Muther, 1983). Therefore, the effect on serum estradiol is considerably less sensitive than the effects on the uterine receptor. This comparison has led investigators to conclude that the antiestrogenic actions of dioxins are primarily caused by effects on ER levels in reproductive tract tissues. Consistent with this hypothesis, Fernandez and Safe (1992) have shown that TCDD is antimitogenic in human breast cancer cells. Final evaluation of the role of estrogen metabolism awaits data on concentrations of estrogens in responsive cells of control and TCDD-treated rats, which may be different from serum estradiol levels. In any event, it appears clear that TCDD does possess antiestrogenic properties that are likely to be important to decreased tumor incidences in some reproductive tract and endocrine

organs. Numerous studies have documented that the ER is found in virtually every tissue of the body, although the effects of TCDD on human ER in vivo have not been studied.

6.5.5. Other Biochemical Endpoints

TCDD alters a number of other pathways involved in the regulation of cell differentiation and proliferation (see Chapter 3). The specific relationships of these effects to multistage carcinogenesis are not known, but the broad array of effects on hormone systems, growth factor pathways, cytokines, and signal transduction components is consistent with the notion that TCDD is a powerful growth dysregulator (Table 6-9). It is also consistent with the findings that TCDD alters cancer risks at a large number of sites, possibly reflecting multiple mechanisms of carcinogenicity. Biochemical/molecular/endocrine changes produced by TCDD include the glucocorticoid receptor (Sunahara et al., 1989), tyrosine kinase (Madhukar et al., 1988), gastrin (Mably et al., 1990), interleukin-1beta (Sutter et al., 1991), plasminogen activator inhibitor (Sutter et al., 1991), tumor necrosis factor-alpha (Clark et al., 1991b), gonadotropin-releasing hormone (Moore et al., 1989), testosterone (Moore et al., 1985), and luteinizing hormone (Mably et al., 1992). The importance of these responses to the carcinogenic process should not be diminished by the lack of detail presented here. In every case studied, these responses have been shown to be dependent on the AhR.

6.6. SUMMARY AND WEIGHT OF EVIDENCE FROM ANIMAL STUDIES

There have been several long-term studies designed to determine if TCDD is a carcinogen in experimental animals. All of these studies have been positive and demonstrate that TCDD is a multisite carcinogen, is a carcinogen in both sexes and in several species including the Syrian hamster, is a carcinogen in sites remote from the site of treatment, and increases cancer incidence at doses well below the MTD. In two-stage models for liver and skin cancer, it is clear that TCDD is a potent promoting agent with weak or no initiating activity. Of those compounds that make up the bulk of the human body burdens of TEQ, only three of them, namely TCDD and a mixture of two congeners of hexachlorodibenzo-*p*-dioxin (HCDD) (1,2,3,6,7,8 and 1,2,3,7,8,9), have been tested in chronic rodent bioassays. In both cases, there was clear evidence of carcinogenicity. Commercial mixtures of PCBs that have a high TEQ also have been shown to be carcinogenic in rat liver. While many of the other dioxin-like compounds have not been tested in chronic carcinogenicity studies, 1,2,3,7,8-PCDD; 1,2,3,4,6,7,8-HpCDD; 2,3,4,7,8-PCDF; 1,2,3,4,7,8-HCDF; PCB126; and PCB105 all promote the development of putatively preneoplastic altered hepatocellular foci (AHF) within rodent liver suggesting that they also act as tumor promoters like TCDD (see Table 6-5). Together, dioxins and furans comprising 94% of the total dioxin/furan TEQ, and PCBs comprising 85% of the total coplanar

PCB TEQ, have all shown to be positive in either rodent bioassays, rodent liver tumor promotion studies, or mouse skin tumor promotion studies. In addition, complex mixtures of dioxins and furans and commercial PCB mixtures act as promoters of liver AHF. These data suggest that, while the majority of dioxin-like congeners have not been tested for carcinogenicity in chronic rodent bioassays, it is likely that those individual congeners and mixtures of dioxin-like compounds, which comprise the majority of the dioxin-like activity in human tissues, are carcinogenic to rodents. Furthermore, when one considers the impact of current TEF values on compounds that make up the majority of the current TEQ, it is clear that more than 90% of the current TEQ for either dioxins/furans or PCBs is made up of compounds for which the current TEF is supported by data on relative potencies based on tumor promotion or carcinogenic endpoints. More information on this point is provided in Table 6-10.

The finding of weak or no initiating activity is not surprising because TCDD does not form DNA adducts and is negative in short-term tests for genetic toxicity. The general consensus is that TCDD is an example of receptor-mediated carcinogenesis in that (1) interaction with the AhR appears to be a necessary early step, (2) TCDD modifies a number of receptor and hormone systems involved in cell growth and differentiation, such as the epidermal growth factor receptor and the ER, and (3) sex hormones exert a profound influence on the carcinogenic actions of TCDD. Although tumor promotion data for the polychlorinated dibenzofurans and coplanar polychlorinated biphenyls are limited, it appears that these compounds are liver tumor promoters with potencies dependent on their binding affinity to the AhR.

Some of the central issues in the risk assessment of TCDD and its structural analogues are (1) characterization of the shape of the dose-response curve for receptor-mediated events, (2) evaluation of the relevance of animal data in estimating human risks, and (3) the health consequences of background exposures (1 to 10 pg TEQ/kg/day) of dioxin and its structural analogues. With regard to the shape of the dose-response curve, it is clear from animal studies that there are different dose-response curves for different TCDD effects, which is consistent with the generally accepted dogma for steroid receptor-mediated responses. In general, the biochemical/molecular responses such as cytochrome P450 induction do not show evidence for a threshold, although unequivocal conclusions cannot be made about the mechanistic link, if any, between biochemical responses and toxic effects. In fact, coordinated biological responses such as TCDD-mediated cell proliferation and growth of preneoplastic lesions (foci of cellular alterations in liver) appear to be less sensitive endpoints, although evaluation of these responses is complicated by a high degree of interindividual variation: some animals do not exhibit any increase in cell proliferation in response to TCDD exposure.

The mechanistic basis for interindividual variation is unclear, and this lack of knowledge complicates approaches to estimate human risks from experimental animal data. However,

several studies indicate that, for the most part, humans appear to respond like experimental animals for biochemical and carcinogenic effects. However, data from epidemiology studies are difficult to evaluate because the carcinogenic effects, if any, resulting from background TCDD exposures are not known, although biochemical effects such as cytochrome P450 induction may be produced by background exposures.

Table 6-1. Sites for increased cancer in animal bioassays

Species/Strain	Sex	Site	Reference
Rats/Sprague-Dawley	Male	Tongue Nasal turbinates/hard palate	Kociba et al., 1978
	Female	Lung Nasal turbinates/hard palate Liver	
Rats/Osborne-Mendel	Male	Thyroid Adrenal cortex	NTP, 1982a
	Female	Liver Adrenal cortex Subcutaneous fibrosarcoma	
Mice/B6C3F1	Male	Liver	NTP, 1982a
	Female	Liver Thyroid Subcutaneous fibrosarcoma	
Mice/B6C3 and B6C	Male	Thymic lymphomas	Della Porta et al., 1987
	Female	Liver	
Hamsters/Syrian Golden	Male	Facial skin carcinoma	Rao et al., 1988

Table 6-2. Different evaluations of Kociba study liver tumor data in female rats

			TCDD(ng/kg/day)		
Evaluation	**Tumor classification**	**Control**	**1**	**10**	**100**
Kociba et al., 1978	Hyperplastic nodule	8/86 $p<0.0001$[a]	3/50	18/50 $p<0.001$[b]	23/49 $p<0.001$
	Hepatocellular carcinoma	1/86 $p<0.0001$	0/50	2/50	11/49 $p<0.001$
	Hyperplastic nodule; hepatocellular carcinoma[c]	9/86 $p<0.001$	3/50	18/50 $p<0.001$	34/48 $p<0.001$
Squire, 1980	Neoplastic nodule[d]: hepatocellular carcinoma	16/86 $p<0.0001$	8/50	27/50 $p<0.001$	33/47 $p<0.001$
Goodman and Sauer, 1992	Hepatocellular adenoma	2/86 $p<0.0001$	1/50	9/50 $p<0.01$	14/45 $p<0.001$
	Hepatocellular carcinoma	0/86 $p<0.01$	0/50	0/50	4/45 $p<0.05$
	Hepatocellular adenoma; hepatocellular carcinoma	2/86 $p<0.0001$	1/50	9/50 $p<0.01$	18/45 $p<0.001$

[a]*p*-values for Mantel-Haenszel trend tests are given below the control group incidences (Huff et al., 1991).
[b]*p*-values for Fisher exact tests are given below the incidence data for TCDD-treated animals.
[c]Combined incidence data for hyperplastic nodule and hepatocellular carcinoma in the Kociba study is as described by Huff et al., 1991.
[d]Hyperplastic nodule, neoplastic nodule, and hepatocellular adenoma are interchangeable lesions.

Table 6-3. Tumor incidences[a] in Osborne-Mendel rats

			TCDD (ng/kg/day)		
Sex	**Target organ**	**Control**	**1.4**	**7.1**	**71**
Male	Thyroid: follicular cell adenoma	1/69 *p*=0.006[b]	5/48 *p*=0.042 [c]	6/50 *p*=0.021	10/50 *p*=0.001
	Liver: neoplastic nodule	0/74 *p*=0.005	0/50 —	0/50 —	3/50 *p*=0.6
	Adrenal cortex: adenoma	6/72 *p*=0.26	9/50 *p*=0.09	12/49 *p*=0.015	9/49 *p*=0.09
Female	Liver: neoplastic nodule	5/75 *p*<0.001	1/49 —	3/50 —	12/49 *p*=0.006
	Adrenal cortex: adenoma or carcinoma	11/73 *p*=0.014	9/49 *p*=0.4	5/49 —	14/46 *p*=0.039
	Subcutaneous fibrosarcoma	0/75 —	2/50 *p* =0.16	3/50 *p*=0.06	4/49 *p*=0.023

[a]NTP, 1982a; Huff et al., 1991.
[b]*p* value obtained from Cochran-Armitage test for dose-related trend.
[c]*p* value obtained from Fisher exact test compared with control group.

Table 6-4. Tumor incidences[a] in B6C3F$_1$ mice

		TCDD (ng/kg/day)			
Sex	**Target organ**	**Control**	**1.4**	**7.1**	**71**
Male	Liver: carcinoma	8/73 p=0.002[b]	9/49 p=0.19[c]	8/49 p=0.28	17/50 p=0.002
	Liver: adenoma	7/73 p=0.024	3/49 —	5/49 p=0.6	10/50 p=0.09
	Lung: adenoma or carcinoma	10/71 p=0.004	2/48 —	4/48 —	13/50 p=0.08

		TCDD (ng/kg/day)			
Sex	**Target organ**	**Control**	**5.7**	**28.6**	**286**
Female	Subcutaneous fibrosarcoma	1/74 p=0.007	1/50 p=0.6	1/48 p=0.6	5/47 p=0.032
	Liver: carcinoma	1/73 p=0.008	2/50 p=0.4	2/48 p=0.4	6/47 p=0.014
	Liver: adenoma	2/73 p=0.11	4/50 p=0.2	4/48 p=0.2	5/47 p=0.8
	Thyroid: adenoma	0/69 p=0.016	3/50 p=0.07	1/47 p=0.4	5/46 p=0.009
	Hematopoietic: all lymphomas	18/74 p=0.011	11/50 —	13/48 p=0.4	20/47 p=0.029

[a]NTP, 1982a; Huff et al., 1991.
[b]p value obtained from Cochran-Armitage test for dose-related trend.
[c]p value obtained from Fisher exact test compared with control group.

Table 6-5. Summary of positive tumor promotion studies for PCDDs and PCDFs in rats

Strain/sex	Initiator	Promoter	Site	Reference
SD/F	PH/DEN	TCDD	Liver	Pitot et al., 1980
F344/F	PH/DEN	TCDD	Liver	Pitot et al., 1987
F344/F	PH/DEN	TCDD	Liver	Hendrich et al., 1986
SD/F	DEN	TCDD	Liver	Graham et al., 1988
SD/F	DEN	TCDD	Liver	Flodstrom and Ahlborg, 1991
SD/F	DEN	TCDD	Liver	Lucier et al., 1991
SD/F	DEN	TCDD	Liver	Clark, 1991
SD/F (ovx)	DEN	TCDD	Lung	Clark, 1991
SD/F	PH/DEN	TCDD	Liver	Flodstrom et al., 1991
F344/F	PH/DEN	TCDD	Liver	Dragan et al., 1991
SD/F	PH/DEN	TCDD	Liver	Waern et al., 1991
SD/F	DEN	TCDD	Liver	Flodstrom and Ahlborg, 1992
SD/F	DEN	PCDFs	Liver	Flodstrom and Ahlborg, 1992
CR/F	PH/DEN	TCDD	Liver	Dragan et al., 1992
SD/F	DEN	TCDD	Liver	Maronpot et al., 1993
SD/F	DEN	PCB 126, PCB 105	Liver	Hemming et al., 1993
Wistar/F	DEN	TCDD, HCDD	Liver	Buchmann et al., 1994
Wistar/F	NNM	TCDD, HCDD, PCDD	Liver	Schrenk et al., 1994
SD/F	DEN	TCDD	Liver	Sills et al., 1994
SD/F	DEN	TCDD, PCB126	Liver	Hemming et al., 1995
Wistar/F	DEN	TCDD	Liver	Stinchcombe et al., 1995
SD/F	DEN	TCDD	Liver	Tritscher et al., 1995
SD/F	DEN	PCB 118	Liver	Haag-Gronlund et al., 1997
SD/F	DEN	TCDD	Liver	Walker et al., 1997
SD/F	DEN	TCDD	Liver	Mann, 1997
SD/F	DEN	TCDD	Liver	Wyde et al., 1999
SD/F	PH/DEN	TCDD	Liver	Teeguarden et al., 1999
SD/F	PH/DEN	PCDD, PCDF, PCB	Liver	van der Plas, 1999
SD/F	DEN	TCDD	Liver	Walker et al., 2000

Abbreviations: DEN, diethylnitrosamine; PH, 2/3 hepatectomy; SD, Sprague-Dawley; F, female; M, male; NNM, N-nitrosomorpholine; ovx, ovariectomized.

Table 6-6. Summary of positive tumor promotion studies for PCDDs and PCDFs in mice

Strain/sex	Initiator	Promoter	Site	Reference
HRS/J hairless	MNNG	TCDD	Skin	Poland et al., 1982
HRS/J hairless	MNNG	TCDD PCDF HCDF	Skin	Hebert et al., 1990
C57/BL6 (M)	DEN	TCDD, Aroclor 1254	Liver	Beebe et al., 1995
DBA/2 (M)	DEN	TCDD, Aroclor 1254	Liver	
B6D2F1 (M)	DEN	TCDD, Aroclor 1254	Liver	
Swiss	NDMA	TCDD	Lung	
Tg.AC transgenic	v-Ha-ras transgene	TCDD	Skin	van Birgelen et al., 1999; Dunson et al., 2000
Tg.AC transgenic	v-Ha-ras transgene	TCDD	Skin	Eastin et al., 1998

Table 6-7. Putatively preneoplastic GGT-positive altered hepatocellular foci (AHF) after 30 weeks of treatment with TCDD as promoter[a]

Endpoint	Ovarian status	Saline		DEN-initiated[b]	
		Control	TCDD[c]	Control	TCDD
AHF/cm^3	Intact	6	5	44	387[d]
	Ovariectomized	0	0	30	80
Volume fraction	Intact	0.01	0.01	0.03	0.37[d]
	Ovariectomized	0	0	0.03	0.08
BrdU LI[e]	Intact	0.3	6.0	0.8	7.3[d]
	Ovariectomized	1.1	1.0	1.1	0.7

[a]Lucier et al., 1991.
[b]Animals were initiated with 175 mg diethylnitrosamine/kg.
[c]Biweekly treatment with 1,400 ng TCDD/kg.
[d]Significantly different from ovariectomized animals.
[e]Bromodeoxyuridine labeling indices; percentage of non-AHF hepatocyte nuclei undergoing replicative DNA synthesis in a 7-day period.

Table 6-8. Preneoplastic altered hepatocellular foci and bromodeoxyuridine labeling indices after 30 weeks of promotion with TCDD

TCDD ng/kg/day [a]	AHF [b] /cm^3	Volume fraction	Mean AHF volume	BrdU LI [c]
0[d]	442.2	0.57	13	5.3
3.5	759.2	0.85	15	3.3 [e]
10.7	791.7	1.00	11	3.3
35.7	530.4	0.93	18	6.4
125	751.7	2.23 [e]	30 [e]	14.4 [e]

[a] Daily averaged dose of a biweekly treatment of TCDD in corn oil.
[b] Placental glutathione-s-transferase positive altered hepatocellular foci (AHF)
[c] Labeling indices (LI) are the percentage of hepatocytes undergoing replicative DNA synthesis in 7 days following 30 weeks of exposure to TCDD.
[d] All animals were initiated with 175 mg diethylnitrosamine/kg, 2 weeks prior to start of treatment with TCDD.
[e] Significantly different from control values.

Source: Maronpot et al., 1993.

Table 6-9. Some biochemical responses to TCDD

CYP1A1	Human chorionic gonadotrophin
CYP1A2	Interleukin-1beta
CYP1B1	Gastrin
GST Ya	TNF alpha
GST Yb	TGF-beta
GST Yc	EGF
UDP glucuronyl transferase	Fibrinogen
QR quinone reductase/ Nmo	Plastin
Aldehyde dehydrogenase	EGFR
Ornithine decarboxylase	c-erbA related hormone receptor
Malic enzyme	Estrogen receptor
Phospholipase A2	25Dx-putative progesterone receptor
60kDa microsomal esterase	MDR-1 multidrug resistance
Aminolevulinic acid synthetase	Aryl hydrocarbon binding protein
Choline kinase	c-fos
EctoATPase	c-jun
Prostaglandin synthetase -2 (COX-2)	Cystatin-like protein
Plasminogen activator inhibitor-2	MHC-Q1
Urokinase plasminogen activator	Protein kinase C
Nedd-4-like ubiquitin protein ligase	pp60 c-src protein kinase
PEPC kinase	p21 ras
Terminal transferase	p27/Kip1
Testosterone 7alpha hydroxylase	bcl-2

Note: This list is not a comprehensive list of all responses known to be affected by TCDD.
Source: Sutter et al., 1992; Lai et al., 1996.

Table 6-10. Relative potency factors based on tumor promotion/cancer endpoints for "high TEQ contribution" dioxin-like compounds

Compound	REP[a]	TEF -WHO_{98}	% TEQ	Reference
2378-TCDD		1.0	17	
12378-PeCDD	0.8-1.04	1.0	32	Waern et al., 1991
1234678-HpCDD	0.02	0.01	3.3	Schrenk et al., 1994
123678/123789-HCDD (binary mixture)[b]	0.05	0.1/0.1	21 + 3.9	NTP, 1980
23478-PeCDF	0.1-0.21	0.5	15	Waern et al., 1991
			Total[c] =92.2 %	
33'44'5 PCB (PCB126)	0.071-0.11	0.1	64	Hemming et al., 1993, 1995
233'44' PCB (PCB105)	<0.0002	0.0001	17	Hemming et al., 1993
233'44'5 HCB (PCB156)	0.001-0.0001	0.0005	11	Haag-Grönlund et al., 1997
23'44'5 HCB (PCB118)	<0.0002	0.0001	4.3	Haag-Grönlund et al., 1997
			Total[d]=96.3 %	

[a]Range of individual relative potency factors based on cancer/tumor promotion (WHO-TEF database).
[b]Relative potency from this document (Chapter 6) based on relative dose levels.
[c]% contribution to total TEQ_{DF}-WHO_{98} in adipose tissue of humans with ambient exposures (Table 4-46 in Part I. Volume 3 Chapter 4).
[d]% contribution to total TEQ_{P}-WHO_{98} in adipose tissue of humans with ambient exposures (Table 4-47 in Part I. Volume 3 Chapter 4).

Figure 6-1. Schematic representation of multistep carcinogenesis including the roles of genetic damage and cell proliferation. It is important to note that several DNA-damaging steps and several cell proliferation steps are likely to be involved during the complete process of chemical carcinogenesis.

Source: Swenberg et al., 1987.

Figure 6-2. Operational model of TCDD/estrogen interactions relative to tumor promotion in a two-stage model of hepatocarcinogenesis. Clonal expansion of initiated cells may reflect stimulation of mitogenesis through receptor-mediated events involving epidermal growth factor receptor, estrogen receptor, and the AhR.

Source: Vickers and Lucier, 1991.

Figure 6-3. Plausible mechanism for the role of EGF-mediated stimulation of mitotic activity.

Source: Stoscheck and King, 1986.

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CHAPTER 7. EPIDEMIOLOGY/HUMAN DATA
PART A: CANCER EFFECTS

7.1. INTRODUCTION

Animal bioassay data provide substantial presumptive evidence of the human carcinogenicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (see Chapter 6), but confirmation must come from well-designed human studies. TCDD is a multiorgan carcinogen in animals. Target organs include the liver, thyroid, lung, skin, and soft tissues. There is no assumption of target tissue concordance from animals to humans, although site concordance would add support to a causal interpretation. This chapter reports on the cancer epidemiology evidence of TCDD and its congeners.

This review and analysis of the epidemiologic literature on dioxins and cancer begins by defining the scope of chemical exposures, cancers, and research reports to be considered. Then, following a brief summary of previous EPA assessments of epidemiologic literature, a description is given of the methods used in the present review. The original research reports are then discussed in four groups: (1) follow-up studies of chemical manufacturing and processing workers, (2) case-control studies in general populations, (3) studies of pulp and paper mill workers, and (4) other studies (including studies of pesticide applicators; Vietnam veterans with potential exposure to Agent Orange; residents of Seveso, Italy, exposed to TCDD during an accidental explosion of a phenoxy herbicide factory; and victims of contaminated rice oil poisonings). Because the discussions of the first two groups of studies are relatively lengthy, brief summaries are given at the end of each of those sections. Conclusions are drawn following an overall discussion of all the studies.

7.2. SCOPE

Epidemiologic studies of cancer among persons exposed to TCDD and other polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) are included in this review. Primary emphasis is placed on studies with exposures to TCDD itself, occurring primarily in the manufacture and use of 2,4,5-trichlorophenol, hexachlorophene, and the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Because exposures to 2,4,5-T and 2,4-dichloroacetic acid (2,4-D) often occur among the same groups who manufacture and use these herbicides, some studies of groups exposed only to 2,4-D are also included. Exposure to lower-chlorinated PCDDs (dichlorinated and trichlorinated isomers) may occur in the manufacture and use of 2,4-D. Also included are studies of groups exposed to higher-chlorinated PCDDs (i.e., the hexachlorinated, heptachlorinated, and octachlorinated isomers), occurring primarily in the manufacture and use of pentachlorophenol (PCP) and in the paper and pulp industries.

A major weakness in nearly all of these studies is the lack of good exposure information. Most studies rely solely on interviews and questionnaires of work history to ascertain exposure surrogates. Until recently, there was little, if any, verification of actual internal dose of these compounds. Some studies use chloracne as a surrogate for exposure to TCDD. This presence of chloracne usually indicates a high dose effect. The absence of chloracne does not indicate lack of exposure. Some of the recent cohort studies of chemical production workers (Fingerhut et al., 1991; Becher et al., 1996; Flesch-Janys, et al., 1995, 1996, 1999; Ott et al., 1996; Manz et al., 1991; Zober et al., 1990) do provide estimates of TCDD exposure in cohort samples via serum blood levels taken decades after cessation of exposure. However, these estimates have been chiefly used to provide support for preselected qualitative categories of estimated exposure. But these can also be used to determine possible dose-response trends and estimate the risk of cancer to populations with low-level exposure to TCDD (see Chapter 8). Measures of exposure by individual study have been discussed.

At the time of EPA's last review in 1988, evidence of human carcinogenicity of TCDD and the phenoxy herbicides focused on soft tissue sarcomas (STSs) and malignant lymphomas. Consequently, this report will update the strengths and weaknesses of the evidence pertaining to these cancers. But emerging as a more important topic are evaluations of the evidence of cancer at other sites. The case-control studies reviewed for EPA's last analysis generally considered herbicide applicators with potential exposures to both 2,4-D and 2,4,5-T. Recent case-control studies of U.S. farmer groups in which exposure to 2,4-D and 2,4,5-T can be separated (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) provide a validation mechanism to separate potential effects of these herbicides and, possibly, their different PCDD contaminants. Thus, these and other recent studies (Hardell and Eriksson, 1988; Eriksson et al., 1990; Woods et al., 1987) will be reviewed and compared with those discussed in EPA's earlier reports.

Five recent cohort mortality studies (Steenland et al., 1999; Fingerhut et al., 1991; Becher et al., 1996; Flesch-Janys et al., 1995, 1998, 1999; Manz et al., 1991; Ott et al., 1996; Zober et al., 1990; Kogevinas et al., 1997; Saracci et al., 1991; Hooiveld et al., 1996, 1998) totaling more than 23,000 workers potentially exposed to TCDD and/or phenoxy herbicides/chlorophenols provide a more important database for analyzing cancer effects and are discussed in Section 7.5. The first three of these, and especially the large U.S. study of Fingerhut et al. (1991) and its update by Steenland et al. (1999), as well as the Dutch cohort study by Hooiveld et al. (1996, 1998), are considered to be the most important new studies in the field of TCDD cancer epidemiology because of their attention to cohort selection, to TCDD exposures or exposure surrogates (chloracne), and to the fact that exposure to dioxin is associated with an increasing risk of cancer at multiple sites. The fifth study (Saracci et al., 1991; Kogevinas et al., 1997) encompasses all the occupational cohorts that are referenced here. Although it has the largest

cohort, it has less reliable information on the TCDD-exposed subcohort and only a little information that would allow a quantitative estimate of exposure. Two other studies of phenoxy acid manufacturers are included (Lynge, 1985, 1993, 1998; Coggon et al., 1986), but their usefulness is limited because of the low unsubstantiated exposure to TCDD. Also included is a study of occupationally exposed women (Kogevinas et al., 1993) who had probable exposure to TCDD.

Four recent cohort studies of workers in the pulp and paper mill industry are also included (Robinson et al., 1986; Jäppinen et al., 1987; Henneberger et al., 1989; Hertzman et al., 1997) because of potential for worker exposure to higher-chlorinated PCDDs but not hexa-, hepta-, or octaphenoxy herbicides, and one with exposure to hexa-, hepta-, and octochlorinated dioxin isomers. However, none of these studies provide any additional information about which PCDD exposures were likely, and these studies are not given much weight.

Studies of Vietnam veterans potentially exposed to TCDD in Agent Orange are reviewed briefly, with only two (Ketchum et al., 1996, 1999; Michalek et al., 1990, 1998) judged to have sufficient information on potential TCDD exposure to be useful for analysis of cancer. Also, the recent studies of cancer in Seveso, Italy, residents are discussed (Bertazzi et al., 1998, 1997, 1992, 1993, 1989a,b; Landi et al., 1998; Consonni et al., 1999; Mocarelli et al., 1991; Pesatori et al., 1999, 1992); these studies provide some exposure data, but the cancer response analysis is limited because of inadequate follow-up time (maximum of 20 years).

Finally, the studies of the rice oil poisonings of residents in Taiwan and Japan with polychlorinated biphenyl (PCB) and PCDF contaminants are reviewed (Kuratsune et al., 1988, 1975; Chen et al., 1980; Koda and Masuda, 1975; Rogan et al., 1988). Even though these poisoned oils did not contain TCDD, they did contain many TCDD-like congeners currently considered by EPA to have carcinogenic potential that can be compared to TCDD. Also, certain dioxin-like PCBs are suspected human carcinogens on the basis of their receptor-binding characteristics and animal studies. Non-dioxin-like PCBs are known animal carcinogens.

Only follow-up and case-control studies are considered in this review. Case reports, other clinical observations, and prevalence surveys are excluded. The review is restricted to studies that have been published or are about to be published and that are available in the open scientific literature. Prepublication reports and studies published only in abbreviated form (as well as abstracts or letters to editors) are included only where they supplement the published articles. These restrictions limit the review to studies that have received at least a minimum of peer review and that have been described fully enough to permit a thorough assessment of materials, methods, and results.

7.3. PREVIOUS EPA REVIEWS

In the Health Assessment Document for Polychlorinated Dibenzo-*p*-Dioxins, dated September 1985 (U.S. EPA, 1985), the majority of the epidemiology studies pertained to groups of herbicide applicators with potential exposure to phenoxy acids and/or chlorophenols. In that report, the analysis emphasized case-control studies of STSs and non-Hodgkin's lymphoma (NHL). That report concluded that the epidemiologic research available at that time provided "limited evidence for the carcinogenicity of phenoxy acids and/or chlorophenols in humans. However, with respect to the dioxin impurities contained therein, the evidence for the human carcinogenicity for TCDD based on the epidemiologic studies was only suggestive because of the difficulty of evaluating the risk of TCDD exposure in the presence of the confounding effects of phenoxy acids and/or chlorophenols." In its next report, the review draft dated June 1988 of A Cancer Risk-Specific Dose Estimate for TCDD (U.S. EPA, 1988), the focus was essentially the same, and EPA concluded that "the human evidence supporting an association between exposure to TCDD and cancer is considered inadequate."

7.4. REVIEW METHODS

This review will follow the spirit of the EPA Risk Assessment Guidelines of 1986 (U.S. EPA, 1987) by considering alternative explanations for results observed in epidemiologic studies. These explanations fall into the general categories of causality, chance, bias, and confounding. The basic approach is akin to a process of elimination, by which one attempts to determine the direction and to quantify the magnitude of the influence that chance, bias, and confounding may have had on the results of each study. Wherever possible, the results of all studies will be reported in units of relative risk estimates and 95% confidence limits.

Most biases in epidemiologic studies can be placed into one of two categories: biases of classification and biases of selection. Classification biases can result from inaccurate ascertainment of exposure, disease, or confounders. Selection biases can result from nonrepresentative sampling of populations, as in the selection of controls in case-control studies, or from incomplete participation by study subjects. Any bias gains tenability as an explanation for an observed result if empirical evidence can be adduced to buttress the mere suggestion that the bias might have occurred. Only those biases considered to be potentially important will be addressed explicitly in this review.

When imprecise exposure estimates are available, such as with much of the epidemiologic data on dioxin, estimates of risk can be potentially biased toward the null. Misclassification, if random, could potentially lead to a masking of a true effect.

Classification biases are of two kinds: differential and nondifferential. Differential misclassification will lead to either an exaggeration or an underestimation of an effect.

Nondifferential misclassification occurs when the exposure or disease classification is incorrect in a portion of the subjects (cases or controls). This type of bias is generally toward the null, and the risk estimate may reflect this. Such misclassification can happen when some subjects are classified as having exposure to dioxin when they really were not exposed. Similarly, some actually may have had exposure but were classified as not having had it. In studies where few or no effects were seen, researchers must seriously consider the problem of nondifferential misclassification. This can be the reason that nonpositive risk estimates or even disparate risk estimates are seen from different studies of the same effect. On the other hand, in studies with significant results, nondifferential misclassification is not likely to be a cause of a significant finding.

Recall bias may produce the opposite effect. Persons with a disease may tend to remember exposure to a substance better when they know that such exposure might be associated with the disease. This could potentially lead to inflated risk estimates. In fact, it has been suggested that such biases are present in many of the case-control studies on dioxin. The Swedish studies by Hardell and colleagues have been particularly singled out for criticism in this respect. That some recall bias may be present is confirmed in a later case-control study (Hardell and Eriksson, 1988) in which some reduction of risk estimates was produced by the use of cancer controls. But then this result could be the result of a general cancer effect as well.

Confounding bias is a tenable explanation for an association between an exposure and a disease if the hypothetical confounder can be named and if a good case can be made that it is a cause of the disease, that it was associated with the exposure in the study population, and that it was not adequately controlled in the study design or data analysis. This review will explicitly mention only those potential confounders that meet all of these criteria.

As stressed in previous EPA reviews (1985, 1988), concomitant exposures present a special problem of potential confounding in the literature on TCDD and related chemicals. As a noteworthy example, an association between 2,4,5-T exposure and a given cancer, if causal, could be due to 2,4,5-T itself, to TCDD, or to some other contaminant. The problem multiplies when it is recognized that, historically, many phenoxy acid herbicide preparations were mixtures of 2,4,5-T and 2,4-D and that many persons who manufactured, processed, and used these preparations were exposed to other chemicals as well. Nevertheless, it may be possible, by examining studies of persons exposed to different combinations of chemicals, to identify "threads" of commonality and differences in the results, especially when specific cancers are considered separately.

Publication bias, sometimes considered a form of selection bias, is the tendency for the results of a study to influence a judgment as to whether or not it will be published. The direction and magnitude of publication bias is difficult, if not impossible, to quantify. It is expected to be

a much greater problem in literature reviews and in studies relying on existing records than in original research in which substantial resources are devoted to collection of data of relatively high quality. The level of effort required for such studies creates a strong incentive to publish the results. There is a tendency to publish studies with positive results as opposed to studies with nonpositive findings.

Strength of association, as measured by the magnitude of the estimated relative risk, is an important feature of a study's results. The stronger the association, the stronger a bias or confounding factor would have to be to explain it. Because questions of bias and confounding are study-specific, no defensible criteria can be set up in advance to place relative risk values into categories of strength of association.

Trends in increased risk by degree of exposure and by time since first exposure (latency) are also important. Different hypothetical causal mechanisms might predict different exposure-response and latency patterns. Hypotheses of steadily increasing effect with increasing exposure (i.e., monotonic exposure-response functions) and hypotheses of effects early in the carcinogenic process (e.g., for factors that operate at the initiation stage) predict that increases in risk will be greatest among persons with relatively high degrees of exposure and after relatively long latency periods. Hypotheses of tumor promotion and/or initiation will be discussed in the appropriate sections.

Replication of results is important in all scientific research. When several studies have shown a positive association of effect with the same exposure but were conducted under different circumstances, the possibility that an unknown confounder or chance produced the observed elevated effect is minimized. When different investigators working with different populations using different methods confirm an original finding, the results are more believable.

The statistical aggregation of results from different studies (meta-analysis) has become a popular feature of epidemiologic literature reviews. In this review, results from separate studies are aggregated only when all key methodologic features and results are reasonably similar. The method of aggregation used here is to take the ratio of the sum of the cause-specific observed deaths to the sum of the cause-specific expected deaths for the individual studies. Because investigators recognize the value of varying their methods to test methodologic hypotheses, and because results often differ appreciably, aggregation of results is not often indicated and is done here with caution.

7.5. FOLLOW-UP STUDIES OF CHEMICAL MANUFACTURING AND PROCESSING WORKERS

7.5.1. United States

Fingerhut and colleagues (1990, 1991) reported a study of 5,172 males who had worked at 12 plants in the United States in the production of chemicals contaminated with TCDD. Five thousand of the cohort members (97%) were identified in company records as having been "assigned to a production or maintenance job in a process involving TCDD contamination" (Fingerhut et al., 1991). The remaining 172 cohort members were "identified in a previously published study on the basis of exposure to TCDD" (Fingerhut et al., 1991). This cohort subsumed, and thereby supplanted, company-specific cohorts from Dow Chemical USA (Ott et al., 1987; Cook, 1981) and the Monsanto Company (Zack and Gaffey, 1983; Zack and Suskind, 1980) that had been the subject of previous reports. This study was initiated in 1978 to determine whether health effects were apparent in humans who were exposed to 2,4,5-T. In 1978, toxicological, teratogenic, and carcinogenic effects data were released that indicated a cancer effect in animals. There was a concern about the potential effects of exposure to Agent Orange on Vietnam veterans and workers who produced products that were contaminated with dioxin (Fingerhut et al., 1992). Follow-up began in 1940 or on the date of the "first systematically documented assignment to a process involving TCDD contamination" (Fingerhut et al., 1991), whichever was later, and closed at the end of 1987. Comparisons were made with the United States population.

The authors stated that approximately 13% of the cohort of 5,172 workers had records of chloracne. The presence of a significant incidence of chloracne in a group of people is an indicator of relatively intense exposure to TCDD. Chloracne can be caused by higher-chlorinated PCDDs, PCDFs, and PCBs as well (O'Malley et al., 1990) and also by Ah receptor agonists such as brominated congeners and with naphthalenes. It is a highly specific indicator of exposure to these compounds because it virtually never occurs among unexposed persons. It is a nonsensitive indicator, however, because many highly exposed persons do not develop it (Manz et al., 1991; Caramaschi et al., 1981; Mocarelli et al., 1991). Exposure to other dioxin-like chemicals that can be found in the workplace produces a form of chloracne that could be indistinguishable from that produced by dioxin (Ott et al., 1993). These chemicals can be dioxin-like in their effects and act through the aryl hydroxylase (Ah) receptor.

Although all members of the cohort had specific assignments to TCDD exposure areas in common, exposures to multiple chemicals generally occur in the chemical industry. At one plant, for instance, considerable overlap existed among persons involved in the production of chlorophenols, 2,4,5-T, and 2,4-D (Ott et al., 1987; Bond et al., 1988, 1989a), and thus exposed to TCDD and higher- and lower-chlorinated PCDDs. Presumably, many persons throughout the

cohort had contact with other chemicals. Comprehensive surveys of chemical exposures were conducted in plant-specific cohorts and may be available through the authors.

Special attention was paid to results for the 3,036 workers who were followed for at least 20 years after first exposure. This group was again divided into those with less than 1 year (N=1,516) and those with more than 1 year (1,520) of exposure (referred to below as the long duration/latency subcohort). One year was chosen as the criterion for duration of exposure because an analysis of 253 workers from 2 plants showed that every worker with 1 or more years of exposure had a lipid-adjusted serum TCDD level greater than the mean value (7 ppt) in a comparison group of unexposed workers (Fingerhut et al., 1990). Although the average level for all 253 workers was 233 ppt, the average increased to 418 ppt in those 119 who were exposed for 1 or more years (Fingerhut et al., 1991). The average serum TCDD level in those exposed less than 1 year was 69 pg/g. The researchers described a plan, utilized by Steenland et al. (1999), that replaced this duration-based exposure scale by using "a dioxin exposure matrix constructed from historic process descriptions, analytic measurements of TCDD and industrial hygiene data . . . to develop the relative ranking of workers exposed to TCDD" (Fingerhut et al., 1990).

The cohort as a whole experienced an estimated 15% (95% CI = 1.0-1.3) elevation of mortality from all cancers combined, with a 46% elevation (95% CI = 1.2-1.8) among those in the long duration/latency subcohort (Table 7-1). An excess of deaths from cancers of connective and soft tissues (STSs) was apparent in the total cohort (RR = 3.4, CI = 0.9-8.6) and in the long duration/latency subcohort (RR = 9.2, CI = 1.9-27.0), but these results were based on only four deaths and three deaths, respectively, from two different plants. A 40% overall elevation in deaths (CI = 0.7-2.5) from NHL was confined to workers in the total cohort and was not seen in the long duration/latency subcohort. Results for Hodgkin's disease were highly imprecise, based on only three deaths (vs. 2.5 expected) in the total cohort. Lung cancer was elevated by 10% overall but by 40% (CI = 1.0-1.9) in the long duration/latency subcohort. A similar 40% excess of stomach cancer (CI = 0.4-3.5) in this subcohort was based on only four deaths; no excess was seen in the total cohort.

The investigators conducted a special study of connective and soft tissue cancers. A review of all available hospital records and tissue specimens failed to confirm the indications of STSs on two of the four death certificates that had been assigned to this cause-of-death category (Fingerhut et al., 1990). The review also provided evidence that two persons in plant 8 whose deaths had been assigned to other causes of death had actually had soft-tissue sarcomas. Because only the exposed cohort's death certificates were subjected to detailed review, the analytic comparisons with the United States population were required to be based strictly on death certificate information. The basic and well-known rule in such situations is that, absent evidence to the contrary, erroneous information on death certificates must be considered to have been

equally frequent in the two groups being compared. But Suruda et al. (1993), in a study of STS diagnoses in cohorts exposed to dioxins and chlorinated naphthalenes, found that death certificates are "relatively insensitive"for detecting STS and that the power of life-table analysis to detect excess risks of STS may be reduced compared with its utility in correctly estimating the risk of other cancers, such as colon cancer or rectal cancer. However, the correct identification of STS as the underlying cause of death on death certificates appears to be much better (82%), based on medical records, than first thought according to the results of this study. Medical records on the remaining 18% could not be found. If a death certificate gives as an underlying cause of death a STS and it is coded as 171x, it is very likely correctly coded, according to the authors. In an earlier study, this figure was estimated by Percy et al. (1981) to be 55%. This nondifferential misdiagnosis could potentially bias risk estimates downward (underestimate the true risks).

Four of the STSs that are discussed in Fingerhut's study (two are included in Fingerhut's life-table analysis while two others are discussed but did not qualify for inclusion in the life-table analysis) are actually from the Nitro, West Virginia, plant. The remaining two cases that were included in Fingerhut's life-table analysis are from a different plant in the study. One of these cases also suffered chloracne. The four cases from the Nitro, West Virginia, plant are also the subject of a later study by Collins et al. (1993). The two cases included in Fingerhut's life-table analysis had previously suffered chloracne from an incident in which 121 workers developed chloracne as a result of a trichlorophenol process accident on March 8, 1949 (Zack and Gaffey, 1983). Collins et al. (1993) included one more STS not previously discussed by Fingerhut from the same plant. The Collins et al. (1993) study is reviewed later.

If the properly diagnosed STSs were correctly assigned to their appropriate plants and the two incorrectly diagnosed STSs were removed, there would be one STS in plant 9 and three in plant 8. No STSs were found at the other plants. This unusually skewed distribution might possibly be related to the accident that happened in plant 8 in 1949. Or perhaps physicians in Nitro, West Virginia, are more likely to diagnose STS than are physicians in other areas of the country. Because of the rarity of STS, there was inadequate statistical power to expect to see STSs in the other individual plants. If an excess risk is associated with exposure to TCDD, then it might be several more years before this cohort will produce STSs at the other facilities that are part of the study.

Cases of STS include a diverse group of histological entities. All STSs arise only from mesenchymal tissue, and all share common features that make them alike in their basic intercellular and intracellular composition rather than different in their morphology and location. Characterizing them as fundamentally different because they are found in different sites of the body is perhaps inadequate for determination of the risk of cancer (Enzinger and Weiss, 1988).

The histological classification of STS is centered on a dozen distinctly different classes of mesenchymal cells that form six relatively well-defined but widely distributed organ systems. By considering the growth pattern and cell morphology with an evaluation of intracellular and extracellular products of the tumor cells, fairly precise histogenetic classification of STSs is possible (Hajdu, 1981). For human cancer risk assessment, all connective tissues developing from the same mesodermal tissue, expressing the same set of "proto-oncogenes"and surrounded by the same chemical milieu of the extracellular matrix, are expected to develop cancer following exposure to certain carcinogens. The grouping of these end-target organs together is therefore necessary to evaluate the risk from exposure to dioxin.

Confounding by cigarette smoking must be considered in interpreting the approximate 40% excess of lung cancer deaths in the long duration/latency subcohort (Table 7-2). For the United States as a whole, the authors (Fingerhut et al., 1990) computed age-adjusted proportions of 24% never smokers, 19% former smokers, and 57% current smokers in 1965 (roughly midway through the follow-up period). The corresponding proportions were 28% never smokers, 14% former smokers, and 59% current smokers among the 87 workers from the study of serum TCDD levels who were members of the long duration/latency subcohort as well. Assuming relative risks of lung cancer of 4.7 for former smokers and 10.9 for current smokers, the authors used a standard technique (Axelson and Steenland, 1988) to adjust the number of expected lung cancer deaths and found essentially no change in the results. It should be kept in mind that the sample of smoking histories was taken from only two plants but the excess in lung cancer risk was chiefly in two other plants. The generalization of smoking habits of employees in 2 of the 12 participating plants to that of the entire cohort may not be representative of the true smoking impact on the risk of lung cancer to the cohort. Most of the lung cancers (56 of 89 observed lung cancer deaths) came from 3 facilities. The remaining 7 plants contributed the other 33 lung cancers to the total because of the small sizes of the respective subcohorts and insufficient latency. It then would be possible to evaluate the effect of smoking on the risk of lung cancer at each individual plant. It should be remembered that national U.S. rates were used to derive expected deaths in each of the 12 plants. It is possible that local or regional rates may be a more appropriate comparison population for the cancer sites examined by the authors, although local rates may be unstable. In addition, if biomonitoring could be extended to the remaining 10 plants, a better idea could be derived concerning the dose levels associated with those plants experiencing higher lung cancer rates. The authors point out that deaths from other diseases associated with smoking, such as diseases of the heart and circulatory system and emphysema, were either not increased or significantly decreased in this cohort (Fingerhut et al., 1990). Although the possible contribution of factors such as smoking and occupational exposure cannot

be excluded, there is no evidence that smoking patterns in this cohort are entirely the reason for the elevated risk of lung cancer (Fingerhut et al., 1991).

One possible explanation for the increase is that the 87 surviving members of the long duration/latency subcohort did not show the well-known tendency for smoking to be more common among blue-collar workers than in the general population. A possible reason is that because smoking appreciably elevates the overall death rate, fewer and fewer smokers will remain in a fixed group of persons as time goes by. Thus, the use of the 87 *surviving* members of the long duration/latency subcohort may have underestimated the proportions of former and current smokers in the subcohort as a whole over the course of mortality follow-up. However, this same phenomenon is also present in the population from which expected deaths were generated, so the effect is probably nullified. The effect on the lung cancer risk as the proportion of smokers increased in the cohort is shown in Table 7-2. The lack of increased mortality from cardiovascular diseases as well as cancer of the buccal cavity and pharynx in this cohort, however, makes this explanation less likely. Furthermore, as the authors point out, mortality from nonmalignant respiratory disease (standard mortality ratio [SMR] = 96), which is often associated with smoking, was less than expected. This strengthens the argument that exposure to dioxin causes lung cancer.

On the other hand, the authors report a correlation coefficient of 0.72 between length of exposure and serum TCDD tissue level. This negative bias is potentially much greater than the positive bias that could possibly be produced by smoking. And because nondifferential bias is the only type of bias that could occur in the Fingerhut study, risk estimates are more than likely lower than the true risk. The only way that dioxin exposure could have a positive bias is if it prevents cancer and the exposure classification is 100% wrong.

The authors of this study also report that two of these cancer deaths were from mesothelioma, a finding that more than likely indicates exposure to asbestos. Although these two mesotheliomas occurred at plants 9 and 12, it is not known whether these persons were exposed in that job or in some previous job. Only one death from asbestosis was noted in the nonmalignant respiratory deaths, and this occurred in Plant 1. These three asbestos-related deaths were more than likely due to exposure in a previous occupation.

Fingerhut et al. (1991) has been updated by Steenland et al. (1999), of the same research group. The SMR for all cancers combined was 1.13 (95% CI = 1.02-1.25). The SMR for all cancers combined for the highest exposure group was 1.60 (95% CI = 1.15-1.82). Recent analyses support the finding that high exposure to TCDD results in an excess of cancer without any marked specificity. Steenland and colleagues' later analyses differ from Fingerhut's in that the authors applied a "job-exposure matrix"to a subcohort of 3,538 workers from the original 5,172 male workers and followed the entire cohort for 6 more years. This job exposure matrix is

not based upon ambient air levels of TCDD or even blood TCDD serum levels. It is based upon the concentration of TCDD (μg/g) present in the process materials to which the workers are exposed *times* the fraction of the day the worker was employed in that process *times* the "contact"level (meaning the likelihood the product will reach the skin or be inhaled) *times* the period of time the worker worked in proximity to TCDD. Steenland et al. did not consider workers and plants where records on the degree of exposure to TCDD were lacking, a detailed work history was lacking, or there was concurrent exposure to pentachlorophenol contaminated by higher chlorinated PCDDs/PCDFs. They also analyzed a subcohort of 608 workers with frank chloracne without regard for any of the exceptions mentioned above, and analyzed a subset of 393 of the 608 who fell into the subgroup of 3,538 workers above.

The results indicated that as cumulative exposure increased through seven exposure categories based upon their "job-exposure matrix," the calculated risk of overall cancer mortality tended to increase (all sites combined). In the chloracne cohort of 393 men mentioned, in the two highest septiles of cumulative exposure the risk was significant at 1.68 (CI = 1.19-2.30).

In the larger subcohort of 3,538, the results tended to be similar but less pronounced. Utilizing either the life-table analytical method or the Cox regression method, trends tended to be positive, although in an inspection of the seven categories, the increasing trends are not monotonic using either method, lagged or unlagged (Table 7-3).

Although the authors believe that this lack of linear trend in cancer with cumulative exposure as a continuous variable is due to the extreme skewedness of the data, this may have more to do with the way in which cumulative exposure is determined in the job-exposure matrix and the fact that the authors use seven exposure categories to generate risks. The fact that quantity of TCDD in process materials is used, rather than ambient air levels of TCDD or even blood serum levels of TCDD, to determine basic exposure potentially removes the estimation process for exposure even further from the truth. There is likely considerable variability in the cumulative exposure indices calculated for individuals in this cohort. Furthermore, the use of so many categories of exposure also makes individual risk calculations within each septile less stable and perhaps even unreliable, because they are based upon smaller numbers.

Despite these problems the authors were still able to detect significantly positive trends in total cancer, several site-specific cancers such as lung cancer, and even ischemic heart disease, especially when they considered the logarithm of cumulative exposure (the more appropriate test statistic for this kind of distribution of exposures). The finding concerning an increased risk of ischemic heart disease seems consistent with what is known about the interaction of serum dioxin with endogenous cholesterol and high-density lipoproteins. There appears to be an inverse relationship between serum TCDD level and high-density lipoprotein and a positive relationship with total cholesterol (Grubbs et al., 1995; Calvert et al., 1996).

Another observation is the finding that the risk of bladder cancer (16 cases) was increased by exposure to 4-aminobiphenyl at the one plant where 10 cases occurred. This is consistent with the fact that 4-aminobiphenyl is a strong bladder carcinogen. This could potentially bias the elevated overall cancer risk because these deaths are included. However, they will probably not affect site-specific cancers such as lung cancer, except that bladder cancer "competes" with other potential causes for the distinction of being designated the "underlying" cause of death. The authors also point out that exposure-related trends remained unchanged for smoking-related cancers when bladder cancers were omitted. This implies that the findings for all cancers remained unchanged when bladder cancers were omitted. The excess is about eight cases over expected.

The analysis done by Fingerhut in her first paper, showing that there is a high correlation between years of exposure to TCDD and in vivo serum levels of TCDD, based upon 253 workers, is strong evidence of a likely dose-response relationship. Endogenous markers of exposure are superior to exogenous man-made constructs. Although markers of exposure that are closer to the target organ for carcinogenicity are better indicators of the actual dose received by the organism at some given point in time, they still tell us little of what may have occurred by way of exposure in the past and exposures in the future. However, indexes of exposure such as "cumulative exposure" are likely to be more accurate and reliable when based upon actual dose measures.

In summary, Steenland et al. (1999) continues to support the hypothesis that dioxin is causally associated with an increased risk of cancer punctuated by increased selected site-specific risks such as lung cancer, STS, etc. There is a significant positive trend for cancer mortality with increasing exposure, with a 60% excess mortality from cancer in general in the highest exposure group. But in addition, the data suggest a potential for an added risk of ischemic heart disease.

The positive association of lung cancer in male workers observed in this study is also consistent with an excess of pulmonary tumors found in male mice and rats exposed to TCDD (see Chapter 6). These same animal data suggest the possibility of a protective hormonal effect from TCDD and the risk of pulmonary cancer in female rats. Because this study dealt with only male workers, this hypothesis could not be verified in female workers. On the other hand, no elevated risk of liver cancer is evident in male workers even in the long duration/latency subcohort. This is also consistent with rat data, where the tumors were only observed in female rats. If there is a promoting effect on liver cancer in human females due to hormonal effects, as suggested by the rat studies, it could not be verified.

Collins et al. (1993) suggested that there is an association of STS with exposure to 4-aminobiphenyl. The authors reported that workers who developed chloracne from an accident in which a chemical mix containing TCDD was scattered throughout a 2,4,5-trichlorophenol plant

had increased mortality from STS, bladder cancer, and respiratory cancer. All individuals who were identified in this study of 754 chemical employees as having STSs or lung cancers, and who were employed at the time of the 1949 accident, were potentially exposed to 4-aminobiphenyl as well as to TCDD. However, it is not known how many were actually working inside the plant when the accident occurred. 4-Aminobiphenyl is thought to be a bladder carcinogen from previous studies. However, this chemical has not been shown to be associated with STS or lung cancer in humans. Unfortunately, no tissue measurements are available to substantiate exposure to TCDD or exposure to 4-aminobiphenyl. It is also of interest that no significant increase in STSs was noted in the "chloracne-free" subgroup exposed to 4-aminobiphenyl. However, the authors report that an additional 106 persons also had indications of chloracne-type conditions noted in their medical files, presumably as a result of exposure to TCDD and not as a result of the accident. Although these individuals probably were heavily exposed to dioxin as well, these workers were included in the "no chloracne" subgroup for the purpose of analysis. It would be of interest to see what effect would occur to the risk estimates if these workers were included in the "chloracne" subgroup. Furthermore, plant employees who left work before March 8, 1949, or began work after November 22, 1949, were not included even if they had received exposure to dioxin or developed chloracne as a result of exposure. The major interest, according to the authors, was in the 122 workers who developed chloracne from the 1949 accident. The authors point out that the numbers are small and that confounding factors, such as misclassification of exposure, cannot be ruled out. 4-Aminobiphenyl has not been reported in plant 9, where one STS was diagnosed. This study presents an interesting explanation that has not been substantiated anywhere else.

It was also noted by Collins that toxicological evidence is available that supports the idea that STSs (i.e., angiosarcomas) have resulted from exposure to 4-aminobiphenyl (Schieferstein et al., 1985). Angiosarcomas and bladder cancer in females were found to be dose-related with oral consumption of 4-aminobiphenyl in drinking water. However, angiosarcomas of the liver arise mainly in the endothelial lining of blood vessels. This type of tissue is more likely susceptible to a hydrophilic carcinogen such as 4-aminobiphenyl during its passage through the blood vessel. Hydrophobic carcinogens such as TCDD might be expected to exert an influence on mesenchymal tissue from which most STSs arise, i.e., fibrosarcoma, histiocytoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, schwannoma, myxoid neurogenic sarcoma, and others. Therefore, the author's assumption that 4-aminobiphenyl can cause other types of STSs remains unproven and highly unlikely.

Ramlow et al. (1995) updated the study of a portion of an earlier cohort of workers studied by Ott et al. (1987). Some 770 workers involved in the manufacture of pentachlorophenol (PCP) were identified for a mortality study. PCP, a broad-spectrum pesticide,

is contaminated with hexachlorinated, septachlorinated, and octachlorinated dioxins but allegedly little or no TCDD as well as PCDFs. Follow-up continued until December 31, 1989. Expected deaths were estimated based upon U.S. white male death rates. Separately, a reference comparison population of employees from the same company but presumably without exposure to PCP was used to develop site-specific relative risk (RR) estimates. Fifty cancer deaths were observed, whereas 52.6 were expected based upon U.S. death rates. When stratified according to a 15-year lag time after initial exposure, and further stratified into subjectively determined cumulative H/OCDD high, medium, and low categories, there appeared to be little evidence of any consistently increased site-specific cancer risks that could be attributed to exposure to PCP other than those induced by the small numbers. The same could be said of the comparison with the nonexposed company cohort. Calculated relative risks by 15-year lag time in each of the three categories of exposure according to site revealed little that could be attributable to PCP exposure. The few significant cancer risks seen were based upon small numbers (kidney cancer, two deaths in the high-exposure category; gastric and duodenal ulcer, four deaths in the medium-exposure category; and accidents, nine deaths, high-exposure category). The authors, however, concluded that the few significantly increased site-specific deaths that were apparent could not be attributed conclusively to PCP exposure. This study could benefit by having TEQ-determined blood serums taken in order to substantiate if and how much exposure actually did occur to members of the cohort, and also a longer follow-up to accumulate additional deaths.

7.5.2. Germany

Manz and colleagues (1991) reported a study of 1,583 persons (1,184 men and 399 women) employed at a German chemical manufacturing facility that produced 2,4,5-T and its precursor, 2,4,5-trichlorophenol. In 1954, a chloracne outbreak had occurred in the working population of the plant, and after that, production of the TCDD contaminant was reduced. Cohort members worked at least 3 months from 1952 through 1984. The start of follow-up was not stated in the report, but presumably began on the date of accumulation of 3 months of employment. The follow-up period closed at the end of 1989. The cohort's mortality experience was compared with that of the West German population and with that of a cohort of workers at a gas supply company. Because limited data on the gas workers forced that comparison to be based on a subset of the TCDD-exposed cohort, and because the results did not differ materially between the analyses, only the results of the comparisons with West Germany are reported here.

The cohort was postdivided by duration of employment and by a three-category exposure scale based on TCDD measurements “in nonsystematic samples of precursor materials, products, waste, and soil from the grounds of the plant, mainly after the plant had closed in 1984" (Manz et al., 1991). This scale was validated to some extent by adipose tissue TCDD levels in 48

volunteers (mean = 296 ng/kg in 37 persons from the highest group, 83 ng/kg in 11 persons from the other two groups). On the basis of these results, the low and intermediate groups are combined for the present analysis.

For the males, this study, with 75 total cancer deaths expected and 24 expected in the high-exposure subcohort, was considerably smaller than the study by Fingerhut et al. (1991), which had 230 total cancer deaths expected and 78 in its long duration/latency subcohort (Table 7-4). Manz et al. presented detailed analyses only for all cancers combined. The high-exposure subcohort, and especially those with longer employment duration, experienced an excess of total cancer deaths (RR = 1.4, CI = 1.0-2.0 for the high-exposure group and RR = 2.6, CI = 1.2-4.9 for the high exposed/long duration subcohort) (Table 7-4). The authors concluded that "the increase in (total) cancer risk of 1.24-1.39 . . . cannot be explained completely by confounding factors, and . . . is associated with exposure to TCDD" (Manz et al., 1991). In a later abstract of an update of this same paper, Dwyer (1992) reported that after using a Cox regression analysis of nine major areas of employment within the plant, the area of work with the strongest relative risk for cancer mortality was 2,4,5-T production (RR = 2.7, CI = 1.7-4.2). These findings are similar to those of Fingerhut et al. (1991).

For the cohort as a whole, the estimated relative risk of lung cancer was 1.4 (CI = 1.0-2.0, 30 observed deaths). Smoking as an explanation for the observed increase is less likely because a comparison using the gas worker reference actually leads to an increased RR of 1.7 (CI = 1.1-2.4). Although smoking histories were not available for the entire Boehringer cohort, of the 361 men, 73% reported that they smoked. Similarly, 76% of 2,860 gas workers smoked. Substantial confounding based on smoking does not appear to be present because smoking seems to be similar in both plants. The estimate for stomach cancer was 1.2 (CI = 0.7-2.1, 12 observed deaths). Three deaths were observed from NHLs and none from connective and soft tissue cancers. (The authors described an additional three deaths from chronic lymphocytic leukemia as NHL deaths, but these deaths would not have been classified as non-Hodgkin's lymphomas in the other studies in this review.) Dr. Lennart Hardell pointed out (letter to David Bayliss, January 10, 1995) that under the most recent classification the category "non-Hodgkin's lymphoma" includes chronic lymphocytic leukemia as one type. Expected numbers of deaths from these cancers were not given. Based on the proportions of expected cancer deaths in the Fingerhut study, one might estimate that approximately 2.4 NHL deaths and 0.4 connective and soft tissue cancer deaths would have been expected in this cohort as a whole, and about 0.1 connective and soft tissue cancer deaths in the high-exposure subcohort. (The numbers of expected deaths from lung cancer, stomach cancer, or NHL in the high-exposure subcohort were not estimated because information is lacking on how many of the observed deaths from these cancers were in that subcohort.)

The authors reported exposure to other industrial chemicals, such as benzene and dimethylsulphite. In addition, manual laborers were "probably" exposed to asbestos to some extent. However, the authors maintain that this exposure explains neither the increased mortality from all cancers nor the patterns of associations with TCDD exposure groups.

Other possible sources of bias include a potential lack of comparability between cause of death ascertainment based on medical records (in some, perhaps many, cohort members) versus only use of death certificates for cause of death certification in the derivation of German national death rates. This is somewhat alleviated by the use of gas workers as a second comparison group. In these workers, the same methods were used for medical certification, making comparison of cause of death somewhat more accurate. However, this is offset by the fact that the gas workers may have somewhat better mortality experience because they had to work a minimum of 10 years to obtain entrance into their cohort, whereas the dioxin cohort had to work only a minimum of 3 months. This could have introduced survivorship bias in this group and consequently lower mortality and higher risk estimates.

Furthermore, the lack of an analysis of mortality data by time since first exposure for individual causes such as lung cancer makes it impossible to assess latent effects.

Of the 399 female cohort members, only 7% worked in high-exposure departments. In total, there were 54 deaths and an overall RR = 0.8 (CI = 0.6-1.0). The RR for all cancers was 0.9 (CI = 0.6-1.4), but the RR = 2.2 (CI = 1.0-4.1) for breast cancer was significantly increased based on 9 deaths. Kogevinas et al. (1997) and Saracci et al. (1991) also report a borderline significantly elevated risk of breast cancer based on nine cases who were exposed to TCDD or high chlorinated dioxins. This is an interesting result in view of a suggestion of reduced mammary cancer based on mechanistic studies and animal bioassays. However, at this point the data do not provide a sufficient basis for any conclusions.

In another update of the Manz et al. (1991) cohort, Flesch-Janys et al. (1995) extended the followup period to 1992. Lifetime exposure to the PCDDs and PCDFs (total toxic equivalencies) was estimated quantitatively for the entire cohort from a subcohort of the workers (n = 190) in the plant as well as estimated TCDD exposure alone. The Cox regression analysis provided estimated RR by dose generated according to successive quintiles of TCDD levels and total toxic equivalencies (TOTTEQ) or (PCDDs/DFs) matched by birth (5-year intervals). Gas workers constituted the first set of controls. The second set of controls were internal. They were formed from the first two quintiles and, lastly, the analysis was repeated excluding workers in the opiate department. TOTTEQs as discussed by Flesch-Janys et al. (1995) are not to be confused with the newer World Health Organization definition of TEQs. These Flesch-Janys TOTTEQs do not include any PCBTEQs or TCDD.

For TCDD alone, the highest relative risks for total cancer occurred in the highest quintile (divided into deciles) of TCDD exposure (RR = 3.30, 95% CI = 2.05-5.31). Estimated levels were between 344.7 and 3,890.2 ng/kg of blood fat, although mortality was elevated nonsignificantly in lower quintiles as well. These were dose-related. For TOTTEQ exposure, significant dose-related relative risks of total cancer were observed for the highest decile of TOTTEQ exposure as well (RR = 3.27, 95% CI = 2.04-5.26), although the concentrations were between 545.1 and 4,362 ng/kg of blood fat.

The authors concluded that the findings indicate a "strong dose-related relationship between mortality due to cancer" and exposure to polychlorinated dioxins and furans. One of the limitations to this kind of analysis is that it does not provide information regarding the contribution of the specific and most potent congener TCDD to the increased risk of cancer from exposure to TOTTEQ. The tables in the text of this paper suggest that when internal controls are used, the risk of cancer is greater for exposure to TCDD alone than with TOTTEQ, which includes TCDD. These data suggest that TCDD could be a confounding influence. However, there are many assumptions about estimates of the parameters utilized in this methodology.

Limitations in the calculation of risk estimates based upon exposure to TOTTEQ in this study are likely. Because the program computes estimates of the half lives of different congeners of the PCDDs and PCDFs from exposure data collected from 1986 to 1994, and these estimates are used in the calculaton of change in dose with time in job, the calculation of potentially inaccurate individual estimates of exposure based upon work histories that date back to as early as 1952 is possible.

Furthermore, no measurements are included from individuals who have died, some 414 (35%). Estimates of exposure from 190 live members of the cohort are generalized to the entire cohort through the regression techniques utilized. If any deaths are dose-related to TCDD, TCDF, or their congeners, their absence from the totals could underestimate doses for such individuals. This in turn could bias risk estimates toward the null, and this could be the explanation for the suggestion that the dose-response relationship for total cancer and increasing TOTTEQs is not stronger.

A corrected Table 4 (Erratum, Flesch-Janys et al., 1996) indicates that for cancer the RR is 2.69 (95% CI = 1.67-4.35). This did not change the bottom-line conclusion that there was a strong dose-dependent relation between mortality from cancer and exposure to polychlorinated dioxins and furans. This study was criticized in a letter to the editor (Swain, 1997) on the grounds that the exposure assessment was inadequate, the choice of reference population was inappropriate, and the statistical analysis was faulty. The author provided evidence in a rebuttal companion letter to the editor (Flesch-Janys, 1997) that the choices he made in the study were

not likely to produce any substantial biases in the results of the kind that were described by Swain.

In an effort to relate the risk of cancer to dose, Flesch-Janys et al. (1998) developed a lifetime cumulative exposure index on each of the 1,189 male German herbicide and insecticide workers discussed above and followed the cohort for another 3 years to the end of 1992. Cancer mortality based upon 124 cases was significantly increased (SMR = 1.41, 95% CI = 1.17-1.68). Mortality from lung cancer was also significantly increased (SMR = 1.51, 95% CI = 1.07-2.08) based upon 38 cases, as well as hematopoietic and lymphatic cancer (SMR = 2.16, 95% CI = 1.11-3.77) based upon 12 cases. Production department-specific dose rates that were used to develop exposure dose levels for all members of the cohort were derived from blood levels and working histories of 275 workers. Four categories of cumulative exposure were developed for TCDD as well as their corresponding TEQs. The cumulative PCDD/F (TEQs) levels were expressed as nanograms/kilograms blood fat times years of exposure and based upon some 382 blood samples as follows:

I.	1.0 ≤ TCDD < 125.2 ng/kg-years;	1.0 ≤ TEQ < 360.9
II.	125.2 ≤ TCDD < 627.1;	360.9 ≤ TEQ < 1,614.4
III.	627.1 ≤ TCDD < 2,503.0;	1,614.4 ≤ TEQ < 5,217.7
IV.	2,503.0 ≤ TCDD	5,217.7 ≤ TEQ

A significant trend of increasing risk with increasing cumulative PCDD/F was evident. The SMR for cancer was significantly increased (SMR = 1.73, 95% CI = 1.21-2.40) at the highest quartile (greater than 2,503 ng/kg-years) (Table 7-5). The authors concluded that these results indicated an elevated risk of total cancer mortality in a cohort with high exposure to PCDD/F, that a dose effect was evident for estimated TCDD levels on total cancer SMR analysis, and that these data could be used for quantitative cancer risk assessment for dioxin.

The authors provided an update to the mortality experience of this subgroup of females from the Manz et al. (1991) study by following them through 1995 (Flesch-Janys et al., 1999). For individuals known to be alive in 1995, mailed questionnaires were sent to elicit information on any cancer diagnoses within the period to 1995. If cancer had been diagnosed during this period, efforts were then made to secure medical records to substantiate the cancer diagnosis. Cancers at particular sites were added to the cancer deaths at that same site to develop incidence data in the cohort. Standardized incidence ratios (SIRs) were developed for all sites with two or more cases. The authors found that the risk of breast cancer was elevated (SIR = 1.55, 95% CI 0.98-2.32) based upon 23 cases. The risk of cancer in general was elevated only slightly (SIR = 1.10, 95% CI = 0.83-1.42). The finding of an increased risk of breast cancer is somewhat contradictory to the suggestion that TCDD/estrogen interactions decrease tumor incidence in organs such as in the mammary gland of Sprague-Dawley female rats (Chapter 6, p. 6-36;

Carcinogenicity of TCDD in Animals). The authors also found a dose-response relationship with I-TEQ (ng/kg blood lipid) as follows:

I-TEQ	RR	95% CI
0 - 1,900.9	0.99	0.4 - 2.05
1,901.0 - 2,823.9	1.5	0.55-3.28
> 2,824.0	2.56	1.23 - 4.71

The authors point out that this cohort is very small, and they maintain that no definite conclusions on individual contributions to the elevated risk can be drawn. They recommend an extension of the follow-up, including additional determinations of blood levels .

These criticisms are not meant to discourage further work in this area. This is one approach that could be taken to analyze whether TCDDs, TCDFs, and their congeners other than TCDD are associated with increasing risks of cancer and other adverse health effects. All of these potential problems could be reduced if exposure data could be collected over a longer span of time and specimens could be included from deceased members who died from diseases that might be attributable to exposure to TCDDs, TCDFs, and their congeners.

Becher et al. (1996) updated the earlier study by Manz et al. (1991). They included three additional cohorts of workers exposed to TCDD in three different factories in Germany, although at lower levels. The cohort of 399 women was not updated and was not studied further. However, the remaining workers within that production facility and two of the three cohorts were followed until the end of 1989. The fourth cohort, which he calls Cohort II, was followed until December 1992. The authors compared mortality within these cohorts to that based upon German national mortality rates. Altogether, some 2,479 workers from the 4 plants were studied. A total of 138 deaths from all malignant diseases produced a borderline significant SMR of 119 (95% CI = 100 - 141). The risk increased with latency and was highest in cohort I, the original study by Manz et al. (1991). It was within this plant that the highest TCDD blood levels were recorded; i.e., 3 to 2,252 ng/kg blood fat. An increased mortality from respiratory cancer (SMR = 154, 95% CI = 115-202), cancer of the buccal cavity and pharynx (SMR = 295, 95% CI = 135-560), and NHL (SMR = 326, 95% CI = 119-710) was found in the total cohort. The authors conclude that their findings are consistent with results from other cohorts, which showed an increased overall cancer mortality and mortality of respiratory cancer after long-term exposure to these phenoxy herbicides and dioxin. Combining several cohorts in order to increase the size of the study population could lead to underestimating risks if the dioxin exposures as evidenced by blood fat measurements are varied over a wide range from one plant to the next. On the other hand, this latter update is an improvement over the earlier study, which relied on gas workers who had to have worked a minimum of 10 years before they could be included in the comparison dioxin-exposed cohort. This eliminated potential survivorship bias, although it increased the potential for the healthy worker effect to play a role.

In another investigation in Germany, Zober and colleagues (1990) studied persons employed at another German chemical manufacturing facility where 2,4,5-trichlorophenol was produced. An uncontrolled decomposition reaction in 1953 and subsequent cleanup activities resulted in substantial TCDD exposures. The cohort contained 247 persons who had worked at the plant from 1953 through 1987, 51% of whom had developed chloracne or erythema (a skin condition that may be suggestive of chloracne), with mortality follow-up covering the same calendar period. Seventy-eight persons had died (RR = 0.95); 23 had died of cancer (RR = 1.2) (CI = 0.8-1.7). Expected deaths were based on national mortality rates in the Federal Republic of Germany. When workers with chloracne (N=114 chloracne plus 13 erythema) were looked at separately, the risk of cancer as expressed by the SMR rose to 1.4 (OBS= 16, CI = 0.9-2.1). Again, within this highly exposed subgroup, if the analysis is restricted to only those workers who were observed 20 or more years after first employment, the SMR was significant at 2.0 (OBS=14, CI = 1.2-3.2). For lung cancer, the SMR is of borderline significance at 2.5 (OBS=5, CI = 1.0-5.3). The authors report that the results "do not support a strong association between cancer mortality and TCDD, but they do suggest that some hazard may have been produced."

Three subcohorts were defined on the basis of the potential for varying degrees of exposure. Subcohort C1 contained 69 persons known to be exposed to TCDD during the accident period. Cohorts C2 (84 persons) and C3 (94 persons) contained workers thought to be exposed to lesser amounts of TCDD. Recent TCDD levels in blood samples from small numbers of persons in each group suggested that exposures were higher in C1 (median 24.5 ppt, 11 samples) than they were in C2 (median 9.5 ppt, 7 samples) or C3 (median 8.4 ppt, 10 samples). Thus, C2 and C3 are grouped together in this review. A second stratification by the authors divides the total cohort into 127 persons with chloracne (N = 114) and erythema (N = 13) versus 120 persons with neither. The average serum TCDD levels in the two subcohorts are 15 ppt and 5.8 ppt, based on 16 samples (with chloracne) and 12 samples (without chloracne), respectively. The two stratifications provide similar results. Only the results of the first stratification, i.e., C1, C2, and C3, are presented here.

This study, with only 20 expected cancer deaths in the total cohort and 4 expected cancer deaths in the members of subcohort C1 with 20 or more years of latency, is much smaller than the studies by Fingerhut et al. (1991) and Manz et al. (1991). The authors, however, did provide detailed analyses of data on specific cancers (Table 7-6).

Elevated mortality rates from lung cancer, stomach cancer, and all cancers combined were confined largely to the members of subcohort C1 with long latency. The confidence intervals for the relative risk estimates are extremely wide, however. No deaths from cancers of connective and soft tissues or from NHL were observed, and expected numbers of deaths from these cancers were not reported. However, one mesothelioma was reported in a plant supervisor

with known asbestos exposure. Based on the proportions of all expected cancer deaths due to these cancers in the study by Fingerhut et al. (1991), one might estimate that approximately 0.6 NHL deaths and 0.1 connective and soft tissue cancer deaths would have been expected in this cohort as a whole, and about 0.2 NHL deaths and less than 0.1 connective and soft tissue cancer deaths among the members of subcohort C1 with long latency. This study lacks power to detect a significant site-specific cancer risk at most sites because of its small size.

In an update of this study, Ott and Zober (1996) added an additional 4 years of follow-up and reduced the size of the cohort slightly to just the 243 male members. They subsequently divided the cohort into four exposure categories based upon estimated TCDD dose expressed in μg/kg body weight. The development of this surrogate involved an appproach that included detailed accounts of each employee's work activities, analyses of TCDD in blood lipid of 138 employees back calculated to time of initial exposure utilizing a half-life estimate of 5.8 years for internal TCDD dose, and internally derived estimates of elimination rates of TCDD. Four categories of cumulative exposure were developed as follows: under 0.1 μg/kg body wieght estimated TCDD dose, 0.1 to 0.99, 1.0 to 1.99, and 2.0+ μg/kg body wieght. They calculated standard mortality ratios (SMRs) for total cancer in each category as well as site-specific cancer mortality after a 20-year latency. By the end of 1992, 47 men were diagnosed with cancer while 31 had died. The risk of cancer tended to increase with dose, although not significantly, because of the reduced power to detect a significant risk based upon decreasing size of the subcategories in the higher dose categories. At TCDD cumulative doses greater than 1 μg/kg, the SMR is 1.6 (95% CI = 0.9-2.6) (Table 7-7).

However, after 20 years' latency, the risk of cancer became significant in the exposure category $\geq$ 1 μg/kg body weight (SMR = 1.97, 95% CI = 1.05-3.36). Of the 13 cancer deaths in this category, 6 of these were due to lung cancer. The risk of lung cancer was also significant in this category (SMR = 3.06, 95% CI = 1.12-6.66). The same pattern of increasing risk with increasing dose was true based upon standard incidence ratios, although the increase was less pronounced. In the higher exposure category, greater than 1 μg/kg body weight, the SIR without regard to latency was 1.3 (95% CI = 0.8-2.0). For lung cancer, based on 8 cases the SIR was significantly elevated at 2.2 (95% CI = 1.0-4.3). The authors concluded that their findings were consistent with a carcinogenic effect induced by TCDD at the high dose category ($\geq$ 1 μg/kg body weight). The authors did note that because the cohort was small, the risk estimates could be affected by selection bias and/or confounding bias.

7.5.3. Ten-Country Study by International Agency for Research on Cancer

A historical cohort study of cancer mortality in 18,390 production workers or sprayers exposed to chlorophenoxy herbicides and/or chlorophenols was reported by Saracci et al. (1991).

Exposure was reconstructed through questionnaires, factory or spraying records, and job histories. Workers were classified as exposed (N = 13,482), probably exposed (N = 416), exposure unknown (N = 541), and nonexposed (N = 3,951). The exposed group contained everyone known to have sprayed chlorophenoxy herbicides and everyone who had worked in any of certain specified departments at factories producing chlorophenoxy herbicides. The criteria for duration or level of exposure required for selection was reported for only 3 of the 10 countries and only 4 of the 20 cohorts; these ranged from at least 1 month to 1 year. For all the other cohorts, the criterion for inclusion was to have ever been employed in production or spraying of these herbicides. The cohort contained 1,537 female workers, but results were not presented separately, except for female breast and genital organ cancers by phenoxy herbicide exposure. Average follow-up for the cohort was 17 years; 5% of eligible workers were lost to follow-up. Three of the cohorts comprising over 10,000 workers have also been reported in separate publications but for different follow-up periods (Lynge, 1985, 1987, 1993; Coggon et al., 1986; Kogevinas et al., 1993); these are discussed briefly in this report following this discussion. Several other occupational cohorts discussed in this report are also included.

Also included in the analysis was a division of the cohort (probable vs. unlikely) by whether or not exposure to TCDD occurred. No definition is given for "probable" exposure to TCDD; exposure to phenoxy herbicides does not necessarily imply exposure to TCDD. The "probably exposed" category includes production workers at two plants producing PCP, 2-(2,4-dichlorophenoxy)propanoic acid (2,4-DP; dichlorprop), 4-(2,4-dichlorophenoxy)butanoic acid (2,4-DB), (4-chloro-2-methylphenoxy)acetic acid (MCPA), or 2-(4-chloro-2-methylphenoxy)-propanoic acid (MCPP; mecoprop). There is not likely to be any TCDD in these processes. Those "unlikely exposed" appear to be so classified because they worked in different factories. There were 181 cases of chloracne among workers in the cohort.

The results are presented below by each of the two divisions of the total cohort: phenoxy herbicide (PH) and/or chlorophenols, and probable TCDD exposure. For the cohort division by PH and chlorophenols, no excess was observed for all-cause mortality, for all malignant neoplasms, for most common epithelial cancers, or for lymphomas. The four STS deaths were all in the "exposed to phenoxy herbicides and chlorophenols" subcohort (RR = 2.0, CI = 0.5-5.2) and all appeared 10 to 19 years after first exposure (RR = 6.1, CI = 1.6-15.5), with the excess risk limited to exposed sprayers (RR = 8.8, CI = 1.8-25.8) based on three observed deaths. None were observed in the 20 years or more category. Increases were also noted in the exposed group for mortality from thyroid cancer (RR = 3.7, CI = 1.0-9.4) based on four deaths, cancer of the testis (RR = 2.2, CI = 0.9-4.6) based on seven deaths, other endocrine glands (RR = 4.6, CI = 0.9-13.5) based on three deaths, and nose and nasal cavities (RR = 2.9, CI = 0.6-8.5) based on three deaths. An increase in lung cancer mortality was limited to the "probably exposed" (to

phenoxy herbicide and chlorophenols) group (RR = 2.2, CI = 1.1-4.0) based on 11 observed deaths.

The authors provided an additional analysis of STS, including five additional cases who were either alive at the end of follow-up or who had died from another cause. They concluded that the results suggest that STS in these workers "is compatible with a causal role for chlorophenoxy herbicides, though not specifically for those probably contaminated with TCDD."

The authors present only a limited analysis based on 215 and 294 expected total cancer deaths in the "probable" vs. "unlikely" exposed groups, respectively. There was a slight increase in mortality from all cancers for the probably versus unlikely exposed groups (RR = 1.1, CI = 1.0-1.2 versus RR = 0.9, CI = 0.8-1.1), but no increase in either STS or NHL based on 4 and 11 total cases, respectively. There was also an increased mortality for testicular cancer in the group probably exposed to TCDD versus those probably not exposed (RR = 3.0 vs. 1.6) based on seven total deaths, and for thyroid cancer (RR = 4.3 vs. 3.1) based on four total deaths. These latter two differences are not significant and, while interesting because of TCDD's known effects on these organs, add little to the information base.

While the Saracci et al. cohort was significantly larger than the other three worker cohorts (Steenland et al., 1999; Fingerhut et al., 1991; Manz et al., 1991; Zober et al., 1990), the lack of both a clear definition of exposure and uniformity of exposure classification between and within plants makes the results difficult to interpret and lessens the confidence in these results. When several studies have shown a positive association of effect with the same exposure but were conducted under different circumstances, the possibility that an unknown confounder or chance produced the observed elevated effect is minimized. When different investigators working with different populations using different methods confirm an original finding, the results are more believable. TCDD tissue levels were available only from a sample of 9 of the 181 workers with chloracne (median = 340 ng/kg, range 98 to 659 ng/kg). For 17 external controls, the median was 16 ng/kg while the range was 0 to 23.3 ng/kg. This suggests that some of the controls were exposed to TCDD. Unfortunately, no further analysis was presented on these workers.

There are several problems with this study. A portion of the Saracci et al. cohort consists of Danish workers from the Lynge (1985) study. None of them are reported by Saracci et al. (1991) as having had any exposure to 2,4,5-T. Lynge indicates that 2,4,5-T was produced at the Kemisk Vaerk Køge (KVK) facility in Denmark from 1951 until the end of 1980. However, in a later update (Lynge, 1993), the author maintains that the excess is due to exposure to phenoxy herbicides other than 2,4,5-T because only 5.3 tons of 2,4,5-T were produced in 1951-1952. This statement is somewhat contradicted in the author's methods paper (Lynge, 1987), where the author discloses that 350 tons of 2,4,5-T esters were produced during the period 1951-1981, on the basis of purchased 2,4,5-T acid. Perhaps more exposure to 2,4,5-T occurred than was

asserted by the author. This suggests the possibility that exposure misclassification may be present in the Saracci et al. study. There may be potentially as many as 3,844 workers who had exposure to 2,4,5-T and consequently TCDD. Many if not all of them were considered as unexposed in the Saracci et al. study.

Lynge in her studies reported on five histologically confirmed cases of STS. These are listed as cases 2, 3, 4, 5, and 9 in Table IV of the Saracci et al. study. Two were considered alive in the Saracci et al. study, even though in the later 1993 Lynge study these same two are listed as deceased. The remaining three are reported by Saracci et al. as deceased. Two of these three are coded to cancer sites other than STS; only one is correctly coded to STS. This suggests that underreporting of STS as the underlying cause of death is a problem in this study, which is consistent with the findings of Suruda (1993) that STS is underreported generally on death certificates. Added evidence of underreporting of STS is provided by the death certificate's cause of death for the two who were deceased after 1984. Both were coded to a cancer site other than STS. Altogether, four out of five of the confirmed STSs in the Lynge study were coded to causes other than STS.

In a followup study of this same cohort (Kogevinas et al., 1995), two nested case-control studies were conducted on 11 identified cases of STS and 32 NHL cases from this cohort. Four STSs and 20 NHLs were included in the earlier IARC study as deceased with the given diagnosis. These were matched with 55 and 158 controls, respectively, by country of residence, sex, and age through the use of incidence density sampling.

A panel of 3 industrial hygienists carried out the assessment of exposure to 21 chemicals or mixtures without knowledge of the subject's case control status. Live cases were included as well as deceased cases that were coded to causes other than code 171, "sarcomas of connective and other soft tissue," of the 9th Revision of the International Classification of Diseases and Causes of Death. Few actual tissue measurements of serum TCDD or other contaminants were available on any of the cases or controls.

The authors found a significantly elevated risk of STS from exposure to "any dioxin or furan" (OR = 5.6; 95% CI = 1.1-28); a nonsignificant increased risk with respect to TCDD (OR = 5.2; 95% CI = 0.85-32), and a significantly increased risk from exposure to "any phenoxy herbicide" (OR = 10.2; 95% CI = 1.2-91). There is also the suggestion of an increasing risk of STS with increasing intensity of exposure to TCDD. However, these are based upon small numbers and are subject to much variability. Additionally, there may be a problem with random misclassification in the estimates of intensity of exposure because the designation of intensity was a subjective decision by the three industrial hygienists.

However, these findings tend to support the likelihood that exposure to any dioxin or furan as well as TCDD alone is responsible for the elevated risk of STS seen in these workers

from many different countries. There is a suggestion of a weak increased risk of NHL from exposure to "any dioxin or furan" (OR = 1.84; CI = 0.8-4.3) and to TCDD (OR = 1.93; CI = 0.7-5.1). These studies suggest an association with total PCDD/DF TEQ exposure.

In a recent update of this IARC study, Kogevinas et al. (1997) expanded the study group to 26,976 workers by adding additional cohorts of workers from 12 plants in the United States (Fingerhut et al., 1991) and 4 plants in Germany (Becher et al., 1996; Manz et al., 1991; Flesh-Janys et al., 1995). A core protocol was developed by the participating countries to find appropriate study populations of workers who produced or sprayed phenoxy herbicides or chlorophenols. The study coordination was handled by IARC. The enlarged cohort includes almost all of the phenoxy herbicide production workers who have ever been studied. Vital status follow-up has been updated for most of the cohort.

The authors separated from the cohort those workers who were exposed to phenoxy herbicides believed not to be contaminated with TCDD on the basis of information abstracted from individual job records and company exposure questionnaires. This includes some 4,160 workers, mainly from Denmark and the Netherlands. Thus 1,012 women and 20,851 men remain who presumably were exposed to varying amounts of TCDD in their jobs. Of the 36 cohorts examined, measurements of serum TCDD have been done on 573 workers from 10 companies in 7 countries. Measured mean blood serum TCDD levels (pg/g) range from a mean low of 3.2 pg/g in one German plant to a high of 401.7 pg/g in another German plant. Some of these blood serum levels could be considered so low as to be indistinguishable from population levels outside of the plants where the measurements were taken. However, it should not be assumed that these current levels reflect exposures received by the members of the cohorts at the time of exposure in the past. They could either reflect very little exposure received over the years during and after employment in the industry (background levels) or they could represent reduced levels following reductions expected after the 7-year half life of dioxin in the body has been factored in. Conditions have probably improved at these plants over the years.

The authors report that among those exposed to TCDD containing phenoxy herbicides, mortality from malignant neoplasms (710 deaths; SMR = 1.12, 95% CI = 1.04-1.21) was slightly but significantly elevated. Incidence of STS, lung cancer, and NHL was also elevated, but not significantly so. The authors conclude that exposure to herbicides contaminated with TCDD and higher chlorinated dioxins may be associated with a small increase in overall cancer risk and in risk for specific cancers.

However, the same problems that plagued the Saracci et al. (1991) study also appear to plague this update. If the mean blood serum TCDD data and the confidence intervals provided around these means are any indication, it would appear that exposures varied considerably from one plant to the next. Many if not most workers had exposures similar to those of the

comparison populations from which the expected deaths were derived. Following such workers through time to determine their risk for the development of diseases related to exposure to TCDD will produce few if any significantly elevated risks that could be attributable to exposure to TCDD and will only serve to depress the SMRs.

Furthermore, although it was noted above that Kogevinas and his colleagues separated some 4,160 workers (mostly Danish) believed not to be exposed to phenoxy herbicides containing TCDD, some of these workers may actually have had exposure to 2,4,5-T and therefore its contaminant TCDD. In an earlier methods paper (Lynge, 1987) discussing job departments and production processes in the two plants that are the subject of her study of Danish workers (Lynge, 1985; 1993), she describes how "limited amounts of 2,4,5-T have been processed" in the Kemisk Vaerk Køge plant, "mainly in the formation of esters based on a purchased acid." The handling of 2,4,5-T lasted from 1951 to 1981. However, in Table 1 of Kogevinas et al. (1997), some 2,118 of the 2,341 workers at the two Danish plants are listed as having no exposure to "TCDD or higher chlorinated dioxins." Coincidentally, several STSs were identified from that same plant (Lynge, 1985, 1993).

In summary, this study is very little improved from the earlier study by Saracci et al. (1991). The few blood serum TCDD samples that have been measured differ so much that they indicate great variability in what the actual exposures might have been. And because many if not most of these workers have very likely always had blood serum TCDD levels close to background, the inclusion of such workers in the study cohort could introduce a potential bias in the results and could serve to drive estimated risk ratios toward the null. Furthermore, the definitions utilized in the feeder studies to decide who should be included or excluded cannot be easily "retrofitted" to meet the rigor required by the core protocol of the present study. Theoretically, all cohort members should enter the study at the *same* time. The study should have only *one* ending date and there should be only *one* qualifying period of employment (or exposure), not several, before inclusion as a member of the cohort, say 3 months or 6 months. There are questions that can be raised concerning the quality of the follow-up in each study, and whether the vital statistics and comparison populations are similar from one country to the next. The potential problems that need to be addressed are numerous and overwhelming.

The nested soft tissue case-control sarcoma study and the non-Hodgkin's lymphoma case-control study by Kogevinas et. al. (1995) discussed earlier in this chapter are methodologically superior to the conglomerate larger cohort study by Kogevinas et al. (1997). They have none of the design problems of the cohort study, although they are still limited by the lack of endogenous measurements of exposure similar to the parent cohort study. This chief drawback, i.e., the use of occupational data regarding proximity of the subjects to materials contaminated with dioxin as a surrogate for exposure, raises the possibility that misclassification of exposure led to a

reduction in risk estimates. Although this appears not to be the case with the STS study, where the risk ratios were significantly elevated, it could be a problem with the lymphoma study and other planned studies of site-specific cancer where no elevated risk was found. However, it is noteworthy that a significantly elevated risk of STS was found in association with exposure to materials contaminated with dioxin. Tallying the STS cases across all study cohorts in Kogevinas et. al. (1997) and matching them with members from the same international cohort to produce the excess significant risk estimates despite the drawbacks mentioned lends support to the theory that dioxin activates the Ah receptor to produce the STSs as well as other site-specific cancers.

7.5.4. Other Studies

Four studies containing portions of the same cohort reported above were reported elsewhere (Lynge, 1985, 1987, 1993, 1998; Coggon et al., 1986; Kogevinas et al., 1993; Bueno de Mesquita et al., 1993; Hooiveld et al., 1996, 1998). Lynge (1985) reported a study of cancer incidence among persons employed in the manufacture of phenoxy herbicides in Denmark. The cohort consisted of 4,459 persons from two factories. One factory contributed 615 cohort members who had worked in the years 1951-1981. The only phenoxy acids manufactured and packaged at this plant were MCPA and mecoprop, unlikely to contain TCDD. The other factory, Kemisk Vaerk Køge, contributed 3,844 cohort members who had worked in the years 1933-1981. At this plant, MCPA, 2,4-D, and lesser amounts of mecoprop, dichlorprop, and 2,4,5-T were manufactured and packaged. The investigators were unable to classify cohort members by the specific types of phenoxy herbicides to which they were exposed. However, in this plant, where exposure to TCDD-contaminated 2,4,5-T probably did occur, a significant excess risk of STS (4 observed vs. 1.00 expected, CI = 1.09-10.24) was noted by the author in those workers who had achieved a minimum 10 years of latency. Unfortunately, individual tissue measurements of TCDD were not included in this study.

In an update of the earlier study, Lynge (1993) continues to report an increase in the risk of STS with four cases reported to be in persons exposed to phenoxy herbicides (standardized incidence ratio [SIR] = 2.3, CI = 0.6-5.8). Just as before, this excess occurred in workers employed for more than 1 year in the Kemisk Vaerk Køge factory (SIR = 6.4, CI = 1.3-18.7). The author concluded that her study continues to provide evidence that exposure to phenoxy herbicides increases the risk of STS.

However, Lynge maintains that only small amounts of 2,4-D and “negligible” amounts of 2,4,5-T were produced at the KVK factory. That this amount of 2,4,5-T was negligible is somewhat at odds with data from an earlier paper in which she discussed the design of her ongoing cohort study (Lynge, 1987). In the 1987 paper, she reported that although 5.3 tons of

2,4,5-trichlorophenol were produced in 1951 and 1952, 350 tons of 2,4,5-T esters were produced from 1951 to 1981 based on purchased 2,4,5-T acid. This varied from zero to as much as 63 tons in any one year. Very likely, the term "negligible" is used in a relative sense—relative to the other herbicides in the KVK factory, which were produced in much larger amounts. Actual exposure to 2,4,5-T may have been greater than the impression given in Lynge's 1993 study. Most of the potential exposure was to MCPA, MCPP, 2,4-DP, and various dyes and pigments. MCPA, MCPP, 2,4-DP, and the nondioxin-containing phenoxy herbicides have not heretofore been seriously thought of as possible causes of cancer in humans.

Lynge also found that the risk of NHL was not elevated in persons potentially exposed to phenoxy herbicides. She did find what she calls a "puzzling" 3.5-fold excess risk in employees of KVK employed in other manufacturing departments. No detailed information on production in these areas was included in the study.

Little additional information is provided concerning any increased risks of other forms of cancer, except for a statement that multiple myeloma and cervical cancer in women and malignant melanoma in men were significantly increased. No numbers are given for these statements. A significant excess risk of lung cancer seen in the earlier study is now borderline significant in this study (obs = 13, SIR = 1.6, CI = 0.9-2.8). The author had planned to have serum tissues in some of her subjects analyzed for their PCDD and PCDF content although none have been forthcoming.

In a later update, Lynge (1998) identified 2,119 workers from the two factories described above who had exposure to phenoxy herbicides, 940 in the manufacture and packaging of phenoxy herbicides and 1,179 in manual service functions. These workers were followed until December 31, 1993, and all tumors diagnosed during this time were tallied and compared with cancer incidence rates for the Danish population for sex, 5-year age, and calendar-time period. Standard incidence ratios were calculated for numerous tumor sites including STS and NHL. The overall cancer incidence was lower than expected (SIR = 0.87) based upon 204 observed cases. The SIR for STS was 1.62 (95% CI = 0.4-4.1) based upon four observed cases, all among men employed at the KVK, where the SIR was 2.38 (95% CI = 0.7-6.1). On the other hand, there were only six cases of NHL, and the SIR was 1.10 (CI 0.4-2.6). The author concluded that on the basis of small numbers there is a suggestion that an increased risk of STS is associated with exposure to MCPA and related phenoxy herbicides. However, the author maintains that there is no indication of an increased risk of NHL or of other cancer diseases as well. The author does caution the reader that these findings are based upon small numbers. Few cancer cases (including deaths) have been identified thus far. It may require several more years of follow-up before any conclusive findings can be derived from this data.

Coggon and colleagues (1986) conducted a study of 5,754 workers at a British plant that manufactured and formulated MCPA from 1947 until 1982 and operated its own aerial and tractor-mounted spraying service from 1947 until 1972. The authors stated that other phenoxy acids were handled "at times" and that "in comparison with MCPA, 2,4,5-T was handled only on a small scale." Overall mortality was less than that of the national population, as was mortality from cancer. Among workers whose jobs meant potential exposure to MCPA, there was a deficit of deaths from cancer, all sites (297 observed versus 314.0 expected), but with one STS occurring when 0.6 were expected. If a rural adjustment factor were applied, the expected deaths would be 276.3. This would produce an SMR of 106. No significant site-specific deaths were reported. As MCPA contains no 2,4,5-T, these persons would not have exposure to dioxin. However, because no exposure information was collected it would be difficult to confirm this.

Coggon et al. (1991) conducted a study of four British cohorts of manufacturers of phenoxy herbicides, including 2,4,5-T, comprising 2,239 men employed sometime during the period 1963 to 1985. All four of these cohorts were included in the Saracci et al. study previously discussed. Follow-up was to the end of 1987 through the National Health Service Central Register and the National Insurance Index. Comparisons were with the national population. Factory A produced 2,4,5-T beginning in 1968, while the remaining three factories formulated it beginning in 1959, 1960, and 1970, respectively. No tissue measurements were conducted on any members of the cohort. A slight excess of lung cancer was noted (19 observed, 14.2 expected). Two NHLs also were observed (0.87 expected). No STSs were observed (0.18 expected). Total cancer also was not increased (37 observed, 36.85 expected).

This cohort has not been followed for a long enough time to expect latent effects to manifest themselves. The authors assumed that the slight increase in lung cancer was probably due to cigarette smoking or a chance occurrence based on the observation that most of the lung cancer deaths occurred less than 10 years after first exposure to phenoxy compounds. Phenoxy herbicides produced or formulated at these factories included 2,4-D, MCPA, 2,4-DP, 2-methyl-4 chlorophenoxy butyric acid (MCPB), MCPP, phenoxybutyric acid (PBA), parachlorophenoxyacetic acid (PCPA), and phenoxyacetic acid (PAA), as well as other herbicides. The author says they were exposed to a multiplicity of chemicals. Except for the slight increase in lung cancer, which is in the same direction as the findings from the earlier cohort studies, this study contributes little to the elucidation of the risk of cancer from exposure to TCDD.

Kogevinas and colleagues (1993) studied a group of 701 occupationally exposed women enrolled in IARC's International Registry of Persons Exposed to Phenoxy Herbicides and Their Contaminants. These workers are also included in the Saracci et al. (1991) study as well as the Kogevinas et al. (1997) study. The likelihood of exposure to TCDD was based on individual job

histories, company records, and company exposure questionnaires. Actual measurements of TCDD serum levels in women were not available, according to the authors, so that confirmation of exposure could not be accomplished. Both national cancer incidence rates and national death rates were used to generate expected cases and deaths utilizing the methods of the Saracci IARC study.

The overall cancer risk did not exceed expected (SIR = 96, CI = 0.6-1.4) based on 29 cases. However, the group with the greatest potential for exposure to TCDD-contaminated chlorophenoxy herbicides produced a significant excess risk of cancer of all sites (SIR = 222, CI = 1.0-4.2) based on nine cases. The risk was observed within the first 10 years of exposure, with no elevated risk appearing after the 10th year of observation. For those women who had probable exposure to TCDD, the risk of dying from cancer was slightly elevated as well (SMR = 165, CI = 0.4-4.8) based on three deaths.

This study suffers from many of the same problems as the Saracci et al. (1991) and Kogevinas et al. (1997) studies. In addition, it is a study of a small population and as such cannot be considered sensitive to the detection of small risks. These same workers were also subject to exposure to other toxic chemicals in the workplace, which may also have an effect on the risk of cancer.

However, the elevated cancer risk in women exposed to TCDD-contaminated phenoxy herbicides is consistent with a hypothesis of overall increased cancer risk seen in other studies from exposure to TCDD or TCDD-like contaminants.

Recently, another study was published (Bueno de Mesquita et al., 1993) of a cohort of 2,310 workers in two plants involved in the manufacture and preparation of phenoxy herbicides (not necessarily 2,4,5-T) in the Netherlands. These workers were also included in the IARC International Registry of Persons Exposed to Phenoxy Herbicides and Their Contaminants and hence were part of the Saracci et al. (1991) study. Some 963 were considered by the author to be exposed to phenoxy herbicides, while 1,111 were considered not exposed. The follow-up periods were somewhat skewed between the two subcohorts as well. The workers of one plant were followed from 1955 to 1985, and those at the other were followed from 1965 to 1986.

Only a slight increase occurred in total cancer mortality based on 31 deaths (SMR = 107, 95% CI = 73-152) utilizing The Netherlands' national rates. A slightly higher risk of total cancer was seen based on 10 deaths (SMR = 137, CI = 66-252) in 139 workers probably exposed to dioxins during or immediately after a 1963 industrial accident in which dioxin was released into the atmosphere.

When compared with nonexposed workers, mortality due to all cancers was insignificantly elevated (RR = 1.7, 95% CI = 0.9-3.4) while that due to respiratory cancer was

also insignificantly elevated (RR = 1.7, 95% CI = 0.5-6.3). This group was too small to provide enough power to detect significant site-specific cancers.

Although the size of the cohort seems large, actually only about 549 workers in Factory A had a potential for exposure to TCDD-contaminated 2,4,5-T and the higher chlorinated dioxins. No one at Factory B was exposed to 2,4,5-T because it was not produced there. At Factory A, the SMR for lung cancer was elevated insignificantly to 165 based on 6 deaths in the 20-year latent category. No serum dioxin measurements are available to substantiate exposure to dioxin. However, the authors did conclude that the SMR of 73 for Factory A, the SMR of 118 for Factory B, and the SMR of 137 for the cohort exposed to the accident are not inconsistent with the possibility of a carcinogenic effect of TCDD in humans.

Hooiveld and co-workers (1996) updated the earlier study by adding additional years of follow up to December 31, 1991. Cancer mortality remained statistically significantly high (SMR = 146, 95% CI = 109-192) in factory A. By latency after 20 years, a statistically significant SMR = 160 (95% CI = 110-225) is evident. On the other hand, no unusually high mortality occurred in factory B, possibly because of the small size of the cohort and the fact that few deaths from cancer were expected. The authors concluded that relative risks were highest in the highest exposure category, indicating a dose-response relationship with TCDD exposure level.

Hooiveld et al. (1998) in still another update studied the 562 workers exposed to 2,4,5-T that were discussed earlier. The authors followed the cohort to December 31, 1991, and identified 139 deaths to the 549 males of the cohort. In addition, serum TCDD levels were also gathered on 47 surviving workers of this cohort. Of these, 14 were exposed in the accident of 1963. Seventeen were exposed to phenoxy herbicides or chlorophenols but were not involved in the accident. The remaining 16 of the 47 were never exposed to phenoxy herbicides or chlorophenols. The arithmetic mean serum TCDD levels of the three groups defined as accident, exposed but no accident, and nonexposed were, respectively, 96.3, 16.6, and 7.6 ppt. These data were collected in 1993. On the basis of these data the authors extrapolated back in time to get some idea of what the maximum potential serum TCDD levels could have been at the time of the accident. These estimated values were 1,841.8, 244.1, and 7.6 ppt, respectively. The SMRs in 140 male workers who were exposed during the accident and who presumably had higher levels of serum TCDD also exhibited a significantly higher risk of malignant neoplasms (SMR = 1.7, 95% CI = 1.1-2.7) while in the larger exposed group of 549 male workers, with lower levels of serum TCDD, the risk of malignant neoplasms was significant as well (SMR = 1.5, 95% CI = 1.1-1.9).

However, when mortality in the 549 exposed workers was contrasted against mortality in the 482 nonexposed workers from the larger cohort, the exposed group exhibited a significantly

increased risk of death from cancer (RR = 4.1, 95% CI = 1.8-9.0) and specifically, respiratory cancer (SMR = 7.5, 95% CI = 1.0-56.1). The authors concluded that the results of this cohort study support the evidence of an exposure-related high risk of cancer in workers exposed to phenoxy herbicides, chlorophenols, and their contaminants.

Wiklund and Holm (1986) studied a massive cohort of 354,620 Swedish men who were recorded as having an agriculture or forestry job according to the census of 1960, versus 1,725,845 Swedish men in all other industries. The primary exposure in those jobs was postulated to be primarily MCPA, and 2,4-D and 2,4,5-T to a lesser extent. The authors found that the relative risk of STS was 0.9. This study has several deficiencies that reduce its usefulness in determining the risk of STS due to exposure to TCDD: (1) a lack of individualized exposure data (men were classified into six major subgroups by occupation from census data); (2) only 15% of Swedish agricultural and forestry workers were estimated to be exposed to phenoxyacetic acids (a smaller percentage was exposed to dioxin-contaminated phenoxy herbicides) and 2% to chlorophenols; (3) Swedish agricultural workers have a decreased cancer risk and tend to use health services less frequently; (4) classifying workers according to a 1-week employment status in October of 1960 as reported in a census invites the possibility of misclassification; and (5) the crude rate of STS in agricultural and forestry workers based on data in the study was 5.45 per 100,000 person-years, versus 5.00 per 100,000 person-years in the remaining workers. Both rates are high compared with rates from other nations (1 to 3 per 100,000 person-years).

A few years later, Wiklund et al. (1988, 1989) produced two new cohort studies that superficially appear to contradict the earlier findings of Hardell and Eriksson. Wiklund et al. followed some 20,245 licensed pesticide applicators in Sweden from date of license in 1965 or after until December 31, 1984. Some 72% were estimated to have been exposed to phenoxy herbicides 1 day or longer (based on questionnaire data sent to a random sample of 273 persons in the cohort). The relative risk for STS reported in the first study was found to be 0.9, with a mean follow-up time of 13.9 years. Even after a 10-year latency, the risk for STS was only 1.0 based on four deaths. With respect to the second study of all other cancer sites, major significant deficits were found in several sites followed for an average of 12.2 years until December 31, 1982. No report is given concerning loss to follow-up or vital status.

The authors describe a major disadvantage of these studies to be a “lack of individual exposure data” and that information is available “for only a sample of the cohort.” Even the length of exposure of individual applicators to phenoxy herbicides is not available. What is presented is information that herbicide use in the 1950s was only 19%, and in the 1960s it increased to just 49%. By the 1970s, however, it was up to 67%. On the other hand, pesticide use is reported to be 92% during the same period. This seems to indicate that perhaps less than

half had any exposure to the phenoxy herbicides at the time of licensing and perhaps for many years afterwards. Furthermore, no information is presented about the presence or absence of chloracne, another marker of exposure to TCDD.

In addition to missing important information regarding the vital status of this cohort by the end of the follow-up, no information is available concerning the distribution of person-years "at risk" generated by the "lost to follow-up" group. Among the cancer sites reported to have significantly reduced risks are total cancer, liver, pancreas, lung, and kidney.

Furthermore, the extent of exposure to the agent of concern, TCDD, may not be extensive among licensed applicators in Sweden. The entire discussion is centered on exposure to "phenoxy herbicides." The authors state that the most widely used phenoxy herbicides in Sweden are MCPA, mecoprop, and dichlorprop. None of these contain TCDD as a contaminant. 2,4-D and 2,4,5-T have also been used to a "lesser extent" according to the authors. Sweden prohibited the use of 2,4,5-T in 1977. If, as the authors state, only 19% used herbicides in the 1950s, increasing to 49% in the 1960s, it suggests that far fewer applicators were exposed to small quantities of TCDD for a long enough period of time to produce any effects. Furthermore, only 68.2% of the cohort could have attained the age of 59 by the close of the study in 1984. This hints at the likelihood that the full impact of exposure on mortality has not yet been achieved. In fact, the authors report that the "latency time may anyhow be too short to detect increasing risks of cancer . . . ."

7.5.5. Summary

The cohorts assembled by Fingerhut et al. (1991), Steenland et al. (1999), Manz et al. (1991), Becker et al. (1996), Flesch-Janys et al. (1995, 1998, 1999), Zober et al. (1990), and Ott et al. (1996) are important because they contain sizable proportions of persons with substantial TCDD exposures. These exposures were documented, at least in subsets of the cohorts, by blood and/or adipose tissue measurements, workplace measurements, and the occurrence of chloracne. The Saracci et al. (1991) cohort and later Kogevinas et al. (1997), while significantly larger, were assembled with nonuniform exposure criteria for TCDD exposure, leading to less confidence in the results.

The exposures and methods in the three studies in males (Fingerhut et al., 1991; Manz et al., 1991; Sober et al., 1990) were similar enough to warrant aggregating the results. Within each study, relative risks were estimated by summing the observed and expected numbers of deaths across categories of age, race, and calendar time, and then dividing the totals to produce relative risk estimates in the form of standardized mortality ratios. Thus, aggregate relative risks can be obtained simply by summing the observed and expected numbers of deaths across the studies. Alternatively, the aggregate relative risk could have been derived by weighting the individual

relative risks from each study by the inverse of the variance. A separate analysis of the three studies using estimates of lifetime dose intake is presented in Section 8.5. As shown in Table 7-8, the studies by Manz et al. (1991), Becker et al. (1996), Flesch-Janys et al. (1995, 1998, 1999), Zober et al. (1990), and Ott et al. (1996) add to the information provided by the study by Fingerhut et al. (1991) and Steenland et al. (1999), i.e., they increase the precision of the relative risk estimates (as indicated by a narrowing of the confidence intervals). They suggest increased risk—especially among persons with relatively high exposure and relatively long latency—for connective and soft tissue cancers, for lung cancer, and for all cancers combined.

The elevations for these cancers also appear to be more pronounced in the subcohorts of relatively high exposure and relatively long latency than in the total cohorts. Because they come from comparisons between blue-collar workers and national populations, it is reasonable to suspect that these estimates—especially for lung cancer—are influenced to some degree by confounding from cigarette smoking. However, the limited analyses presented suggest that the association is not a chance occurrence (Table 7-2). The counterinfluences of the healthy worker effect, exposure misclassification, and/or diagnostic error would tend to force risk estimates downward.

The results in males are consistent with results from animal studies. In Chapter 6, it was shown that in a lifetime TCDD bioassay male rats developed lung cancer, and in an initiation-promotion study ovariectomized rats exposed to TCDD developed lung tumors, while intact rats similarly exposed did not. Furthermore, the mice in the NCI study developed fibromas and fibrosarcomas. Also, TCDD affects the immune system and has been shown to be a tumor promotor in animal liver, lung, and skin assays. Either or both of these actions could lead to increased total cancer. With respect to health effects in females, the study by Saracci et al. (1991) and its update by Kogevinas et al. (1997) suggest a possible increase in breast cancer, but the results are considered preliminary in view of the small numbers and less certain exposure. On the other hand, although Kogevinas et al. (1993) reported an increase in cancer incidence from all causes among women who were exposed to chlorophenoxy herbicides contaminated with TCDD, no excess was observed for breast cancer. Still, in another study by Bertazzi et al. (1993, 1997, 1998) to be discussed later in the section on Seveso, Italy, a nonsignificant deficit of breast cancer and endometrial cancer was seen in women living in geographical areas contaminated by dioxin. TCDD exposure might be expected to result in decreased breast cancer in females, on the basis of similar observations in rats and on TCDD's action on downregulation of the estrogen receptor in the mammary gland. However, this is species-, tissue-, and age-specific.

In conclusion, these studies in occupationally exposed workers are highly supportive of a causal relationship between exposure to phenoxy herbicides and the risk of cancer.

7.6. CASE-CONTROL STUDIES IN GENERAL POPULATIONS

In this section on case-control studies, the discussion will focus chiefly on the cancer sites, i.e., STS and NHL, that have been suggested by the earlier Swedish studies as being associated with exposure to the phenoxy herbicides. This is a reflection of the intense interest shown in these two cancer sites over the past decade. Few, if any, case-control studies have been completed on other cancer sites. And of course, if other cancer sites are not studied, the risk of cancer cannot be evaluated.

7.6.1. Sweden

Hardell, Eriksson, and colleagues conducted four studies of STSs (Hardell and Sandström, 1979; Eriksson et al., 1981, 1990; Hardell and Eriksson, 1988) and one study of malignant lymphomas (Hardell et al., 1981) among men living in different parts of Sweden. In all studies, cases and their matched controls were considered exposed if they reported phenoxy acid or chlorophenol exposures lasting at least 1 day and occurring at least 5 years before the case's date of diagnosis. These studies were initiated by clinical observations in 1976 made by Dr. Hardell and his colleagues at the Center of Oncology, University Hospital, Umea, Sweden, and documented in his 1977 case report (Hardell, 1977).

The nature of the phenoxy acid exposures differed across the Swedish study locales. In northern Sweden, most exposures occurred in the use of 2,4,5-T and 2,4-D in combination in forestry applications, often by knapsack spraying (Hardell and Sandström, 1979; Hardell and Eriksson, 1988; Hardell et al., 1981; Hardell, 1981a,b). Phenoxy acid exposures not involving 2,4,5-T became progressively more common, on a proportional basis, in the central and southern regions in which agricultural herbicide uses predominated (Eriksson et al., 1981, 1990). Although exposures not involving 2,4,5-T made up only 22% of all phenoxy acid exposures in the first northern sarcoma study (Hardell and Sandström, 1979; Hardell, 1981a, b), they accounted for 27% in the study in central Sweden (Eriksson et al., 1990) and 58% in the study in southern Sweden (Eriksson et al., 1981). Exposures defined only as phenoxy acid exposures are therefore less useful as indicators of exposure to TCDD and related compounds in southern Sweden than in the central and northern parts of the country. Furthermore, none of these studies provide information on how much exposure each subject may have had.

The reports contain little information on the specific chlorophenol preparations to which the cases and controls were exposed. Occasional statements in some of the manuscripts suggest that most chlorophenol exposures occurred in the sawmill and pulp industries, that they primarily involved pentachlorophenol, and that they seldom involved trichlorophenols. Thus, most of the reported chlorophenol exposures entailed exposures to the higher-chlorinated PCDDs and PCDFs but not to TCDD.

Because exposure prevalences were generally low and because phenoxy acids and chlorophenols tend to be used in different occupations, very few persons reported joint exposures. Thus, it is efficient to control potential confounding in the analysis of data from these studies by comparing each exposure category (phenoxy acids vs. chlorophenols) with the category composed of all persons who reported no exposure to phenoxy acids or chlorophenols. Based on this method of analysis, relative risk estimates from all five studies are presented in Table 7-9, with the sarcoma studies arranged in order of publication. The measure of effect here is the "odds ratio" that is an estimate of the RR when the cancer is relatively rare and henceforth will be called the RR.

The results for 2,4,5-T are the only results pertinent to TCDD exposures only. Because of the small number of cases and controls reporting 2,4,5-T use in southern Sweden, the confidence interval for the relative risk estimate from the study in that part of the country (Eriksson et al., 1981) is extremely wide. A separate relative risk estimate for 2,4,5-T could not be computed from the data in the second northern sarcoma study (Hardell and Eriksson, 1988). The published report, however, did state that all of the cases and most of the controls exposed to phenoxy acids were exposed to preparations including 2,4,5-T (Hardell and Eriksson, 1988). The report also gave a relative risk of 3.5 for TCDD exposure, but no confidence interval or counts of cases and controls were provided.

The studies were conducted in two phases. The lymphoma study (Hardell et al., 1981), the first northern sarcoma study (Hardell and Sandström, 1979), and the southern sarcoma study (Eriksson et al., 1981) were published between 1979 and 1981. The remaining two sarcoma studies (Hardell and Eriksson, 1988; Eriksson et al., 1990) appeared about a decade later. The relative risk estimates from these more recent studies are consistently lower than those from the earlier studies (Table 7-9). Thus, systematic differences between the two sets of studies may be an explanation for the heterogeneity of results.

The first set of studies received a considerable amount of criticism concerning the methods by which the exposure information had been obtained (Hardell, 1981b; Cole, 1980). The basic concern was the possibility of bias from differential exposure misclassification between cases and controls (sometimes called "observational bias" or "interviewer and recall bias"), with false-negative reports of exposure suspected as being more common among the controls and false-positive reports more common among the cases. Much of the discussion focused on telephone interviews that were conducted by research staff who were aware of the purpose of the study and of the case or control status of the respondents. These interviews were conducted with selected participants to confirm reported exposures and to resolve uncertainties on postal questionnaires, which were the primary sources of exposure information. For living cases, controls were selected from the Swedish National Population Registry. For deceased

cases, controls were selected from the Swedish National Registry for Causes of Death. Hardell controlled for age by stratifying his cases and controls into four age groups and calculated Mantel-Haenszel point estimates of the odds ratios. As the criticisms of these procedures have echoed through the years (Bond et al., 1989b; Colton, 1986), no quantitative analysis has been made of the degree of bias that would have been required to produce the very strong associations reported in the first three studies (Table 7-9). Of greater importance, analyses by Hardell based solely on the questionnaire information (Hardell, 1981b) have been largely overlooked. These analyses produced relative risk estimates very similar to those obtained when the information from the supplemental interviews was used.

Hardell also enrolled a series of colon cancer patients (Hardell, 1981) as a sort of "positive control" group. In contrast to STSs and malignant lymphomas, colon cancer turned out not to be associated strongly with phenoxy acid or chlorophenol exposures. Hardell and Eriksson made a similar finding in one of the newer studies (Hardell and Eriksson, 1988) when they included a control group consisting of a variety of cancers along with a set of general population controls. The cancer controls were drawn at random from the Swedish Regional Cancer Registry.

Despite Hardell's conclusion that "the previously reported associations . . . cannot to any essential degree be explained by observational bias in the studies" (Hardell, 1981b), he and his colleagues imposed procedures designed to reduce the potential for such bias in their subsequent studies (Eriksson et al., 1990; Hardell et al., 1981). When lower relative risk estimates were produced (Table 7-9), the researchers suggested that one explanation might have been the improved methods of exposure assessment. Again, controls were from national population registries. A second explanation suggested by the authors is that the use of cancer referents could have reduced recall bias.

The investigators suggested that another explanation for the reduced relative risk estimate for phenoxy acids and STSs in the study in central Sweden (Table 7-9) "could be the decade in which exposure occurred" (Eriksson et al., 1990), with the implication that exposures were higher in earlier decades. They supported this suggestion with an analysis in which only those phenoxy acid exposures occurring in the 1950s were considered. This analysis yielded a higher relative risk estimate of 2.3 (95% CI = 1.0-5.4). Unfortunately, no basis of comparison exists because analyses by calendar time of exposure were not conducted in any of the other studies. However, this is reasonable given what we know about processes.

As an alternative explanation for the lack of an elevated relative risk estimate in connection with chlorophenols in the second northern sarcoma study (Table 7-9), the authors offered "random variation" due to a low number of exposed subjects (Hardell and Eriksson, 1988). The prevalence of chlorophenol exposures among the controls in that study (10.9%) was several times *higher* than in the earlier northern sarcoma study (2.9%) (Hardell and Sandström,

1979) and virtually identical to the prevalence in the lymphoma study (10.4%) (Hardell et al., 1981). The phenoxy acid exposure prevalences were highly uniform in all three northern studies: 7.2% in the lymphoma study (Hardell et al., 1981), 6.8% in the first sarcoma study (Hardell and Sandström, 1979), and 7.1% in the second sarcoma study (Hardell and Eriksson, 1988). The chlorophenol exposure prevalence among the controls in the first northern sarcoma study (Hardell and Sandström, 1979) seems to have been low. However, the overall consistency of some excess risk is perhaps more important than actual levels of the excess.

For three of the studies by Hardell and colleagues, relative risk estimates can be computed restricting the data to persons who had worked in agriculture and the other occupational categories in which the exposures of interest tended predominantly to occur (Table 7-10). For the lymphoma study (Hardell et al., 1981) and the sarcoma study in southern Sweden (Eriksson et al., 1981), the results for exposure to phenoxy acids, chlorophenols, or both in the restricted analyses are virtually identical to those obtained with the data for all subjects (Table 7-9). For the sarcoma study in central Sweden (Eriksson et al., 1990), however, the relative risk for phenoxy acids was higher (2.3) within the special occupational categories than among all subjects.

Interestingly, Eriksson and his colleagues stated that the association with the risk of STS seemed to strengthen with exposure to the higher-chlorinated dioxin isomers. His conclusion was that not only may TCDD be a risk factor for STS, but also that other higher-chlorinated dioxins may be risk factors.

The risk calculated for exposure to 2,4,5-T in the 1950s was somewhat higher at 2.94 (95% CI = 1.1-8.0). However, exposure to 2,4,5-T during the span of the study was nonsignificant at 1.8 (95% CI = 0.9-3.9), excluding the chlorophenols. Exposure to dioxin-containing phenoxyacetic acids or chlorophenols, excluding nondioxin-containing herbicides, produced a significant risk estimate of 2.4 (95% CI = 1.3-4.5). Exposure to high-grade pentachlorophenols produced a risk ratio of 3.9 (95% CI = 1.2-12.9).

These analyses are important because many of the mechanisms by which biases might occur would be related to occupation. For instance, biases in case identification, control selection, or nonparticipation that might be related to occupational status (e.g., by its link to socioeconomic status) would not be expected to be as great in analyses conducted within the occupational categories as in analyses of the overall data. The potential for confounding by occupational exposures encountered in the same lines of work would also be reduced in the occupationally restricted analyses. Several researchers and reviewers (Johnson, 1990; Pearce et al., 1985; Blair et al., 1985) have noted reports of farmers being at increased risk of malignant lymphomas and other cancers and have mentioned a wide range of potentially responsible exposures, “including pesticides, solvents, oils and fuels, dusts, paints, welding fumes, zoonotic

viruses, microbes, and fungi" (Blair et al., 1985). (Studies of farmers and other agricultural workers are not included in this review because mere membership in these occupational categories is insufficient as an indicator of exposure to such substances as 2,4,5-T or chlorophenols.)

In the original reports, occasional attempts to assess exposure-response trends produced mixed results. In general, the reported exposure periods were short in all of the studies. In the first northern sarcoma study, for instance, 93% of all reported phenoxy acid exposures lasted 1 year or less, 74% lasted 6 months or less, and 33% lasted 30 days or less (Hardell and Sandström, 1979; Hardell, 1981b). Reported exposures in southern Sweden were even briefer, with 53% lasting 30 days or less (Eriksson et al., 1981).

Hardell et al. recently aggregated the four STS studies in a re-analysis examining exposures to herbicides contaminated with TCDD and other dioxins (Hardell et al., 1991). Increasing trends in risk with duration of exposure (<1 year and ≥1 year) and "latency" (5-19 years and ≥20 years since first exposure) were numerically impressive, being based on the totals of 434 cases and 948 controls from all the studies (Table 7-11). The problem of concomitant exposures was not solved in these analyses, however, and an analysis of the aggregated data obscured the pronounced heterogeneity of results among the individual studies (Table 7-10).

Regardless of the exposure definition, considerable heterogeneity exists among the relative risk estimates from the four STS studies (Table 7-10). (Tests of homogeneity yield two-tailed *p*-values of 0.002 for phenoxy acids, chlorophenols, or both; 0.02 for phenoxy acids; 0.03 for 2,4,5-T; and 0.01 for chlorophenols.) In this circumstance, aggregation of results across studies is not indicated and, instead, a search should be made for explanations for the heterogeneity.

Two additional studies of malignant lymphomas and one study of STSs were conducted by independent research teams in southern Sweden. Olsson and Brandt's (1988) study consisted of 167 men diagnosed with NHL in the years 1978-1981 and 140 controls from the Swedish National Population Registry. Men who reported handling phenoxy acids or chlorophenols for at least 1 day were considered exposed. However, the main focus of the study was to evaluate the contribution of organic solvent exposure to the risk of NHL. Persson et al. (1989) studied 54 cases of Hodgkin's disease, 106 cases of NHL, and 275 controls of both genders from the population registry of Sweden. The cases were diagnosed in the years 1964-1986, but only those who were still alive in 1986 were included. The authors did not ask specific questions about phenoxy acid use. Wingren et al. (1990) studied 96 men with STSs diagnosed in the years 1975-1982, 450 general population controls, and 200 cancer controls from the regional cancer registry. Because the results did not differ substantially between the two control groups, only those obtained from analyses with the general population controls are reported here. The authors had

to resort to job-associated uses, of which one was called “unspecified chemical work, potential exposure to phenoxy herbicides and chlorophenols,” because only limited information could be obtained about specific chemical exposures from postal questionnaires and selected supplemental telephone interviews. Results from these three studies are summarized in Table 7-12. Persson et al. (1989) found strong associations, Wingren et al. (1990) found an association of intermediate strength, and Olsson and Brandt (1988) found very little association. These studies are limited by the lack of specificity in their exposure information.

7.6.2. United States

Zahm, Cantor, and colleagues from the National Cancer Institute have reported results from three case-control studies of exposure to 2,4,5-T or 2,4-T as well as other pesticides and herbicides in four Great Plains States (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992). The first study was conducted in Kansas (Hoar et al., 1986). It included STSs, Hodgkin's disease, and NHLs, but detailed analyses were confined to the NHLs. The two subsequent studies, one conducted in eastern Nebraska (Zahm et al., 1990) and the other in Iowa and Minnesota (Cantor et al., 1992), evaluated NHLs. Cancer risks at other sites from exposure to 2,4-D calculated from these groups are the subject of later studies. These studies did not consider chlorophenol exposures, and only those persons who ever lived or worked on a farm were asked questions about pesticide exposures. Farmers and nonfarmers were asked about home and garden use of pesticides. Thus, all nonfarmers were considered unexposed. As in southern Sweden (Table 7-10), the vast majority of phenoxy acid exposures did not involve 2,4,5-T, and those that did virtually always involved 2,4-D as well. The relevance of these studies to the focus on TCDD and related compounds in this review is therefore somewhat limited. Only 3 out of 299 cases and 18 out of 1,005 controls were exposed to 2,4,5-T, the herbicide known to be contaminated with dioxin.

Results for 2,4,5-T from the three studies are summarized in Table 7-13. Among all subjects and among farmers, only the study in eastern Nebraska (Zahm et al., 1990) suggests an increase in risk. All three studies were conducted with virtually identical methods, and no information on herbicide application methods in any of the reports indicate any exposure conditions peculiar to eastern Nebraska.

The third set of relative risk estimates in Table 7-13 was computed using the investigators' procedure of including only the exposed farmers and the unexposed nonfarmers, with the unexposed farmers excluded. Comparing exposed farmers with unexposed nonfarmers makes it possible that risk estimates could be influenced by confounding effects that are germane to farmers, i.e., exposure to other pesticides or herbicides in large quantities. Furthermore, if the results of follow-up efforts are markedly different in farmers than in nonfarmers, this difference

also might add some uncertainty to the accuracy of risk estimates. In these analyses, the relative risk estimates from the studies in Kansas, Iowa, and Minnesota are somewhat higher and the estimate from the eastern Nebraska study is somewhat lower than in the two more conventional analyses.

Formal homogeneity tests across the three studies yield two-tailed *p*-values of 0.4 in the analysis of all subjects, 0.3 in the analysis restricted to farmers, and 0.6 in the third analysis. Ordinarily, especially considering the virtually identical methods used in the three studies, these results would be considered sufficient justification to compute summary estimates. Summary (maximum likelihood) estimates of relative risk are virtually identical in all three groups of subjects, with point estimates of 1.2, lower 95% confidence limits of 0.8, and upper 95% confidence limits of 1.7 to 1.8.

Woods and colleagues (1987) conducted a study of STSs and NHLs in western Washington State. In this study, the principal method of phenoxy acid and chlorophenol exposure assessment was to place job titles, activities, and chemical preparations reported during interviews into categories of potential exposure. The categories were created "in consultation with local industrial and university representatives who had long-term experience with forestry, wood products, and agricultural industries in the Pacific Northwest" (Woods et al., 1987). No statement is given about the relative prevalence of 2,4-D and 2,4,5-T among the phenoxy acids used in this region. The authors did not present any information regarding tissue levels of TCDD in either cases or controls.

The results (Table 7-14) show no association between STSs or NHLs and estimated potential for exposure to phenoxy acids or chlorophenols. The authors report, however, that the relative risk of NHLs associated with more than 15 years of potential exposure to phenoxy acids increased with time since the accumulation of that exposure. The relative estimates were 1.3 (95% CI = 0.9-2.2) for exposures more than 5 years before diagnosis, 1.7 (95% CI = 1.0-2.8) for exposures more than 15 years before, and 2.5 (95% CI = 0.5-13.0) for exposures more than 25 years before. The authors stated that similar trends were not seen in any of the analyses of STSs and phenoxy acids or of either cancer in connection with chlorophenol exposures. It is not possible with the available data from this study to conduct analyses restricted to persons who worked in forestry, agriculture, and the wood products industry, and in which the exposed persons are those who reported specific exposures to phenoxy acids or chlorophenols.

The western Washington State study reported two unique results. One consisted of elevated relative risks in connection with a history of chloracne based on personal interviews: 3.3 (95% CI = 0.8-14.0) for STSs and 2.1 (95% CI = 0.6-7.0) for NHLs. However, the diagnoses were not medically confirmed, and because only 1% of all cases and controls reported chloracne histories, the confidence intervals were extremely wide. The other intriguing result consisted of

elevated relative risks of STSs among persons with Scandinavian surnames (12% of the cases and controls). The estimates from this analysis were 2.8 (95% CI = 0.5-15.6) for "high" estimated potential for phenoxy acid exposure and 7.2 (95% CI = 2.1-24.7) for "high" estimated potential for exposure to chlorophenols. The authors noted that similarly elevated relative risks were not found for NHLs.

In a later study of the same study population, Woods and Polissar (1989) found a significant excess risk (OR = 1.33, 95% CI = 1.03-1.7) of NHL among farmers compared with nonfarmers. When further examined to determine if 2,4-D or 2,4,5-T was responsible, risks from both tended to be nonsignificantly decreased. However, frequency of use of these herbicides was not considered by the authors.

Brown et al. (1990) conducted a population-based, case-control interview study of 578 white males with leukemia in Iowa and Minnesota matched to 1,245 controls living in those same States. The purpose of the study was to investigate potential agricultural hazards that may be related to a diagnosis of leukemia. The cases were derived from the Iowa Tumor Registry and a network of hospitals and pathology laboratories in Nebraska between March 1981 and October 1983. Areas with little farm activity were excluded from the study. There was a slight but marginally significant elevation of leukemia risk (OR = 1.2, CI = 1.0-1.5) in farmers versus nonfarmers. But for those who mixed, handled, or applied 2,4,5-T, the risk was slightly but nonsignificantly elevated (OR = 1.3, CI = 0.7-2.2).

Eriksson and Karlsson (1992), in a population-based case-control study of 275 myeloma cases matched with 275 controls in 4 counties of northern Sweden, found a significant excess of myeloma (OR = 2.22, CI = 1.15-4.66) in persons who worked with phenoxy herbicides. Significant associations were also found with "farming," DDT, and certain domestic animals. Specific exposures to dioxins or dibenzofurans were not determined.

In another case-control study of Iowa agricultural influences on multiple myeloma, Brown et al. (1993), using similar methodology as in her earlier study, matched 173 white males with multiple myeloma to 650 controls from Iowa. Although a slight nonsignificant elevated risk (OR = 1.2, CI = 0.8-1.7) was seen in farmers, the risk of multiple myeloma from exposure to 2,4,5-T was found to be nonsignificant (OR = 0.9, CI = 0.4-2.1). The same was true for numerous other herbicides, pesticides, and insecticides.

The authors concluded that there was little evidence to suggest any association of multiple myeloma with farming or pesticides. Neither of these studies on leukemia or multiple myeloma has shown that exposure to dioxin occurred. This is only presumed; no actual measurements were taken. Both of these studies could be considered hypothesis-generating studies because they involved multiple exposures to many different chemicals used in farming.

The major problem with U.S. case-control studies is that specific exposure to TCDD and

related compounds is not identified or quantified, although information on the use of 2,4,5-T and 2,4-D is available in some studies. In some, only potential exposure to phenoxy herbicides is the exposure surrogate. This limits the usefulness of these studies.

7.6.3. New Zealand

Smith, Pearce, and colleagues conducted two studies of STSs (Smith et al., 1982a, 1983, 1984; Smith and Pearce, 1986) and one study of NHLs (Pearce et al., 1986, 1987) among men in New Zealand. In these studies, persons were first asked whether or not they "had worked in particular occupations in which there was potential for exposure to phenoxyherbicides or chlorophenols" (Smith et al., 1984). If the response was affirmative, "a series of subsidiary questions were asked to clarify the work done and the actual potential for exposure, firstly in general terms, and then in specific terms, seeking the identity of the chemicals used" (Pearce et al., 1986). The authors indicated that 2,4,5-T was widely used as a phenoxy acid herbicide in New Zealand over the years pertinent to these studies (i.e., prior to the early 1980s) (Smith et al., 1984). Thus, in these studies, the phenoxy acid exposure designation was considered a suitable indicator of exposure to 2,4,5-T and, thus, to TCDD. Typical uses of 2,4,5-T were in the spraying of gorse, blackberry, pasture, cereal, and peas. No actual measurements of TCDD were made in these studies.

In the analyses of phenoxy acids, the authors distinguished between "potential" and "probable or definite" exposure. The latter category was created by deleting persons with only "possible" exposures from those with "potential" exposures. It is not clear whether the "probable or definite" designation included inferences from job titles, activities, and the like, or whether it was based solely on affirmative responses to specific questions about phenoxy acid exposures. For chlorophenols, only the "potential" designation was employed.

In these studies, the controls were patients diagnosed with other cancers. Unlike a control group selected from the entire study population, a cancer control group offers less certainty about the degree to which its exposure distribution represents that of the study population, but greater certainty that differential exposure misclassification through elimination of interviewer bias and recall bias is negligible. However, inclusion of cancer sites in the controls that may be associated with the exposure could potentially bias the risk estimate toward the null. In these particular studies, the cancer controls had an additional advantage in minimizing any bias that might have resulted from the inability of the researchers to include patients diagnosed at private hospitals. Private hospitals in New Zealand have only recently been contributing to the National Cancer Registry. In an interim report of the NHL study, a second control group was drawn from the New Zealand electoral roll. The authors concluded that this control group "gave very similar

findings to those obtained with the main control group of other cancer patients" (Pearce et al., 1986).

Another unique feature of the New Zealand STS studies is that, like the mortality follow-up studies of chemical manufacturing and processing workers previously reviewed, they included only those cases classified to the International Classification of Diseases (World Health Organization, 1977) category 171, malignant neoplasms of the soft and connective tissues. This category, which does not include STSs occurring in parenchymatous organs such as the stomach or uterus, accounted for about 60% of the STS cases in the studies in Sweden (Fingerhut et al., 1984). There is no indication from the Swedish studies, however, that the associations with phenoxy acids or chlorophenols differed between STSs that would be classified in category 171 and those that would be classified in the categories for the involved organs (Hardell and Sandström, 1979; Eriksson et al., 1981; Hardell and Eriksson, 1988; Eriksson et al., 1990; Hardell, 1981a,b).

In the New Zealand study, investigators divided their STS research into two studies with very similar, but not identical, methods. The first study (Smith et al., 1982a, 1983, 1984) consisted of patients and controls with cancer registrations in the years 1976-1980. The second study (Smith and Pearce, 1986) extended case finding through 1982 and was the subject of an extremely abbreviated report. The controls in the second study consisted of 315 of the 338 cancer controls from the NHL study (Pearce et al., 1985) whose cancer registrations were during the period 1977-1981. (The results for the additional 23 controls, who were interviewed near the end of the NHL study, evidently were unavailable at the time the analyses for the second STS study were conducted.)

The first sarcoma study (Smith et al., 1982a, 1983, 1984) reported very similar results for phenoxy acids and chlorophenols when all subjects were included in the analyses, with relative risk estimates of 1.3 for any "potential" exposure and 1.6 for exposures ("definite or probable" for phenoxy acids, "potential" for chlorophenols) lasting more than 1 day and occurring more than 5 years prior to diagnosis (Table 7-14). For phenoxy acid exposures classified by the latter definition, sufficient data were presented to permit an analysis restricted to farmers. Thirty of the 82 cases, 13 of the 17 exposed cases, 44 of the controls, and 9 of the 13 exposed controls were farmers. Thus, the estimated relative risk is 3.0 (95% CI = 1.1-8.3) among farmers. Controlling for farming by ("indirect") standardization yields an estimated relative risk of 1.9 (95% CI = 0.8-4.5). Thus, as in some studies previously reviewed, accounting for the farmer/nonfarmer distinction has a material impact on the results from this study.

Very few details were presented for the second sarcoma study (Smith and Pearce, 1986). In comparison with a relative risk of 1.6 in the first study, the second study reported a relative risk of 0.8 for the principal measure of phenoxy acid exposure (Table 7-14, homogeneity-test *p*-

value = 0.2 contrasting the two studies). The exposure prevalences in the two control groups were virtually identical (14.1% in the first study and 14.6% in the second), but the prevalences in the two case groups differed (exposure odds ratio = 2.0, 95% CI = 0.7-5.4). Because of this difference, and because a relative risk estimate restricted to farmers cannot be computed with the data available from the second study, aggregation of the results would not be warranted.

The NHL study (Pearce et al., 1986, 1987) reported little or no association with phenoxy acids and a somewhat stronger association with chlorophenols (Table 7-15). The latter association did not increase when the more restrictive measure of exposure was used. The various activities involving exposure to chlorophenols include the treatment of fence posts as well as treating pelts in meat works tanneries. Data that would permit an analysis restricted to farmers were not reported.

The authors continue to maintain that herbicide spraying is a full-time occupation in New Zealand and that none of the STS or malignant lymphoma cases had been commercial sprayers. Smith et al. (1984) estimated the prevalence of current and former commercial sprayers at approximately 1,500, which would be 0.17% of the male population of New Zealand in the early 1970s (Waterhouse et al., 1982). On the null hypothesis, therefore, only about 0.1 commercial sprayers would be expected among the cases in each of the two STS studies, and about 0.3 commercial sprayers would be expected among the NHL cases. Thus, STS risk could have been increased manyfold and NHL risk could have been increased about threefold before even one commercial sprayer would be expected in any of the case groups. As a consequence, the absence of commercial sprayers in any of the case groups is not strong evidence against an effect.

In a letter to the editor, Pearce (1989) produced tabular data from his earlier case-control study by duration of use and by frequency of use. Although he maintained that his data exhibited little evidence of an association with NHL, a nonsignificant increase in the risk was seen in the category 10-19 days of use per year (OR = 2.2, 95% CI = 0.4-12.6) before dropping back to 1.1 in the category greater than 19 years.

In a study of nine selected applicators in New Zealand who had sprayed herbicides (and hence 2,4,5-T) for a minimum of 180 months, Smith et al. (1992) found a high correlation between tissue levels of TCDD and months sprayed. This is analogous to Fingerhut's finding that tissue levels of TCDD correlate well with duration of employment in the herbicide manufacturing industry. TCDD serum levels ranged from 131.0 ppt in a sprayer with 31 years of spraying to a low of 3.0 ppt in a sprayer who sprayed for only 7 years. The average was 53 ppt for the nine sprayers who sprayed an average of 16 years. Actually, the mean average TCDD serum level in Fingerhut's lowest exposure group who worked less than 1 year was higher (69 ppt) than the mean average of sprayers in the Smith et al. study. Smith's conclusions were based on his analysis that brief exposures to TCDD probably do not contribute to the increased cancer

risks seen in studies in other countries. Although it is an interesting inference, this conclusion may be somewhat overstated without some information regarding what the tissue levels of TCDD were in the individual cases and controls of those other studies, information that only recently is becoming available and not for all studies.

Unfortunately, the finding suggested by several occupational accidents, such as in Seveso, Italy, and Nitro, West Virginia, that one-time large doses of exposure to TCDD could, in fact, lead to residual high tissue levels of serum TCDD years later, could not be tested in the studies of Swedes. Hardell and colleagues have provided little information regarding tissue levels of TCDD, past or present, in individuals who were participants in their studies. One study by Nygren et al. (1986) is cited frequently as evidence that Swedish subjects who were involved in spraying phenoxy herbicides have low levels of TCDD in adipose tissue samples. Thirty-one patients from the Regional Hospital in Umea were each relieved of a sample of adipose tissue for analysis of dioxin content. After "careful interviewing," it was determined that 13 of these patients had "sprayed" herbicide at some time during their past. Adipose tissue measurements indicated a mean of 2 ppt of TCDD. The remaining 18 nonsprayers revealed a mean of 3 ppt.

However, in correspondence with C. Rappe (1987) regarding this study, it was determined that in the only three cases that were STSs, adipose tissue measurements of TCDD are reported to be 2, 2, and 9 ppt. The one STS with the highest TCDD level (9 ppt) of any of the 31 subjects is stated by the authors to have had only 10 days of "knapsack spraying" some 25 to 29 years earlier. What is striking about these 13 "cases" is that the total levels of *all* chlorinated dioxins are considerably greater, i.e., from 168 ppt to as much as 936 ppt per patient, and that TCDD levels are a mere fraction of the total. There is no TEQ conversion here. The vast majority consist of the higher-chlorinated PCDDs. It is not clear that spraying herbicides is or ever was a major occupational endeavor of this group of 13 or that any of these patients was exposed to TCDD in large quantities. Based on recent correspondence with Hardell (1993), none of the patients reported by Nygren were members of any of his case-control studies. Nor does Nygren claim in his study that any of the cases he considered are from Hardell or Eriksson's studies. The total PCDD levels in the three STSs ranged from 674 ppt to 792 ppt (Rappe, 1987). These were nearly all highly chlorinated. Although the cases with tissue samples came from Hardell's clinic, they did not come from any of his case-control studies. In fact, since these case-control studies were done in the late 1970s and early 1980s, most, if not all, subjects were deceased by the time that the technology became available to measure serum TCDD levels.

This analysis provides little information on tissue levels in Swedish applicators with STS. Furthermore, there may be some differences in applicator practices between New Zealand and other countries such as Sweden. Professional applicators in New Zealand are registered with the New Zealand Agricultural Chemicals Board (Smith et al., 1982b, 1992). And although it might

appear that they could be expected to receive a great deal of exposure to TCDD, more than half of the applicators show serum TCDD levels below 50 ppt (Smith et al., 1992). Considering that they were spraying 2,4,5-T for 7 to 31 years until just recently, it seems remarkable that the distribution of serum TCDD levels is as low as it is. The authors report that professional pesticide applicators in New Zealand are "perhaps the group most heavily exposed to agricultural use of 2,4,5-T in the world." In other studies, shorter exposures to large quantities of TCDD-containing herbicides have occurred to a few personnel such as in the Ranch Hands cohort; Seveso, Italy; and the Nitro, West Virginia, accident. In Fingerhut's study, employees with less than 1 year of exposure to phenoxyacetic acids had mean serum levels averaging 69 ppt TCDD.

7.6.4. Italy

Vineis and colleagues conducted a case-control study of STSs in three provinces in northern Italy (Vineis et al., 1986). Phenoxy acid exposure classifications were based on job information provided on interviews or questionnaires. The assessments were made by "two experts with experience in chemical aspects of agriculture." Cases and controls were classified into three categories: "certainly unexposed," "exposure could not be ruled out" (abbreviated below as "possibly exposed"), and "certainly exposed." The authors implied that phenoxy acid herbicides of all types (2,4-D, 2,4,5-T, and MCPA) were used in the area during the periods of interest, but were able to document only the use of 2,4-D and MCPA. Thus, this study may have limited relevance to TCDD exposures.

The study indicated an inverse association between possible or certain phenoxy acid exposure and STS risk among men and a positive association among women (Table 7-16). This latter association was restricted to women who were alive at the time the exposure information was collected. (In the other studies in this review, in which the results were stratified by vital status at the time of the interview, no appreciable differences were found.) As shown in Table 7-16, when the analysis is restricted to persons who had ever worked in agriculture ("farmers"), the relative risk among all women is reduced from 1.9 to 1.1. Sufficient data are not available for an analysis that is both restricted to farming women and stratified by vital status.

The authors offered overmatching by location of residence as an explanation for the lack of association among deceased subjects. It would be extraordinary for overmatching or nondifferential misclassification (the latter being the usual explanation when reduced relative risks are obtained with exposure information from proxy respondents) to be so strong as to bias a relative risk of 2.4 to 0.8.

Rice is the principal agricultural crop in the study area, and rice weeding was historically a predominantly female occupation. (Of 29 rice weeders in the study, all but two were women.)

Rice weeding during the period 1950-1955 was manual and contact with the phenoxy herbicides was mainly through the skin.

Among all women in this study, rice weeding during the early 1950s is associated with a relative risk of 2.3 (95% CI = 0.7-7.7). When the analysis is restricted to women who were farmers, however, the relative risk drops to 1.4 (95% CI = 0.3-6.5).

7.6.5. Finland

Lampi et al. (1992) completed a case-control study of colon cancer, bladder cancer, soft tissues, lymphoma, and leukemia in the municipality of Karkola, Finland, where residents consumed fish from a local lake that was contaminated with chlorophenols. The main employer in Jarvela, the industrial center of Karkola, is a sawmill that has been operating since before the 1940s. Large amounts of chlorophenol have been found in the ground water between the sawmill and the intake plant for the drinking water. A person was considered exposed if he answered positively to any one of a series of questions about personal exposure asked on a questionnaire. These include sawmill work, farming, source and duration of drinking, and quantity of fish consumed. Four controls per case were randomly selected from the national population registry of the Tiirismaa health-care district which includes Karkola. However, exclusion of controls who failed to reply as well as nonparticipant cases resulted in a final 3 to 1 ratio of matching. One hundred and twenty-three cases were matched by age, sex, and residing in the Tiirismaa health-care district at the time the cancer was diagnosed, with up to 494 controls depending on whether a reply was received for each of the questions asked.

No increased risk of colon or bladder cancer was associated with any of the exposure categories listed. However, an elevated risk of NHL from exposure to consumption of fish and/or drinking water was found (RR = 6.9, 95% CI = 1.1-70.0). The authors concluded that this could be attributable to chlorophenol exposure through the consumption of fish or the drinking water. The authors also noted a nonsignificant slightly increased risk of STS (RR = 4.0, CI = 0.3-55) in persons exposed to “drinking water” and/or “residence” and/or “fungicide” (tetrachlorophenol, the main ingredient of the fungicide, has been used by the sawmill since the 1940s to inhibit the growth of bluestain fungus in timber) and/or “fish” based upon only three cases versus two controls.

Levels of chlorophenol found in the drinking water of Jarvela ranged from 70 to 140 μg/L. This is reported by the authors to be near the maximum allowable levels. Fish from nearby Lake Valkjarvi, which are caught for local consumption, contain high levels of chlorophenols as well, i.e., 175 μg/kg in perch and 925 μg/kg in zander per net weight.

Although PCDDs and PCDFs have been found in technical and commercial products, this population was not likely to be exposed to these substances in great quantities if at all, according

to the authors. It was reported by the authors that none were found in contaminated drinking water. No actual personal measurements of any of the chlorophenols or the phenoxy herbicides were taken during the conduct of this study. Additionally, the number of cases per cancer site is small, thus providing little power to detect significantly elevated risks where they are not now seen. Efforts should be undertaken to determine if fish are contaminated by PCDDs or PCDFs.

7.6.6. Summary

From the standpoint of exposures to TCDD, the most important results from general-population case-control studies come from those studies conducted in northern Sweden (Hardell and Sandström, 1979; Hardell and Eriksson, 1988; Hardell et al., 1981), central Sweden (Eriksson et al., 1990), and New Zealand (Smith et al., 1982a, 1983, 1984; Smith and Pearce, 1986; Pearce et al., 1986, 1987). These studies were conducted in areas in which high proportions of phenoxy acid exposures involved 2,4,5-T. The exposure-assessment methods in these studies included the posing of specific questions about particular chemicals and herbicide preparations. Moreover, for all but the NHL study in New Zealand (Pearce et al., 1986, 1987), available data permit analyses restricted to farmers and the other occupational categories within which the relevant exposures predominantly occur.

For STSs, the Swedish studies are perhaps best represented by a relative risk of 2.3 (95% CI = 1.0-5.4) for phenoxy acids among workers in agriculture, horticulture, and forestry in the study in central Sweden (Table 7-10) (Eriksson et al., 1990). This is justified by the following factors: the proportion of exposures to 2,4,5-T was high in this study, the methods of assessment were better, and there were analyses within relevant occupational categories. The authors in their current studies have redesigned their methods to accommodate readers' criticisms of their earlier studies and have made an effort to present risk estimates that are adjusted to reflect these criticisms.

The relative risk estimate of 3.0 (95% CI = 1.1-8.3) for phenoxy acid exposure among farmers in the first STS study in New Zealand (Smith et al., 1982a, 1983, 1984) seems to indicate that farming may be a confounder in this study. Indirect standardization for farming produces a relative risk of 1.9 (95% CI = 0.8-4.5).

For malignant lymphomas, the case-control studies provide less evidence of a positive association. The relative risk estimates from the study by Hardell and colleagues (Hardell et al., 1981) were very high, even among persons employed in the special occupational groups, but this study was conducted before the researchers had improved their data collection methods. The studies in New Zealand (Pearce et al., 1986, 1987), Kansas (Hoar et al., 1986), eastern Nebraska (Zahm et al., 1990), and Iowa and Minnesota (Cantor et al., 1992) are more consistent with a much smaller increase in risk, or no increase at all, from exposures to TCDD.

The remaining case-control studies (Eriksson et al., 1981; Olsson and Brandt, 1988; Persson et al., 1989; Wingren et al., 1990; Woods et al., 1987) offer mixed results, some suggesting increases in the risk of STS or malignant lymphoma and others suggesting little or no increase. The informativeness of each of these studies, however, is limited by one or more of the following important drawbacks: study areas in which most phenoxy acid exposures did not involve 2,4,5-T, a lack of information on specific chemicals and preparations to which cases and controls were exposed, and an inability with available data to conduct analyses restricted to farmers and the other occupational groups in which the exposures of interest primarily occur. Apparently, farming as an occupation appears to affect risk estimates based on the findings from several studies where occupation is considered and should be considered as a potential confounder.

Vineis et al. (1992) presents the hypothesis that the excess risk of NHL seen among farmers exposed to phenoxy herbicides may be caused by viruses. Such viruses induce proliferation and immortalization of B-cells, followed by T-cell impairment leading to cell-mediated immunity. Increased risks of NHL have been observed in immunologically deficient individuals. Hypothetically, the same effect could be the result of exposure to TCDD, as suggested in some mouse studies (see Chapter 4, Immunotoxicity).

Lampi et al. (1992) conclude that the role of contamination of drinking water and fish due to chlorophenol from sawmills must be considered as a possible cause of the significantly elevated risk of NHL seen in Finland.

7.7. STUDIES OF PULP AND PAPER MILL WORKERS

Table 7-17 summarizes results for cancers of interest from three follow-up studies of pulp and paper mill workers. A fourth study, not summarized in the table, produced inconsistent results based upon choice of analytical method used. Both potentially produce biases that are contradictory and will redue accuracy in the estimates. These studies are important because of the potential for exposure to PCDDs and PCDFs in this line of work. The study by Robinson et al. (1986) was of 3,572 persons who had worked for at least 1 year between 1945 and 1955 at any of five mills in the States of California, Oregon, or Washington. The study by Jäppinen et al. (1987) was of 3,454 workers in the Finnish pulp and paper industry who had worked continuously for at least 1 year between 1945 and 1961. The study by Henneberger et al. (1989) was of 883 persons who had worked for at least 1 year at a mill in New Hampshire. Jäppinen et al. (1987) studied cancer incidence. The other two studies were mortality studies.

Individually and in the aggregate, these studies give little indication of appreciable increases in the risk of NHLs, lung cancer, or stomach cancer among pulp and paper mill workers. Overall, the rate of all cancers combined was somewhat lower than expected. None of

the studies examined connective and soft tissue cancers specifically. Analyses of specific cancers by work location, duration of employment, and latency were only occasionally conducted in these studies. No consistent results were found that would alter substantially the impression given by the results for the total cohorts. These studies do not specifically mention exposure to the PCDDs/PCDFs and are not designed to evaluate the risk of cancer from PCDDs/PCDFs.

Other studies of cancer among paper and pulp mill workers have been restricted to information on deaths, using either proportional mortality ratios (Milham, 1976; Milham and Demers, 1984; Schwartz, 1988; Solet et al., 1989) or mortality odds ratios (Wingren et al., 1991) as measures of relative risk. These studies are not highly informative because they usually rely on minimal information in death records and because they are subject to an upward bias due to the "healthy worker effect" (i.e., a tendency for employed groups to have favorable total mortality experience and causes of death other than cancers, when compared with the general population). The degree of bias in such studies varies, but it can be appreciable. For instance, in the cohort studied by Robinson et al. (1986), 915 deaths from all causes were observed and 1,150.3 were expected. If the relative risk estimates for stomach cancer and NHLs had been computed as proportional mortality ratios or mortality odds ratios, they would have been 1.5 and 1.7, respectively, instead of the values of 1.2 and 1.3 that were obtained from the authors' more valid comparisons of mortality rates (Table 7-17).

A more recent mortality and cancer incidence cohort study of 26,000 British Columbia (B.C.) sawmill workers by Hertzman et al. (1997) offered mixed results regarding the cancer-causing potential of exposure to chlorophenates that are contaminated with hexa-, hepta-, and octa-chlorinated dioxin isomers but not TCDD. An analysis was accomplished in two parts. First, B.C. vital statistics were used to generate expected deaths while B.C. incidence rates (from the B.C. Cancer Agency) were used to generate expected cases. However, person-years were generated in two ways. The first was to truncate the accumulation of person-years at the time the subject was lost to follow-up; in the second analysis person-years were accumulated until the end of the study period, which was 1990 even if the subject could not be traced to the end of 1992. This treatment of the data served to produce conflicting results. In the former method multiple significantly elevated site-specific cancer risks as well as significant total cancer appeared, whereas in the latter analysis site-specific standard mortality ratios (SMRs) and total cancer were all nonsignificant and close to what would be expected if there were no risk from exposure. Presumably, this discrepancy in the findings is due to an inability of the authors to identify vital status on 3,791 sawmill workers (14.3% of the total). Furthermore, those members of the cohort who were diagnosed with cancer outside of British Columbia could not be included in the analysis because these cases would not be known to the B.C. Cancer Agency. The authors

assumed this loss would be around 4.4%, on the basis of deaths that were recorded outside of British Columbia. A combination of these two factors could explain the disparity. Perhaps if the remaining 14.3% could be followed until vital status was determined, and the underlying cause of death could be identified on the 4.4%, more accurate estimates of the true site-specific cancer risks would be known and, consequently, the studies's two sets of results would converge.

Another problem with this study is that the observed deaths do not appear to add up from one table to the next where they should and no explanation is provided. The authors conclude that their results are "consistent with the borderline positive associations seen in other recently reported studies of chlorophenate-exposed workforces." This conclusion may be somewhat overstated given the potential problems with this study, which appears to have ended prematurely prior to the completion of vital status followup.

7.8. OTHER STUDIES

Studies of pesticide applicators are not informative because they contain little information on specific compounds and preparations to which individual persons were exposed, and so there is no evidence of exposure to TCDD. Studies with no information of this type include studies of licensed pesticide applicators by Wang and MacMahon (1979), Barthel (1981), Blair et al. (1983), Wiklund et al. (1987), Corrao et al. (1989), and a study of gardeners by Hansen et al. (1992). These studies contribute little or nothing to the discussion of TCDD or compounds like TCDD.

Axelson and Sundell assembled a cohort of 348 Swedish railroad workers who had applied amitrol, 2,4-D, and 2,4,5-T (Axelson and Sundell, 1974). In the most recent report (Axelson et al., 1980), 17 deaths from tumors were observed (11.85 expected, relative risk 1.43, $p = .09$). The relative risk estimate for lung cancer was 1.4 (three observed deaths, $p = .37$) and the estimate for stomach cancer was 2.2 (three observed deaths, $p = .15$). Again, as in most studies, no actual measurements of TCDD are available from this paper. Only potential exposure to the herbicides 2,4-D and 2,4,5-T are mentioned without any effort to quantify the exposure.

Riihimäki et al. (1982, 1983) followed a cohort of 1,971 Finnish men who had applied 2,4-D and 2,4,5-T. With allowance for a 10-year latency period, 20 cancer deaths were observed (24.3 expected, RR = 0.8, 95% CI = 0.5-1.2). The relative risk for lung cancer was 1.1 (12 deaths observed, 95% CI = 0.6-1.8). The author points out that because of limitations in the study materials, only powerful carcinogenic effects are likely to be seen.

7.8.1. Vietnam Veterans

Distributions of TCDD levels in serum and adipose tissue are typically indistinguishable between Vietnam veterans and comparison populations unless the Vietnam veterans group has

been carefully defined on the basis of military records to have engaged in activities known to have involved herbicide exposure (Centers for Disease Control Veterans Health Studies, 1988; Devine et al., 1990; Gross et al., 1984; Kahn et al., 1988; Kang et al., 1991; Pirkle et al., 1989; Schecter et al., 1989). Thus, the mere designation "Vietnam veteran" is insufficient as an indicator of exposure to 2,4,5-T or TCDD exposure. This conclusion is also supported by Stellman and Stellman's (1986) review of military records for the purpose of developing an Agent Orange exposure index. Stellman and Stellman drew the further conclusion that "it is impossible to give any credence to any health effects study in which assignment of herbicide exposure levels to individual veterans is based solely on self-reports" (Stellman and Stellman, 1986). It is also insufficient to base an exposure index among Vietnam veterans on such crude information as military branch (Army, Marine, etc.), corps, or region of duty within Vietnam. Thus, a large number of studies of cancer experience among Vietnam veterans are uninformative from the standpoint of hypothetical effects of TCDD. These include studies by Breslin et al. (1988), the Centers for Disease Control (1987), Dalager et al. (1991, 1995a,b), Fett et al. (1987), Greenwald et al. (1984), Kang et al. (1986), Kogan and Clapp (1988), Lawrence et al. (1985), O'Brien et al. (1991), and Watanabe et al. (1995).

One Vietnam veteran study by Kang et al. (1987) that further examined mortality in a subgroup of veterans who had ventured into areas at the time when Agent Orange was being sprayed reported a nonsignificant odds ratio of 8.64 (CI = 0.77-111.84) for STS. The number of cases was not provided. Presumably, these would be ground troops with a high likelihood of exposure.

The only study of cancer among Vietnam veterans at present with information on activities involving TCDD exposure is a small mortality study by Michalek et al. (1990) of 1,261 Air Force veterans of Operation Ranch Hand. These persons were responsible for the aerial herbicide spraying missions in Vietnam. The researchers compared the Ranch Hand group with a group of 19,101 other Air Force veterans who were mainly involved in cargo missions in Southeast Asia and who did not have herbicide exposure. A total of 12 cancer deaths were observed in the Ranch Hand cohort (17.0 expected, RR = 0.7, 95% CI = 0.3-1.1) by December 31, 1987, the cutoff date for followup. Interestingly, one of these was a STS. Out of 229 deaths reported in the comparison population, one STS death was also found. Calculated death rates of all specific cancers of interest in this review were equal to or less than the rates in the comparison group, with the exception of bone, connective tissue, skin, breast, and genitourinary organs. These numbers are too small for any meaningful comparisons.

Serum TCDD measurements were taken on 888 Ranch Hands (total). A few of the Ranch Hands, who were enlisted ground crew, exhibited serum levels above 200 ppt of TCDD, but the median serum level was 12.4 ppt (range 0 to 618 ppt) for the entire group. The median serum

level in the controls averaged 4.2 ppt (Wolfe et al., 1990). The subgroups of Ranch Hands that appear to have had the greatest exposure are nonflying enlisted personnel. The median serum TCDD levels in 407 of them was 23.6 ppt. The next highest levels were in flying enlisted personnel with a median of 17.2 ppt. The remaining Ranch Hands exhibited levels that were not much elevated (under 10 ppt) from background (flying officers, both pilots and navigators, as well as nonflying officers). Based upon these findings, it is likely that the majority of Ranch Hands received little exposure to TCDD. Not a great deal of cancer mortality can be expected in this relatively youthful group, which had not reached the 20-year latency milestone.

In a followup report through 1992 published in 1994 on the Ranch Hands (Wolfe et al. 1994), the authors report 111 deaths in the Ranch Hands versus 111.47 expected in a cohort of 1,261. Twenty-six deaths from cancer were reported versus 30.68 expected. Again no increased risk of any site-specific cancer was found over expected. The comparison population from which expected deaths were generated is very likely the same 19,080 Air Force veterans discussed above who flew or serviced C-130 cargo aircraft in Southeast Asia during the same period that the Ranch Hands were active in Vietnam, although it is not specifically stated in that report. It would be of greater interest and more useful to continue follow-up of the enlisted Ranch Hands only. They appear to be the subgroup with the greatest exposure, although their TCDD levels cannot be considered high. Further follow-up of officers probably will not reveal useful information that could be attributed to exposure to TCDD.

A more appropriate group in which to observe effects are members of the South Vietnamese Army who did the mainstay of the spraying around the perimeters of the military bases in Vietnam.

In another update of the Ranch Hands study, Ketchum et al. (1996) reported on mortality through December 31, 1993. The number of reported cancer deaths increased to 30 versus 33.22 expected (SMR = 0.90, 95% CI = 0.63-1.27). Presumably, the comparison population is the same as the one discussed above, i.e., 19,101 other Air Force veterans, but not stated in the report by Ketchum. No unusual excess cancer risks occurred to any of the three main subgroups of Ranch Hands discussed above. But then, it is still a relatively youthful cohort and few person-years have aggregated beyond the 20th year since exposure, too few to do an adequate latency analysis. It is reported by the authors that some 991 Ranch Hands have quantifiable dioxin levels (presumably blood levels, although not stated). The authors maintain that survival time was not significantly associated with dioxin levels. There was apparently no effort to assess levels of dioxin in each of the three main subgroups, but only between those who were deceased and alive. The levels overall were somewhat higher in the deceased ($\overline{X}$ = 35.0 ppt) versus the living ($\overline{X}$ = 26.7 ppt). The number of deceased Ranch Hands with dioxin levels was 23, precluding assessment of dioxin level averages in deceased veterans by occupational category. Overall,

there is little in this report to support the hypothesis that exposure to dioxin is or is not causally related to an increased risk of cancer. But of course, this study is subject to the same limitations. The levels of dioxin found are not much greater than background and the mortality is still rather low. Furthermore, the analysis should be confined to that group with the highest levels of serum dioxin, i.e., the enlisted nonflying Ranch Hands.

In a slightly different analysis of the same cohort of Ranch Hands that was followed for the same period of time until December 31, 1993, Michalek and colleagues (1998) assessed mortality in the different occupational subgroups—pilots and navigators, administrative officers, enlisted flight engineers, and finally, enlisted ground personnel—observed for less than 20 years since service and after 20 years since service in Vietnam for certain site-specific cancers. The authors found no significant increase in the risk of death from cancer, all sites combined (SMR = 1.1), for persons who survived more than 20 years since military service, while they reported a nonsignificant increase in the number of deaths due to cancers of the bronchus and lung (SMR = 1.3) in Ranch Hands in that group. The authors reported that this latter finding was consistent with an increase in respiratory cancer mortality seen in Fingerhut et al. (1991) in workers observed for 20 years. Michalek recommends that followup should continue to determine whether these slight increases persist. A nonsignificant increase in deaths due to digestive diseases (SMR = 1.7, CI = 0.9-3.2) was reported but not evaluated. A single STS occurred to a Ranch Hand officer (OBS = 1, Exp = 0.3). Again, this study is subject to the same limitations as in earlier renditions. It is based on small numbers and very few deaths from cancer. Dioxin levels were summarized but not analyzed.

Ketchum et al. (1999) simulated what the risks of cancer would be in Ranch Hands on the basis of expected dioxin exposures extrapolated from current dioxin measurements back to the time of exposure as if such hypothetical exposures were real at the time. The authors assumed a first order model for dioxin elimination from the body and a half-life of 8.7 years in constructing synthetic exposure levels at the time when military service ended in Vietnam. The comparison population again was the same group of Air Force veterans that served in Southeast Asia at the same time as the Ranch Hands but did not serve in Vietnam. The Ranch Hands were subdivided into three groups designated as having “background,” ”low,” or “high” exposure. The “background” Ranch Hands consisted of only those personnel whose current measurements of dioxin level never exceeded 10 ppt. The “low” and “high” categories consisted of personnel whose current levels were over 10 ppt. After extrapolation to the supposed “initial” levels at the time they left the service, if the “initial” level exceeded 94 ppt then the Ranch Hands were considered to have “high” exposure. If the “initial” level was under 94 ppt then the Ranch Hands were considered to have had only “low” exposure.

The risk of cancer at sites other than skin in Ranch Hands with less than 20 years of observation from end of service was significantly elevated only in the "low" exposure group (OR=3.4, CI = 1.5-8.0). Although the "high" exposure category also was elevated, it was not significant (OR=2.7, CI = 0.9-8.0). The risks calculated in the more-than-20-years-since-service group were even less remarkable. Based upon 39 individuals diagnosed with cancer who fell into this category, the risks were all under 1.0 and nonsignificant. The findings seem to resemble an *inverse* relationship of cancer with that of latency and dose. The authors believed that their results were inconsistent with that of the Fingerhut et al. (1991) study, and felt that the increased risks seen within 20 years from service may not have been due to dioxin exposure.

The most important question concerns the possibility that misclassification of exposure may have contributed to the supposed inverse relationship of exposure with risk. The assumption that Ranch Hands with a current dioxin measurement under 10 ppt should be placed in a "background" category may be inaccurate. It seems possible that with a lapse of as much as 25 years since service in Vietnam, the actual exposure in these individuals could have been anywhere from 40 ppt to more than 80 ppt. Furthermore, without checking to determine if exposure to dioxins had *not* occurred following service in Vietnam, the authors cannot be certain that the high current levels measured were not due to post-Vietnam exposure to dioxin, in which case the "initial" exposure determinations may be exaggerated.

Furthermore, considering the tabular data, were person-years allocated back to the higher extrapolated exposure and latency categories when the expected cases were calculated for each category? This could explain the apparent inverse relationship of risk to exposure.

Lastly, the authors stated that their results differed from those of Fingerhut and her colleagues discussed earlier. Actually, the "current" measurements that were derived in the Fingerhut study were considerably greater than the "current" measurements seen in this study. As it is likely that most of the Ranch Hands were exposed to only low levels of dioxin, it would be inappropriate to compare the results of this study with those of Fingerhut and her colleagues.

7.8.2. Residents of Seveso, Italy

Residents of Seveso, Italy, were exposed to TCDD in a chemical accident in 1976. Nearly 200 cases of chloracne reported (Caramaschi et al., 1981). Children (Bertazzi et al., 1992) and adults (Bertazzi et al., 1989a,b) who were exposed at the time of the accident are being studied separately. The group residing in the zone (zone A) of highest potential exposure (determined by levels of dioxin found in the soil) consists of 556 adults and 306 children. The group residing in the zone of intermediate estimated exposure (zone B) is larger, with 3,920 adults and 2,727 children. The group with lowest estimated exposure (zone R) is larger still, with 26,227 adults and 16,604 children. The accuracy of the three estimated exposure zones has

been questioned (Caramaschi et al., 1981; Merlo et al., 1986; Ratti et al., 1987; Merlo and Puntoni, 1986), especially because the ranking does not correspond to the occurrence of chloracne in the area. Some parts of region R are almost adjacent to the site of the accident and the factory where the accident happened, while region B begins about 1 kilometer away. Even the nearest part of the "referent" region to the site of the accident is located about the same distance as the nearest part of region B. Only region A and region R appear to come closest to the site. It is entirely likely that many persons residing in region R were exposed to TCDD.

There is no question that at least some of the residents of the most heavily contaminated area (zone A) received considerable exposure to TCDD (Mocarelli et al., 1991). The 1990 analysis, based on tissue specimens taken in 1976, found that the highest detected levels were recorded just after the accident. Six children at the time who subsequently developed severe chloracne had serum TCDD levels ranging from 12,100 ppt to 56,000 ppt. Four other persons with slightly less severe chloracne exhibited levels ranging from 828 ppt to 17,300 ppt. These were similar to those of nine other residents of zone A who did not develop chloracne whose serum TCDD levels ranged from 1,770 to 10,400 ppt (Mocarelli et al., 1991). None of the latter group of nine were reported to be ill at the time of sampling.

Support for the original division of the area of exposure into the three zones (A, B, R) was strengthened by data from studies of tissue levels of plasma TCDD by Landi et al. (1996, 1998). Twenty years after the accident, randomly selected residents of the three areas affected were chosen to have their tissue plasma TCDD levels measured. Plasma TCDD levels were measured in 62 subjects from zones A and B. Their mean tissue levels ranged from 1.2 ppt to 89.9 ppt with a geometric mean value of 53.2 ppt (n = 7) in zone A. In zone B (n = 51) the mean was 11.0. In the non-ABR region (n = 52), it was 4.9 ppt. In the most polluted areas of the three zones, in adults over 13 years of age the estimated median TCDD levels were 443 ppt (zone A, 177 residents), 87 ppt (zone B, 54 residents), and 15 ppt (zone R, 17 residents), respectively (Bertazzi et al., 1998).

The authors report that women have significantly higher TCDD levels than men in the entire study area which they maintain are not due to location, consumption of meat, age, body mass index, or even smoking. Levels decrease by distance from the accident site, according to the authors. However, none of these levels appear to be excessively large. The authors caution that "elevated TCDD levels in women may contribute to adverse reproductive, developmental, and cancer outcomes."

The population in zones A, B, and R around Seveso were initially followed for 10 years (Bertazzi et al., 1992, 1989a,b) to 1986. Ten cancer deaths, too few to support a meaningful analysis of specific cancers, have been observed among children (Bertazzi et al., 1992). (Bertazzi et al., 1989b). No excesses of mortality from lung cancer, stomach cancer, or all

cancers combined were apparent. A moderate and statistically imprecise elevation in the death rate from a subset of the cancers that make up the NHLs is evident in the second 5-year period of follow-up. An excess of greater relative magnitude, but even more imprecisely estimated, in mortality from cancers of connective and soft tissues appears to have occurred in the same time period.

In a preliminary study of cancer incidence in the same Seveso population (Pesatori et al., 1992), the relative risk estimate of connective, subcutaneous STS of males living in zone R is reported to be significantly elevated at 2.81 based on six cases (CI = 1.1-7.4). In zones A and B, none were observed, but 0.4 were expected to occur in males and 0.2 in females. For females, the risk in zone R of STS was 1.43 based on two cases. Other cancer sites that are also elevated are certain hematologic neoplasms in males (lymphoreticulosarcoma) and hepatobiliary tract cancers in both males and females.

One year later, in a cancer incidence study (Pesatori et al., 1993) of a population of young persons (ages 0 to 19 years) with some small changes in the definition parameters, the number of identified cancer cases equaled 17, although the followup period remained unchanged. The authors observed a slight tendency toward increased leukemia (5 observed versus 2.6 expected) and cancer of the thyroid ((2 observed versus 0.4 expected) based upon a small number of cases. These results are equivocal.

Bertazzi et al. (1993) refined his earlier study to include a more complete vital status ascertainment without adding additional years of follow-up to the cancer incidence data in the contaminated areas surrounding the factory where the accident took place. Cancer occurrence ascertainment was confined chiefly to the Lombardy region of Italy (with a population of 9 million persons) because only there can be found an efficient hospital and discharge registration system, according to the authors. Lombardy hospitals routinely provide hospitalization data to the regional health department.

Of note in this update is the information that only 14 cases of cancer were reported to have occurred in zone A. This is not unexpected, based on population estimates. This number was based on the assignment of addresses by the municipal vital statistics offices. But it is far too small to produce any meaningful results. However, in the more populated zone B, with about 4,800 residents, and zone R, with some 32,000 residents, several findings were noted (Table 7-18). In zone B, hepatobiliary cancer in females (RR = 3.3, 95% CI = 1.3-8.1), lymphoreticulosarcoma in men (RR = 5.7, 95% CI = 1.7-19.0), and multiple myeloma in women (RR = 5.3, 95% CI = 1.2-22.6) were significantly elevated.

In zone R, STSs in men (RR = 2.8, 95% CI = 1.0-7.3) were the only site-specific cancers that were significantly elevated. Cancer of the genitourinary system in women was significantly depressed (RR = 0.8, 95% CI = 0.6-1.0) chiefly because of a low risk of cancer of the uterus.

This is consistent with the animal data that suggest estrogen-induced protective effects in female rats.

The authors explain that the absence of cancer among the chloracne victims is not unexpected at this time because of the relatively young age of the group and the small number of individuals affected. They state that at this time only 0.5 *total* cancer deaths could be expected in this subgroup.

The fact that elevated risks of cancers have appeared within a relatively short period of time following the accident may have been the result of exposures received from a 2,4,5-T production plant that existed in that area many years prior to the accident. Earlier potential exposure to dioxin from the preexisting plant could have been the initiating event for the cancers. Furthermore, hematopoietic tumors have a shorter latency than most carcinomas.

In their update of their earlier studies of the Seveso population, Bertazzi et al. (1997, 1998) continue to report excess risks of cancer mortality resulting from the accident. The populations around Seveso were followed for 15 years until December 31, 1991, with the following results: There was no increase in overall cancer mortality in any zone utilizing the population outside of zones A, B, and R as a comparison. Zone A had the fewest number of exposed persons. Only 6 male (13.5 expected) and 10 female (8.5 expected) cancer deaths have been reported after 15 years of observation in zone A, too few to provide any meaningful information regarding potential increased cancer risks. On the other hand, in zone B significant excess cancer mortality risks occurred at four sites in males (rectum, pleura, lymphohemopoietic, and leukemia) but only one in females (myeloma) (Table 7-19).

In zone R significant excess mortality risks were observed at two sites: esophagus in males and bone cancer in females. These significantly elevated site-specific mortality risks are based on a sufficient number of deaths as to rule out the possibility of a small-numbers effect. Only males in zone R reported any deaths from STSs (4 observed versus 1.9 expected) and this was not significant. The authors conclude that the specific excesses seen here could not be explained by bias or confounding and that their association with dioxin exposure is plausible. There appears to be little consistency in the reported findings. Again, not much can be concluded based upon mortality data after only 15 years' follow-up from the time of the accident. The authors pointed out that the study had several limitations linked to exposure categorization, time elapsed since exposure, and small size.

A more recent follow-up (Bertazzi et al., 2001a) of the same group of residents in Zones A and B was completed after 20.5 years on December 31, 1996. No reports of findings in Zone R and in the reference region are presented although the authors report that results from the "least contaminated zone R failed to suggest increased cancer risks." The residents of zones A and B continued to exhibit effects similar to those reported in the earlier updates.

All cancer mortality was modestly increased. When latency is considered from the time of the accident, the risk increases modestly in males (RR = 1.1, 95%CI = 1.0, 1.3) in regions A & B combined, but not in females. This analysis assumes that all effects may have been induced by exposure from the explosion despite the fact that the factory occupied the site for many years. Specific cancer sites that also exhibit elevated risks, both sexes combined, are cancer of the rectum (RR = 1.8; 95%CI = 1.0-3.3); lymphatic and hemopoietic cancer (RR = 1.7; 95%CI = 1.2-2.5) and Hodgkin's disease (RR = 3.1; 95% CI = 1.1-8.6). After 15 years, the risks for non-Hodgkin's lymphoma and myeloid leukemia were significantly elevated (RR = 2.8; 95% CI = 1.1-7.0) and (RR = 3.8; 95% CI = 1.2-12.5), respectively.

Female mortality was significantly elevated for lymphohemopoietic system (RR = 1.8; 95%CI = 1.1-3.2) and multiple myeloma (RR = 3.2; 95%CI = 1.2-8.8). No latent trends are evident in females (Table 7-20).

However, in males all cancer mortality was significantly elevated (RR = 1.1; 95%CI = 1.0-1.3). After 15 years latency, all cancer mortality the risk increased significantly elevated (RR = 1.3; 95%CI = 1.0-1.7). Rectal cancer (RR = 2.4; 95%CI = 1.2- 4.6) and lung cancer (RR = 1.3; 95%CI = 1.0- 1.7) were also significantly elevated after 15 years latency. Risks were elevated in the shorter latent categories of these same two site-specific cancers. No apparent trend of increasing or decreasing risks were evident when latency was considered at other selected sites as well from the time of the accident. But then, the potential influence of exposures received by the residents of the community from the preexisting factory cannot be assessed for its effect on the relative risks and latency.

No soft tissue sarcomas were observed in zones A and B. However, less than one case would have been expected to occur by the end of the followup. For instance, in Zone A, where exposure was highest, the expectation of a STS was only 0.1, there was little power to detect a significant risk in that region.

In a special study group of 182 persons exhibiting chloracne, mostly children, and who might be expected to have had much greater exposure to dioxin than most, only two had died by the end of the follow-up extension. Interestingly, 114 of these individuals with chloracne resided in zone R and the reference region. Efforts should be made to confirm the TCDD dioxin levels by blood lipid analyses on all 182 members of this group. They should form a separate group for study.

Estimated exposure levels in the blood of random samples of residents of zones A and B at different time intervals are provided in Table 7-22. During the 16- to 18-year lapse from the initial blood lipid measurements in 1976-1977 until 1993-1994, there appears to have been a near 7-fold drop in blood levels of TCDD. This is consistent with what would be expected given the approximate 7 year half life expectation of TCDD in the body.

The results of this latest update continue to support the finding of an increased risk of certain site-specific cancers in the population exposed by the industrial accident in1976 although all cancer risk is only modestly increased. This can be explained by the fact that the most heavily exposed members of the population (Zone A) make up only 12% of the population of the two zones examined by the authors and that the blood levels over time as evidenced in Table 7-22 have fallen as expected during the 20.5 year span of time since the accident. Furthermore, the observed blood lipid levels of TCDD initially were, on average, much less than those observed by Fingerhut et al. (1991) in industrial workers in the U.S. (Section 7.5.1.) who were involved in the making of chemicals contaminated with TCDD. The accident in Seveso produced an intense exposure to the population of that region that may have supplemented potential earlier exposures received by workers at the preexisting factory and residents living nearby but, in general, body burden levels were within an order of magnitude of background levels at the time when total TEQ is considered.

After the accident, little additional exposure would have been expected to occur directly except as part of the contamination of the surrounding crops and animals in the region, possibly through the food chain. Any additional exposure received in this way probably would be minuscule compared with the greater exposure received by the industrial chemical workers over a long period of time. This is reflected in the blood lipid levels seen in such workers. Furthermore, there is no follow-up of this group beyond the 20.5th year. Hence, latent effects, if any, may not have had a chance to be expressed yet. Not so with the industrial workers in Fingerhut et al. (1991) who were followed for over 30 years. The Seveso population should continue to remain under surveillance for a longer follow-up period. More attention should be given toward identifying exposed persons in Zone R and in the reference region through blood lipid analyses so that they can be included for study. Despite these issues concerning estimates of dose, the authors have stated that their results support the evaluation of TCDD as a human carcinogen, especially with the increased estimates of relative risk for several causes of cancer in the >15 year latency period.

In a commentary on this study by Smith and Lopipero (2001), two “key” problems were identified. The “likely” exposure levels back-calculated to the time when the exposures had occurred indicate that the weighted average for the two highest exposure zones in Seveso is only 136 ng/kg TCDD versus a mean of 3,600 ng/kg TCDD in the combined U.S. industrial cohorts. Smith and Lopipero concluded that one would not expect to find detectable increases in all-cancer mortality in the Seveso cohort for any latency. Thus, in their opinion, the results do not add to or subtract from the findings from the industrial cohorts. Secondly, they point out, smoking in the Seveso population may have influenced risk estimates of several causes of death

that are associated with smoking, thus presenting the potential of a confounding effect. Slightly elevated risks of lung cancer, myocardial infarction, and chronic respiratory disease are evident.

Bertazzi et al. (2001b) in a rebuttal agreed that exposures appear to be less than those of the industrial cohorts, but they are still two orders higher than background environmental exposures to TCDD, hence the increase in cancer mortality cannot be considered to be totally unexpected. These authors also argue that smoking is not necessarily the cause of the increase in the cancer mortality. Dioxin exposure also has been related to increased cardiovascular mortality in recent studies and that if smoking were a cause of the increased cancer, then one would see an increase in the risk of cancer of the larynx, esophagus, pancreas, and bladder and these risks were not elevated in Seveso males after 15 years of observation.

Pesatori et al. (1999) briefly reported on the 20-year followup of the incidence of cancer in the same cohort but in combined zone A and B. The risk of lymphatic and hematopoietic neoplasms was borderline significantly increased in adult females (RR = 1.7; 95% CI = 1.0-2.9) and in adult males (RR = 1.6; 95% CI = 1.0-2.7). The authors also report that biliary tract (four cases) and central nervous system neoplasms (six) were also elevated in females. Rectal (12) and pleural (3) tumors were elevated among males. Significance levels are not provided. STSs were elevated only in R-zone males (RR = 2.2; 95% CI = 0.9-5.1) based on seven cases. The RR for sarcomas any site was 1.3 based upon 15 cases. No other information is available from this sketchy description.

7.8.3. Rice Oil Poisonings in Taiwan and Japan Involving Compounds Structurally Related to Dioxin

This section discusses two similar incidents involving ingestion of rice cooked with oils accidently poisoned with PCBs and PCDFs. PCBs and PCDFs are structurally similar to the polychlorinated dioxins, and some of these are considered to be dioxin-like in their activity. The dioxin-like effects of these compounds are mediated through a cytosolic receptor (Chapter 2). The dioxin-like polychlorinated biphenyl congeners, chlorinated dibenzofurans, and dioxins that have a high affinity to bind the Ah receptor induce similar effects in both animals and humans but appear to differ quantitatively in toxicity (Ahlborg, Chapter 3 and 4). They appear to harm growth and reproduction, they damage the immune system, and they also appear to cause cancer. These same effects have been observed in a number of different species, including humans.

Two accidents involving ingestion of food contaminated with PCBs and dibenzofurans, in Yusho (Japan) and Yu-Cheng (Taiwan), have been reported. The Yusho incident involved 1,900 people who in 1968 accidentally consumed up to 2 grams each of PCBs that had leaked into the rice oil at the facility where the rice oil was canned. The PCBs were primarily Kanechlor 400 that had been used as a heat exchange medium thousands of times. Commercial-preparation

Kanechlor 400 had a concentration that was 49% chlorinated. The use of this medium for exchange of heat resulted in an increase in the dibenzofuran contamination of approximately 250 times. The final mixture that was actually present in the rice oil had a ratio of one molecule of PCDFs to every 200 molecules of PCBs.

These victims suffered many ill effects from their massive exposure that lasted only a few months. Tissue studies by the Japanese of the victims indicated that some of the PCBs and PCDFs were retained for many years after the initial exposure. Certain congeners of the PCDFs are eliminated at a slower rate than PCBs. Concentrations measured several years following the Yusho accident indicated that the mass ratio of PCDFs to PCBs remaining in the adipose tissue of the victims was about 1 to 4 (Kuratsune et al., 1975). Japanese researchers have attributed most of the noncancer toxic effects to the presence of the PCDFs, although these effects are consistent with PCB exposure. These toxic effects include comedo formation, acneform eruptions, hyperpigmentation, and hyperkeratosis. In addition, ocular lesions such as swollen meibomian glands filled with yellow infarct-like material and pigmentation of the conjunctiva were seen, similar to effects of TCDD. For further discussion of these and other effects, see Part B of Chapter 7, which addresses noncancer health effects in humans.

Kuratsune et al. (1988) reported a significantly increased risk of liver cancer in male victims (9 observed vs. 1.6 expected; SMR = 559, $p<.01$) and a nonsignificantly increased risk in female victims (2 observed vs. 0.66 expected; SMR = 304), as well as a significantly increased risk of lung cancer in male victims (8 observed vs. 2.45 expected; SMR = 326, $p<.01$). Some 1,761 patients (887 males and 874 females) were followed from date of registration to the end of 1983, 15 years after the accident in October of 1968. Thirty-three male cancer deaths had occurred by this time versus 15.51 expected. In female victims, 8 cancer deaths had occurred while 10.55 were expected. Comparisons were with the age-, sex-, and cause-specific death rates of Japan and, separately, of Nagasaki and Fukuoka prefectures in 1970, 1975, and 1980. The author reports that the risk of liver cancer remained elevated even after the influence of latency, alcohol consumption, and liver disease had been evaluated. Kuratsune said that because there was an uneven distribution of deaths in the provinces where most of the victims lived, it was too early to draw any conclusions. Apparently, most of the liver cancers occurred in Fukuoka prefecture. A statistically significant excess mortality was still present in males of Fukuoka even when liver cancer deaths occurring less than 9 years after the accident were eliminated. The author stated, “Such a markedly uneven geographical distribution of deaths can hardly be explained by exposure to the toxic rice oil alone.” However, he cautioned that his findings suggest that the poisoning might have caused liver cancer at least in male patients. He concludes, “Our findings should not be disregarded, however, because the hepatocarcinogenicity

of PCBs in animals has been well documented." Deaths from chronic liver diseases and cirrhosis were also elevated but not significantly.

An outbreak of illness similar to Yusho was reported among some 2,000 persons in the Taichung and Changhwa provinces of Taiwan in March 1979. The illness consisted of chloracne, hyperpigmentation, and meibomian gland dilatation. In October 1979, the illness was found to be the result of the ingestion of cooking oil contaminated with PCBs and PCDFs. Chen et al. (1980) reported on the blood PCB levels of 66 victims for which gas chromatograms had been prepared. Basically, blood concentration residues ranged from 11 ppb to 720 ppb in these patients. The mean value was 49 ppb; most values were under 100 ppb. In only two instances were the concentrations greater, at 120 ppb and 720 ppb. The authors reported that the higher value of 720 ppb occurred in a patient who had difficulty metabolizing and excreting PCB components. They also maintain that blood PCB levels of these patients are "much higher" than those of 72 Japanese Yusho patients (Koda and Masuda, 1975). Koda and Masuda reported the mean PCB value in Yusho patients was 5.9 ppb with a standard deviation of 4.5 ppb in 1973 and 1974. Chen et al. (1980) maintained that this difference is due to a lengthy time lapse from the exposure to PCB in Yusho patients before measurements were taken compared with a much shorter time lapse in Yu-Cheng patients. Furthermore, the Yu-Cheng patients consumed a larger proportion of higher-chlorinated PCBs compared with those of Yusho and, as a result, the substance would be retained longer in the body, according to the authors.

7.9. SUMMARY AND CONCLUSIONS

The strongest evidence that exposure to TCDD leads to an increased risk of generalized cancers at multiple organ sites, including lung cancer, comes from the four occupational cohort studies (Fingerhut et al., 1991; Steenland et al., 1999; Manz et al., 1991; Flesch-Janys et al., 1995, 1998, 1999; Becher et al., 1996; Zober et al., 1990; Ott et al., 1996; Bueno de Mesquita et al., 1993; Hooiveld et al., 1996, 1998) discussed earlier as well as studies of the victims of the 1976 Seveso accident in Italy (Caramaschi et al., 1981; Bertazzi et al., 1989a,b, 1992, 1993, 1997, 1998, 2001a; Landi et al., 1996, 1998; Pesatori et al., 1993, 1999). See Table 7-20 and 7-21. These studies provide evidence of in vivo exposure to TCDD, with actual measurements of TCDD serum levels in exposed individuals or their surrogates positively correlated with significantly increased risks of cancer mortality of between 40% and 100% (SMRs range generally from 1.4 to 2.0). Although it is clear that congeners of the PCDDs/PCDFs are also present in the blood serum of exposed subjects, TCDD predominates. Flesch-Janys et al. (1995, 1998, 1999), in fact, have provided measurement data showing that when the PCDD/PCDF congeners were converted to their toxic equivalences (TOTTEQs) they were found to be dose-related to increasing risks of cancer, cardiovascular disease, and ischemic heart disease. In the

Yusho accident (Kuratsune, 1988), victims exposed to PCBs and dibenzofurans that were similar in structure to TCDD also reported a significant risk of lung cancer, as did the subjects of the occupational cohort studies mentioned in this summary. At the highest levels of exposure, the cancer risks are statistically significant. These data, together with the presence of dose-response relationships in the occupational studies, lend support to the concept of a likely causal relationship between cancer at multiple sites and exposure to TCDD, its congeners, and dioxin-like congeners of the PCBs, based on epidemiological studies.

Although some confounding or synergism by tobacco smoke cannot be excluded entirely, the limited analyses conducted and the lack of an excess risk of other smoking-related noncancer diseases suggests that smoking as a confounder cannot entirely explain the significantly elevated cancer risks seen in these studies. Although it is likely that exposure to asbestos fibers occurred prior to employment in the herbicide manufacturing industry in a few subjects, it is improbable that the two or three cases of asbestos-related diseases seen in these cohorts indicate widespread confounding from asbestos. Furthermore, if other chemicals and hazardous agents are present in the workplace of the chemical industry, that could be responsible for the excess cancer risks seen in these studies whose sources have not been identified, except for 4-aminobyphenyl. The 4-aminobyphenyl exposures were identified in one plant only, in one cohort studied, and were suggested as a cause of the bladder cancers observed in these studies. But this observation does not explain the increased risks of total cancer seen in the remaining cohorts, where it has either not been looked for or not been found. The idea that other hazardous agents present in the phenoxy herbicide industry are causing the increases in the risk of all cancer in these cohorts is unlikely because this is a rare event in occupational studies, and there is no reported association between exposure to other hazardous cancer agents and the increase in the risk of all cancers that have been reported in this industry despite extensive study. Furthermore, in the Seveso accident, residents living in the local area received almost exclusive exposure to TCDD, and have exhibited some significantly elevated site-specific risks of cancer that appears to be dose-related to TCDD.

Some studies discussed in this chapter report little or no increased risk of cancer from exposure to TCDD or its congeners. These studies generally suffer from one or more deficiencies that render them not relevant to provide information that could assist in determining the carcinogenicity of dioxins. These deficiencies fall into the following categories that impact the statistical power to detect an effect, if it was present: no measurements of in vivo exposure to TCDD, leading to misclassification of exposure between subjects and controls; the measured exposures are lower than those seen in the studies cited above and similar to those of the comparison population; and finally, there has been no consideration of latency. In short, these non- or weakly positive studies lack one or more strengths of the cohort studies discussed above.

From case-control and follow-up studies, STS has previously been reported to provide some evidence of an association with PCDD and its congeners. The original reports by Hardell (1977); Hardell and Sandstrom (1979), Eriksson et al. (1981, 1990), and Hardell and Eriksson (1988) of an association between STS and exposures involving TCDD-contaminated phenoxy herbicides have been extensively questioned (see Section 7.6.1). The degree of risk, as estimated in later studies by Hardell's research group, does not appear to be as great as originally suggested. The results of the recent Lynge (1998) study suggest that exposure to MCPA and related phenoxy herbicides may by itself increase the risk of STS. The results from the cohort study by Fingerhut et al. (1991) of 5,000 chemical production and processing workers exposed to TCDD are supportive of an association between TCDD exposure and STS, although the association is not statistically significant. These findings are similar to those from the 10- and 15-year follow-up studies of victims exposed to TCDD in Seveso (Bertazzi et al., 1989a,b, 1993, 1997, 1998) in Region R, although the numbers are small and no in vivo exposure information is available. The large IARC Registry cohort mortality study by Kogevinas et al. (1997) and Saracci et al. (1991) also suggests an association between STS and TCDD and the higher chlorinated dioxins. In a recently published nested case-control study by Kogevinas et al. (1995) based upon diagnosed cases of STS from the Saracci Study, support is also given to the finding of an association of exposure to other dioxin congeners, although the association with TCDD is stronger. The first New Zealand sarcoma study (Smith et al., 1983, 1984) also appeared to produce positive results when the analysis, presented above, was restricted to farmers to minimize bias. But because of conflicting data or even contradictory evidence regarding the likelihood of exposure to TCDD, a direct linkage could not be made that exposure specifically increases the risk of STS. Therefore, the epidemiologic findings regarding an association between exposure to TCDD or other dioxin-like compounds and STS do not add significantly to the weight of the evidence regarding human cancer hazard of these compounds.

Earlier suggestions of an increased risk of malignant lymphomas from exposure to TCDD have not been substantiated, but recent evidence suggests an association between NHL and exposure to the herbicide 2,4-D (Zahm and Blair, 1992), which may contain dioxins other than 2,3,7,8-TCDD. The evidence from two large industrial cohort studies (Fingerhut et al., 1991; Steenland et al., 1999; Saracci et al., 1991; Kogevinas et al., 1997), except for the Seveso accident, suggest little, if any, evidence of increased risk of NHL. In the Bertazzi et al. (2001a) study, a statistically significant excess of NHL occurs in the latent category (15+ years). The limited evidence of TCDD exposure that can be extracted from the extensive case-control studies on NHL by the National Cancer Institute (Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992) also does not indicate a consistent and pronounced increase in risk. At the present time,

existing studies do not present a consistent picture of increased risks of malignant lymphoma among persons probably exposed to TCDD.

Few studies of females are to be found in the case-control and cohort studies of the effects of exposure to dioxin. The only reported female cohort with good TCDD exposure surrogate information was that of Manz et al. (1991), which reported a borderline statistically significant increase in breast cancer. Although Saracci et al. (1991) did report reduced female breast and genital organ cancer mortality, this was based on few observed deaths and on exposure to chlorophenoxy herbicide, rather than TCDD. In the later update and expansion of this cohort Kogevinas et al. (1997) provided evidence of a reversal of this deficit and produced a borderline significant excess risk of breast cancer in females. Bertazzi et al. (1993, 1997, 1998, 2001a) reported nonsignificant deficits in the risk of breast and endometrial cancers in women living in geographical areas around Seveso contaminated by dioxins. Although Kogevinas et al. (1993) noted an increase in cancer incidence among female workers most likely exposed to TCDD, no increase in breast cancer incidence was observed in a small cohort studied. In sum, TCDD cancer experience for women may differ from that of men, but currently there are few epidemiologic data to support this conclusion.

Animal studies suggest that males and females respond differently to TCDD and its congeners. Dioxins have been shown to reduce estrogen levels in reproductive tissues and are also known to reduce estrogen-receptor binding in rat and mouse liver. The female mouse liver is more sensitive than the male mouse liver. These antiestrogenic effects might be responsible for decreased tumor incidences seen in the mammary gland, uterus, and pituitary of TCDD-treated female rats, although the decreases occurred in the high-dose group and may be due to decreased body weight. Antiestrogenic effects may also be partially responsible for increased liver cancer seen in female but not male rats (see Part II, Chapter 6, Sections 6.4.1 and 6.5.4). These female rat liver tumors may be ovary-dependent, while at the same time the ovaries appear to protect against TCDD-mediated tumor promotion in the rat lung (see Section 6.4.2). Thus, these complex mechanisms might very well affect human carcinogenicity of dioxin-like compounds in males and females differently.

TCDD-related receptor-mediated responses on cell differentiation and proliferation, hormonal effects, and immune suppression probably produce multiorgan sensitivity and contribute to the overall increased mortality from all malignancies combined seen in the four production worker subcohorts and Seveso victims with higher estimated PCDD exposures. The increased relative mortality risks (SMRs =1.4 to 2.0) seen in the most exposed subcohorts are consistent and statistically significant. This is important because significant increases in common tumors are difficult to demonstrate in epidemiological studies, even when dealing with relative risks generated from incidence data. With mortality data, which do not include those who

survived their cancer, it is even more unlikely that an effect will be detected when present, given the insensitive nature of the epidemiological method. Therefore, a significantly elevated risk of mortality from generalized cancer should be considered a significant contributor to the evaluation of cancer hazard, particularly when the mode of action of the subject compounds is consistent with promotion of existing lesions and/or immune suppression and multisite carcinogenesis.

In conclusion, although there are uncertainties associated with the epidemiologic evidence that could have influenced the risk estimates rendering these data "limited," the overall weight of evidence from the epidemiologic studies suggests that the generally increased risk of overall cancer is more likely than not due to exposure to TCDD and its congeners. The consistency of this finding in the four major cohort studies and the Seveso victims is corroborated by animal studies that show TCDD to be a multisite, multisex, and multispecies carcinogen with a mechanistic basis.

Table 7-1. Relative risks of selected cancers in study of chemical manufacturing workers exposed to TCDD in United States, by exposure duration and latency

Cancer	Measure[a]	Latency <20 years	Latency ≥20 years		Total cohort
			Exposure <1 year	Exposure ≥1 year	
Connective and soft tissues	Observed deaths	1	0	3	4
	Relative risk	1.4	0.02	9.22	3.4
	95% confidence interval	0.1 - 7.0	0.0 - 15.0	1.90 - 27.0	0.9 - 8.6
Hodgkin's disease	Observed deaths	2	0	1	3
	Relative risk	1.1	0.0	2.8	1.2
	95% confidence interval	0.2 - 3.5	0.0 - 15.0	0.1 - 15.3	0.3 - 3.3
Non-Hodgkin's lymphomas	Observed deaths	6	2	2	10
	Relative risk	1.6	1.5	0.9	1.4
	95% confidence interval	0.7 - 3.4	0.2 - 4.9	0.1 - 3.30	0.7 - 2.5
Lung cancer	Observed deaths	32	17	40	89
	Relative risk	0.9	1.0	1.4	1.1
	95% confidence interval	0.7 - 1.3	0.6 - 1.5	1.0 - 1.9	0.9 - 1.4
Stomach cancer	Observed deaths	3	3	4	10
	Relative risk	0.6	1.8	1.4	1.0
	95% confidence interval	1.5 - 1.6	0.4 - 5.2	0.4 - 3.5	0.5 - 1.9
All combined	Observed deaths	103	48	114	265
	Relative risk	1.05	1.02	1.46	1.15
	95% confidence interval	0.8 - 1.2	0.76 - 1.4	1.2 - 1.8	1.0 - 1.3

[a]Relative risks and confidence intervals are based on rounded values and may differ slightly from those in the original reports (Fingerhut et al., 1990, 1991).

Source: Fingerhut et al., 1991.

Table 7-2. Relative risks of lung cancer in subcohort of chemical manufacturing workers exposed to TCDD in United States for at least 1 year and with at least 20 years latency, adjusted for alternative hypotheses about its smoking distribution

Proportion of subcohort (percent)[a]			Expected lung cancer deaths (40 observed)	Relative risk	95% confidence interval
Never smokers	Former smokers	Current smokers			
24	19	57	28.8	1.4	1.0 - 1.9
28	14	59	29.2	1.4	1.0 - 1.8
25	10	65	30.5	1.3	0.9 - 1.8
20	15	65	31.2	1.3	0.9 - 1.7
15	15	70	33.2	1.2	0.9 - 1.6
10	20	70	33.9	1.2	0.9 - 1.6
15	10	75	34.4	1.2	0.8 - 1.6
10	15	75	35.1	1.1	0.8 - 1.5

[a]The first set of proportions assumes no difference between the subcohort and the U.S. population. The second set is basedon 87 surviving members of the subcohort (Fingerhut et al., 1990). The remaining sets are hypothetical values used to test thesensitivity of the results. Relative risks of lung cancer are assumed to be 4.7 for former smokers and 10.9 for current smokers (Fingerhut et al., 1990).

Source: Fingerhut et al., 1991.

Table 7-3. Life-table results for exposure-level subcohorts: standardized mortality ratios (SMRs) for total cancer by cumulative exposure categories to TCDD content in process materials with and without 15-year lag time for total cancer; U.S. population as referent

SMR (No. of observed deaths)				
Category	**Exposure level[a]**	**No lag**	**Exposure level[a]**	**15 year lag**
Septile 1	0 to <19	1.14 (34)	0 to <39	0.98 (67)
Septile 2	19 to <139	1.15 (39)	39 to <224	0.90 (27)
Septile 3	139 to <581	0.85 (29)	224 to <791	1.14 (31)
Septile 4	581 to <1,650	1.10 (36)	791 to <2,120	1.18 (30)
Septile 5	1,650 to <5,740	1.15 (40)	2,120 to <6,140	1.33 (34)
Septile 6	5,740 to <20,200	1.34 (38)	6,140 to <15,800	1.69[b] (33)
Septile 7	≥ 20,200	1.60[b] (40)	≥ 15,800	1.54[b] (34)
Two-sided *p* for trend CE LCE		0.02 .10		0.02 .002

[a] Estimated exposure = product of concentration of TCDD (μg/g) in process materials × contact level × fraction of day exposed × time.
[b] $p < .05$, two-sided.

CE = Cumulative exposure.
LCE = Logarithm of cumulative exposure.

Source: Steenland et al., 1999.

Table 7-4. Relative risks of all cancers combined in study of chemical manufacturing workers exposed to TCDD in Germany, by duration and category of exposure

		Exposure category (median adipose TCDD level)		
Exposure duration	**Measure**	**Low and medium (60 ng/kg)**	**High (137 ng/kg)**	**Total**
<20 years	Observed deaths	49	26	75
	Relative risk	1.1	1.2	1.1
	95% confidence interval	0.8 - 1.4	0.8 - 1.8	0.9 - 1.4
≥20 years	Observed deaths	10	8	18
	Relative risk	1.5	2.6	1.9
	95% confidence interval	0.8 - 2.7	1.2 - 4.9	1.1 - 2.9
Total	Observed deaths	59	34	93
	Relative risk	1.2	1.4	1.2
	95% confidence interval	0.9 - 1.5	1.0 - 2.0	1.0 - 1.5

Source: Manz et al., 1991.

Table 7-5. Relative risks of all cancers combined in study of chemical manufacturing workers exposed to TCDD (ng/kg) in blood in Germany by industry of exposure

TCDD content (ng/kg)	Observed deaths	Relative risk	95% confidence interval
0 to <125.2	28	1.24	0.82 to 1.79
125.2 to < 627.1	29	1.34	0.9 to 1.92
627.1 to < 2,503.0	31	1.34	0.91 to 1.90
≥ 2,503.0	36	1.73	1.21 to 2.40
Total	124	1.41	1.17 to 1.68

Source: Flesch-Janys et al., 1998.

Table 7-6. Relative risks of selected cancers in study of chemical manufacturing workers exposed to TCDD in Germany, by median blood TCDD level and latency

Subcohort (median blood TCDD level)	Cancer	Measure	Time since first exposure <20 years	Time since first exposure ≥20 years	Total
C1 (24.5 ppt)	Lung	Observed deaths	1	3	4
		Relative risk	1.2	2.5	2.0
		95% confidence interval	0.1 - 6.2	0.6 - 6.9	0.6 - 4.8
	Stomach	Observed deaths	1	2	3
		Relative risk	2.0	4.0	3.0
		95% confidence interval	0.1 - 9.7	0.7 - 13.2	0.8 - 8.1
	All combined	Observed deaths	2	7	9
		Relative risk	0.7	1.7	1.3
		95% confidence interval	0.1 - 2.4	0.7 - 3.3	0.6 - 2.4
C2 (9.5 ppt) and C3 (8.4 ppt)	Lung	Observed deaths	0	2	2
		Relative risk	0.0	1.0	0.5
		95% confidence interval	0.0 - 1.8	0.2 - 3.4	0.1 - 1.8
	Stomach	Observed deaths	0	0	0
		Relative risk	0.0	0.0	0.0
		95% confidence interval	0.0 - 3.2	0.0 - 3.9	0.0 - 1.7
	All combined	Observed deaths	5	9	14
		Relative risk	0.8	1.3	1.1
		95% confidence interval	0.3 - 1.9	0.6 - 2.4	0.6 - 1.8
Total cohort	Lung	Observed deaths	1	5	6
		Relative risk	0.4	1.6	1.1
		95% confidence interval	0.0 - 2.0	0.6 - 3.5	0.4 - 2.2
	Stomach	Observed deaths	1	2	3
		Relative risk	0.7	1.6	1.1
		95% confidence interval	0.0 - 3.4	0.3 - 5.2	0.3 - 3.0
	All combined	Observed deaths	7	16	23
		Relative risk	0.8	1.5	1.2
		95% confidence interval	0.4 - 1.6	0.9 - 2.3	0.8 - 1.7

Source: Zober et al., 1990.

Table 7-7. Relative risks of selected cancers in study of chemical manufacturing workers exposed to TCDD in Germany, by TCDD dose (μg/kg body weight), 1992

Cause of death	Total			TCDD < 0.1 μg/kg body weight			TCDD 0.1- 0.99 μg/kg body weight			TCDD ≥ 1 μg/kg body weight		
Category	**n**	**SMR**	**(95% CI)**	**n**	**SMR**	**(95% CI)**	**n**	**SMR**	**(95% CI)**	**n**	**SMR**	**(95% CI)**
Malignant neoplasms	31	1.2	(0.8 to 1.7)	8	0.8	(0.4 to 1.6)	8	1.2	(0.5 to 2.3)	15	1.6	(0.9 to 2.6)
Respiratory system	11	1.4	(0.7 to 2.5)	3	1.0	(0.2 to 2.9)	1	0.5	(0.0 to 2.7)	7	2.4	(1.0 to 5.0)
Residual sites	5	1.6	(1.6 to 3.6)	2	1.6	(0.2 to 5.7)	1	1.2	(0.0 to 6.4)	2	1.9	(0.2 to 6.7)
Category	**n**	**SIR**	**(95% CI)**	**n**	**SIR**	**(95% CI)**	**n**	**SIR**	**(95% CI)**	**n**	**SIR**	**(95% CI)**
Malignant neoplasms	47	1.2	(0.8 to 1.5)	15	1.0	(0.5 to 1.6)	13	1.2	(0.6 to 2.1)	19	1.3	(0.8 to 2.0)
Respiratory system	13	1.2	(0.6 to 2.0)	1	0.7	(0.2 to 2.1)	2	0.7	(0.1 to 2.5)	8	2.0	(0.9 to 3.9)
Digestive organs	12	1.1	(0.6 to 1.9)	3	0.7	(0.2 to 2.2)	4	1.4	(0.4 to 3.6)	5	1.2	(0.4 to 2.9)

Source: Ott et al., 1996.

Table 7-8. Summary of results for selected cancers from follow-up studies of chemical manufacturing and processing workers exposed to TCDD

		Total cohorts				Subcohorts with high exposure, long latency, or both			
Cancer	Study	Observed deaths	Expected deaths	Relative risk	95% Confidence interval	Observed deaths	Expected deaths	Relative risk	95% Confidence interval
Connective and soft tissue cancers	Fingerhut (1991)	4	1.2	3.3	1.1 - 8.0	3	0.3	10.0	2.5 - 27.3
	Manz (1991)	0	0.4[a]	0.0	0.0 - 7.5	0	0.1[a]	0.0	0.0 - 30.0
	Zober (1990)	0	0.1[a]	0.0	0.0 - 30.0	0	0.0[a]	0.0	0.0 - 99.9
	Total	4	1.7	2.4	0.7 - 5.7	3	0.4	7.5	1.9 - 20.4
Non-Hodgkin's lymphomas	Fingerhut (1991)	10	7.3	1.4	0.7 - 2.4	2	2.1	1.0	0.2 - 3.1
	Manz (1991)	3	2.4[a]	1.2	0.3 - 3.4	NA	NA	NA	NA
	Zober (1990)	0	0.6[a]	0.0	0.0 - 5.0	0	0.2[a]	0.0	0.0 - 15.0
	Total	13	10.3	1.3	0.7 - 2.1	2	2.3	0.9	0.1 - 2.9
Lung cancer	Fingerhut (1991)	89	80.1	1.1	0.9 - 1.4	40	28.8	1.4	1.0 - 1.9
	Manz (1991)	30	21.3	1.4	1.0 - 2.0	NA	NA	NA	NA
	Zober (1990)	6	5.6	1.1	0.4 - 2.2	3	1.2	2.5	0.6 - 6.8
	Total	125	107.0	1.2	1.0 - 1.4	43	30.0	1.4	1.1 - 1.9
Stomach cancer	Fingerhut (1991)	10	9.7	1.0	0.5 - 1.8	4	2.9	1.4	0.4 - 3.3
	Manz (1991)	12	9.9	1.2	0.7 - 2.1	NA	NA	NA	NA
	Zober (1990)	3	2.7	1.1	0.3 - 3.0	2	0.5	4.0	0.7 - 13.2
	Total	25	22.3	1.1	0.7 - 1.6	6	3.4	1.8	0.7 - 3.7
All cancers combined	Fingerhut (1991)	265	229.9	1.2	1.0 - 1.3	114	78.0	1.5	1.2 - 1.8
	Manz (1991)	93	75.2	1.2	1.0 - 1.5	34	23.9	1.4	1.0 - 2.0
	Zober (1990)	23	19.7	1.2	0.8 - 1.7	7	4.2	1.7	0.7 - 3.3
	Total	381	324.8	1.2	1.1 - 1.3	155	106.1	1.5	1.2 - 1.7

[a]Estimated as a proportion of expected deaths from all cancers combined (see text).
NA, not available.

Table 7-9. Relative risks of soft tissue sarcomas and malignant lymphomas in relation to phenoxy acid and chlorophenol exposures in five case-control studies in Sweden

Exposure category and measure	Malignant lymphoma Northern Sweden 1974-1978 (Hardell et al., 1981)	Soft tissue sarcoma Northern Sweden 1970-1977 (Hardell and Sandström, 1979)	Soft tissue sarcoma Southern Sweden 1974-1978 (Eriksson et al., 1981)	Soft tissue sarcoma Northern Sweden 1978-1983 (Hardell and Eriksson, 1988)	Soft tissue sarcoma Central Sweden 1978-1986 (Eriksson et al., 1990)
Not exposed to phenoxy acids or chlorophenols					
Cases	108	33	85	41[a]	171[b]
Controls	303	187	206	255[a]	179[b]
Exposed to phenoxy acids, chlorophenols, or both					
Cases	61	19	25	13[a]	47[b]
Controls	32	19	13	56[a]	33[b]
Relative risk (95% CI)	5.3 (3.3 - 8.7)	5.7 (2.7 - 11.8)	4.7 (2.3 - 9.5)	1.4 (0.7 - 2.9)	1.5 (0.9 - 2.4)
Exposed to phenoxy acids					
Cases	41	13	14	9	23
Controls	24	14	5	22	18
Relative risk (95% CI)	4.8 (2.8 - 8.3)	5.3 (2.3 - 12.2)	6.8 (2.4 - 19.4)	2.5 (1.1 - 5.9)	1.3 (0.7 - 2.6)
Exposed to 2,4,5-T					
Cases	29	11	7	NA	19
Controls	23	10	1	NA	11
Relative risk (95% CI)	3.5 (2.0 - 6.4)	6.2 (2.5 - 15.8)	17.0 (2.1 - 140.0)	NA	1.8 (0.8 - 3.9)
Exposed to chlorophenols					
Cases	50	7	11	4	15
Controls	35	6	8	34	3
Relative risk (95% CI)	4.0 (2.5 - 6.5)	6.6 (2.1 - 20.9)	3.3 (1.3 - 8.6)	0.7 (0.2 - 2.2)	5.2 (1.5 - 18.4)

[a]Assuming no joint exposure to phenoxy acids and chlorophenols.
[b]Computed from Table 3 in the original report (Eriksson et al., 1990) with the assumption of no phenoxy acid exposures among persons with low-grade chlorophenol exposures.
NA, not available.

Table 7-10. Relative risks of malignant lymphoma and soft tissue sarcomas in relation to phenoxy acid and chlorophenol exposures in three case-control studies in Sweden[a]

Cancer and study locale	Exposure category	Cases	Controls	Relative risk (95% confidence interval)
Malignant lymphoma, northern Sweden (Hardell et al., 1981; Hardell, 1981)[b]	Exposed to phenoxy acids, chlorophenols, or both	51	28	1.0
	Unexposed	49	145	5.4 (3.1 - 9.5)
Soft tissue sarcoma, southern Sweden (Eriksson et al., 1981)[c]	Exposed to phenoxy acids, chlorophenols, or both	14	8	1.0
	Unexposed	17	39	4.0 (1.4 - 11.3)
Soft tissue sarcoma, central Sweden (Eriksson et al., 1990)[d]	Exposed to phenoxy acids	22	15	1.0
	Unexposed	33	51	2.3 (1.0 - 5.0)

[a]Restricted to persons who worked in the occupational categories in which these exposures predominantly occur.
[b]Analysis restricted to persons employed in agriculture, forestry, or the wood products industry.
[c]Analysis restricted to persons employed in agriculture or forestry.
[d]Analysis restricted to persons employed in agriculture, horticulture, or forestry.

Table 7-11. Mantel-Haenszel odds ratios for soft tissue sarcoma among persons exposed to all dioxins, TCDD, and dioxins other than TCDD in four case-control studies involving 434 cases and 948 controls[a]

Substance and variable	No exposure	Exposure < 1 yr[b]		Exposure ≥ 1 yr	
		Latency 5 - 19 yr	Latency ≥ 20 yr	Latency 5 - 19yr	Latency ≥ 20 yr
All dioxins					
No. of cases	352	24	34	3	21
No. of controls	865	22	52	0	9
OR	1.0	2.4		6.4	
90% CI	--	1.7 - 3.4		3.5 - 12	
TCDD					
No. of cases	352	18	22	1	5
No. of controls	865	14	25	0	2
OR	1.0	3.0		7.2	
90% CI	--	2.0 - 4.5		2.6 - 20	
Other dioxins					
No. of cases	352	6	12	2	16
No. of controls	865	8	27	0	7
OR	1.0	1.7		6.2	
90% CI	--	0.98 - 2.9		2.9 - 13	

[a]OR denotes odds ratio and CI confidence interval.
[b]All subjects were exposed for at least 1 day. Data for latency periods were combined to determine the odds ratios.

Source: Hardell et al., 1991.

Table 7-12. Relative risks of soft tissue sarcomas, non-Hodgkin's lymphomas, and Hodgkin's disease in relation to phenoxy acid and chlorophenol exposures in two case-control studies in southern Sweden

Authors, study period	Cancer	Exposure	Relative risk (confidence interval)[a]
Olsson and Brandt, 1978-1981 (Olsson and Brandt, 1988)	Non-Hodgkin's lymphomas	Phenoxy acids	1.3 (0.8 - 2.1)
		Chlorophenols	1.2 (0.7 - 2.0)
Persson et al., 1964-1986 (Persson et al., 1989)	Non-Hodgkin's lymphomas	Herbicides	4.9 (1.3 - 18)
	Hodgkin's disease	Herbicides	3.8 (0.7 - 21)
Wingren et al., 1975-1982 (Wingren et al., 1990)	Soft tissue sarcomas	Unspecified chemical work, potential exposure to phenoxy herbicides or chlorophenols	1.6 (0.8 - 3.3)

[a]Confidence intervals are 95% in the Olsson and Brandt study and 90% in the other two studies.

Table 7-13. Relative risks of non-Hodgkin's lymphomas in relation to farm use of 2,4,5-T in case-control studies in Kansas, eastern Nebraska, Iowa, and Minnesota

Occupational category	Exposure category and measure	Kansas (Hoar et al., 1986)		Eastern Nebraska (Zahm et al., 1990)		Iowa and Minnesota (Cantor et al., 1992)	
		Cases	Controls	Cases	Controls	Cases	Controls
All subjects	Exposed	3	18	13	27	25	48
	Unexposed	167	930	188	696	597	1,197
	Relative risk	0.9		1.8		1.0	
	95% confidence interval	0.3 - 3.2		0.9 - 3.5		0.6 - 1.7	
Farmers	Exposed	3	18	13	27	25	48
	Unexposed	130	644	134	512	331	650
	Relative risk	0.8		1.8		1.0	
	95% confidence interval	0.2 - 2.8		0.9 - 3.7		0.6 - 1.7	
Exposed farmers and unexposed nonfarmers	Exposed	3	18	13	27	25	48
	Unexposed	37	286	54	184	266	547
	Relative risk	1.3		1.6		1.1	
	95% confidence interval	0.4 - 4.6		0.8 - 3.4		0.6 - 1.8	

Sources: Hoar et al., 1986; Zahm et al., 1990; Cantor et al., 1992.

Table 7-14. Relative risks of soft tissue sarcomas and non-Hodgkin's lymphomas in relation to phenoxyacetic acid and chlorophenol exposure in a case-control study in western Washington State, 1981-1984

Exposure measure	Soft tissue sarcomas	Non-Hodgkin's lymphomas
Estimated potential for phenoxyacetic acid exposure[a]		
Low	0.6 (0.3 - 1.1)	0.9 (0.6 - 1.3)
Medium	1.0 (0.6 - 1.7)	0.9 (0.7 - 1.3)
High	0.9 (0.4 - 1.9)	1.2 (0.8 - 1.9)
Any	0.8 (0.5 - 1.2)	1.1 (0.8 - 1.4)
Estimated potential for chlorophenol exposure[a]		
Low	0.9 (0.5 - 1.6)	1.0 (0.7 - 1.3)
Medium	0.9 (0.6 - 1.5)	0.9 (0.7 - 1.2)
High	0.9 (0.5 - 1.8)	0.9 (0.9 - 1.4)[b]
Any	1.0 (0.7 - 1.5)	1.0 (0.8 - 1.2)

[a]The reference category had no estimated potential for exposure (relative risk 1.0 by definition).
[b]Either the point estimate or the lower confidence limit appears to have been a typographical error in the original report. (On a logarithmic scale, the point estimate should be centered between the two confidence limits.)
Source: Woods et al., 1987.

Table 7-15. Relative risks of soft tissue sarcomas and non-Hodgkin's lymphomas in relation to potential exposure to phenoxy acids and chlorophenols in case-control studies in New Zealand

Measure	Soft tissue sarcomas		Non-Hodgkin's lymphomas (1978-1981) (Pearce et al., 1987)
	First study (1976-1980) (Smith et al., 1983, 1984)	Second study (1981-1982) (Smith and Pearce, 1986)	
Cases	82	51	183
Controls	92	315	338
Phenoxy acids			
Any potential exposure			
Cases	21	NR	44
Controls	19	NR	72
Relative risk (95% CI)	1.3 (0.7 - 2.7)	NR	1.2 (0.8 - 1.8)
Probable or definite exposure >1 day, >5 years before cancer registration			
Cases	17	6	29
Controls	13	46	50
Relative risk (95% CI)	1.6 (0.7 - 3.5)[a]	0.8 (0.3 - 1.9)	1.1 (0.7 - 1.8)
Chlorophenols			
Any potential exposure			
Cases	8	NR	21
Controls	7	NR	27
Relative risk (95% CI)	1.3 (0.5 - 3.8)	NR	1.5 (0.8 - 2.7)
Potential exposure >1 day, >5 years before cancer registration			
Cases	8	NR	20
Controls	6	NR	27
Relative risk (95% CI)	1.6 (0.5 - 4.7)	NR	1.4 (0.8 - 2.6)

[a]Among farmers, 3.0 (1.1-8.3); controlling for farming by standardization, 1.9 (0.8-4.5).
CI, confidence interval; NR, not reported.

Table 7-16. Relative risks of soft tissue sarcomas in relation to phenoxy acid exposure in case-control study in northern Italy, 1981-1983

		Men		Women	
Category	Measure	Unexposed	Possibly or certainly exposed	Unexposed	Possibly or certainly exposed
Living	Cases	21	2	16	5
	Controls	54	8	53	7
	Relative risk	1.0	0.6	1.0	2.4
	(95% confidence interval)	NA	(0.1 - 3.3)	NA	(0.7 - 8.5)
Deceased	Cases	13	1	6	4
	Controls	17	6	7	6
	Relative risk	1.0	0.2	1.0	0.8
	(95% confidence interval)	NA	(0.0 - 2.0)	NA	(0.1 - 4.1)
Total	Cases	34	3	22	9
	Controls	71	14	60	13
	Relative risk	1.0	0.4	1.0	1.9
	(95% confidence interval)	NA	(0.1 - 1.7)	NA	(0.7 - 5.0)
Total, farmers only	Cases	12	3	5	9
	Controls	12	14	8	13
	Relative risk	1.0	0.2	1.0	1.1
	(95% confidence interval)	NA	(0.0 - 0.9)	NA	(0.3 - 4.5)

NA, not applicable.

Source: Vineis et al., 1986.

Table 7-17. Relative risks for selected cancers from follow-up studies of paper and pulp mill workers

Cancer	Study	Observed deaths	Expected deaths	Relative risk	95% confidence interval
Non-Hodgkin's lymphomas	Robinson (1986)	12	8.9	1.3	0.7 - 2.3
	Jäppinen (1987)	2	3.5	0.6	0.1 - 1.9
	Henneberger (1989)	4	3.8	1.1	0.3 - 2.5
	Total	18	16.2	1.1	0.7 - 1.7
Lung cancer	Robinson (1986)	50	62.1	0.8	0.6 - 1.1
	Jäppinen (1987)	78	62.6	1.2	1.0 - 1.5
	Henneberger (1989)	25	28.0	0.9	0.6 - 1.3
	Total	153	152.7	1.0	0.8 - 1.2
Stomach cancer	Robinson (1986)	17	13.8	1.2	0.7 - 1.9
	Jäppinen (1987)	24	28.8	0.8	0.5 - 1.2
	Henneberger (1989)	5	4.2	1.2	0.4 - 2.6
	Total	46	46.8	1.0	0.7 - 1.3
All cancers combined	Robinson (1986)	160	211.5	0.8	0.6 - 0.9
	Jäppinen (1987)	196	203.8	1.0	0.8 - 1.1
	Henneberger (1989)	97	87.9	1.1	0.9 - 1.3
	Total	453	503.2	0.9	0.8 - 1.0

Table 7-18. Relative risks for selected cancers among adults exposed to TCDD in Seveso, Italy, in contaminated areas B and R

Cancer	Males OBS	Males RR	Males 95% CI	Females OBS	Females RR	Females 95% CI
Region B						
All malignancies	76	1.1	0.9 - 1.4	36	0.8	0.6 - 1.1
Trachea, bronchus, lung	18	1.1	0.7 - 1.8	0	---	---
Hepatobiliary	5	1.8	0.7 - 4.4	5	3.3	1.3 - 8.1
Liver	4	2.1	0.8 - 5.8	0	---	---
Hematopoietic system	8	2.1	1.0 - 4.3	6	1.9	0.8 - 4.4
Non-Hodgkin's lymphoma	3	2.3	0.7 - 7.4	1	0.9	0.1 - 6.4
Lymphoreticulosarcoma	3	5.7	1.7 - 19.0	1	2.3	0.3 - 16.9
Hodgkin's disease	1	1.7	0.2 - 12.8	1	2.1	0.3 - 15.7
Multiple myeloma	2	3.2	0.8 - 13.3	2	5.3	1.2 - 22.6
Leukemia	2	1.6	0.4 - 6.5	2	1.8	0.4 - 7.3
Myeloid leukemia	1	2.0	0.2 - 14.6	2	3.7	0.9 - 15.7
Region R						
All malignancies	447	0.9	0.9 - 1.0	318	0.9	0.8 - 1.1
Trachea, bronchus, lung	96	0.8	0.7 - 1.0	16	1.5	0.8 - 2.5
Hepatobiliary	11	0.5	0.3 - 1.0	12	0.9	0.5 - 1.7
Liver	3	0.2	0.1 - 0.7	2	0.5	0.1 - 2.1
Connective & soft	6	2.8	1.0 - 7.3	2	1.6	0.3 - 7.4
Non-Hodgkin's lymphoma	12	1.3	0.7 - 2.5	10	1.2	0.6 - 2.3
Lymphoreticulosarcoma	4	1.1	0.4 - 3.2	6	1.7	0.7 - 4.2
Multiple myeloma	1	0.2	0.0 - 1.6	2	0.6	0.2 - 2.8
Myeloid leukemia	5	1.4	0.5 - 3.8	2	0.5	0.1 - 2.1
Genitourinary organs	75	1.0	0.8 - 1.3	106	1.1	0.9 - 1.3
Breast	1	1.2	0.1 - 10.2			

Source: Bertazzi et al., 1993.

Table 7-19. Standard mortality ratios (SMRs) for selected cancers among adults exposed to TCDD in Seveso, Italy, in contaminated areas B and R

Cancer- cause of death	OBS	Males SMR	95% CI	OBS	Females SMR	95% CI
Region B						
All malignancies	104	1.1	0.9- 1.3	48	0.9	0.7-1.2
Trachea, bronchus, lung	40	1.2	0.9- 1.7	2	0.5	0.1-1.8
Pleura	3	5.3	1.1- 15.5	-	-	-
Hepatobiliary	4	0.6	0.2- 1.5	4	1.1	0.3-2.9
Liver	4	0.6	0.2- 1.7	3	1.3	0.3- 3.8
Rectum	7	2.9	1.2- 5.9	2	1.3	0.1- 4.5
Lymphohemepoietic	12	2.4	1.2- 4.1	7	1.8	0.8-3.7
Non-Hodgkin's lymphoma	2	1.5	0.2- 5.3	0	0	0-3.0
Lymphatic	2	2.9	0.3- 10.6	-	-	-
Hodgkin's disease	2	1.5	0.2- 5.3	2	6.5	-
Multiple myeloma	1	1.1	0- 6.2	4	6.6	1.8- 16.8
Leukemia	7	3.1	1.3- 6.4	1	0.6	0- 3.1
Myeloid leukemia	3	3.3	0.7- 9.6	-	-	-
Region R						
All malignancies	607	0.9	0.9- 1.0	401	0.9	0.8- 1.1
Trachea, bronchus, lung	208	0.9	0.8- 1.1	35	1.1	0.8- 1.5
Esophagus	30	1.6	1.1- 2.3	5	0.9	0.3- 2.2
Hepatobiliary	35	0.7	0.5- 1.0	25	0.8	0.5- 1.3
Liver	31	0.7	0.5- 1.0	12	0.6	0.3- 1.1
Connective and soft	4	2.1	0.6- 5.4	0	0	0- 2.4
Non-Hodgkin's lymphoma	10	1.1	0.5- 2.0	8	0.9	0.4- 1.7
Lymphohemopoietic	27	0.8	0.5- 1.2	29	1.0	0.6- 1.4
Bone	2	0.5	0.1- 1.7	7	2.4	1.0- 4.9
Multiple myeloma	5	0.8	0.3-1.9	5	1.0	0.3- 2.3
Myeloid leukemia	4	0.6	0.2- 1.6	4	0.6	0.2- 1.6
Genitourinary organs	73	1.0	0.8- 1.3	65	1.1	0.8- 1.4
Breast	-	-	-	67	0.8	0.6- 1.0

Source: Bertazzi et al., 1997, 1998.

Table 7-20. Standard mortality ratios (SMRs) for selected cancers among males and females exposed to TCDD in Seveso, Italy, in contaminated areas A and B combined

Cancer- cause of death	OBS	Males SMR	95% CI	OBS	Females SMR	95% CI
Region A&B Combined*						
All malignancies	166	1.1	1.0–1.3	83	0.9	0.7–1.1
Trachea, bronchus, lung	64	1.3	1.0–1.6	5	0.7	0.3–1.7
Pleura	3	5.3	1.1–-15.5	-	-	-
Hepatobiliary	6	0.5	0.2–1.0	7	1.0	0.5–2.2
Liver	6	0.5	0.2–1.1	6	1.3	0.6–2.9
Rectum	9	3.8	1.2–4.6	3	1.1	0.4–3.5
Lymphohemopoietic	15	1.7	1.0–2.8	13	1.8	1.1–3.2
Non-Hodgkin's lymphoma	3	1.2	0.4–3.9	4	1.8	0.7–4.9
Lymphatic	2	1.6	0.4–6.8	-	-	-
Hodgkin's disease	2	2.6	0.6–10.9	2	3.7	0.9–16.0
Multiple myeloma	1	0.6	0.1–4.3	4	3.2	1.2–8.8
Leukemia	9	2.1	1.1–4.1	3	1.0.6	0.3–3.0
Myeloid leukemia	5	3.4	1.3–8.4	1	-	0.1–5.1

Source: Bertazzi et al., 2001a*.

Table 7-21. Standard mortality ratios (SMRs) and relative risks (RRs) of cancer in cohorts with evidence (in vivo) of exposure to dioxin

Population/industry	(N)	Exposure	Effects (95% CI)	Strengths/weaknesses	References
12 plants producing chemicals contaminated with TCDD	5,172	Current serum TCDD level (lipid adjusted) n = 253 Mean = 233 ppt	Total cancer SMR = 115 (102-130) Unspecified sites SMR = 162 (104-241)	<u>Strengths</u> High power, multiple sites (plants) exposure data, dose-response relationship, in vivo exposure information <u>Weaknesses</u> Possible confounding: smoking, other agents such as asbestos. Only 2 plants of 12 sampled for exposure data	Fingerhut et al., 1991
	1,520	>1 year exposed and >20 years latency, 95 sampled = 462 ppt	Total cancer SMR = 146 (121-176) Resp. system SMR = 142 (103-192)		Steenland et al., 1999
		Highest exposed group > 20,200 cumulative exposure score (concentration × fraction of day exposed × contact level × years exposed)	Total cancer = 1.60 (1.2-1.8) Lung cancer SMR = 1.65		
			All cancers / Trachea, bronchus, lung		
	Not provided	<1 yr, mean = 111ppt 1-<5 yr, mean = 413 ppt 5 - 15 yr, mean = 738 ppt ≥15 yr, mean = 2218 ppt	102 (75-133) / 96 (56-147) 165 (119-198) / 26 (73-192) 138 (97-186) / 146 (79-232) 115 (68-175) / 156 (71-272)	Possible nondifferential misclassification of exposure could underestimate true risks.	Aylward et al., 1996
German factory workers who produced phenoxy herbicides	1,189 men 399 women	Current adipose tissue TCDD levels used to obtain cumulative exposure during years when working	All cancer SMR = 1.41 (1.2-1.7) Lung cancer SMR = 1.51 (1.1-2.1)	<u>Strengths</u> Generally increasing risk with dose. Good evidence of in vivo exposure to TCDD congeners. Actual measurements from blood serums. Smoking apparently not a confounder	Becher et al., 1998 Becher et al., 1996 Flesch-Janys et al., 1998 Manz et al., 1991
	689 men	<u>Medium and low</u> 11 sampled Mean = 83 Median = 60 ppt	Nonsignificant exposure >20 years SMR = 1.54 (0.8-2.7)	<u>Weaknesses</u> Measurements are current. Possible misclassification of exposure by TEQ quartile	
	459 men	<u>High</u> 37 sampled Mean = 296 ppt Median = 137 ppt	All cancer exposure duration ≥ 20 years SMR = 2.54 (1.1-5.0)		
	Blood fat 275 workers	Highest TCDD quartiles > 2,503 ng/kg - years	Total cancer SMR 1.73 (1.2-2.4)		
		Highest TEQ quartile >5217.7 ng/kg years	Total cancer SMR = 1.64 (1.2-2.3)		

Table 7-21. Standard mortality ratios (SMRs) and relative risks (RRs) of cancer in cohorts with evidence (in vivo) of exposure to dioxin (continued)

Population/industry	(N)	Exposure	Effects (95% CI)	Strengths/weaknesses	References
Uncontrolled decomposition reaction on 11/17/53 resulting in exposure to TCDD in trichlorophenol production unit	243	Full group- measurement of blood lipid TCDD+ duration of exposure to obtain dose n = 138	Total cancer SMR = 1.2 (0.8-1.7)	Strengths In vivo exposure assessment. 40-year follow-up Weaknesses Possible synergistic effect with smoking, small size of cohort	Ott and Zober, 1996 Zober et al., 1990
	108	<0.1 ug/kg body weight	SMR = 0.8 (0.4-1.6)		
	66	<1.00 0.1 to 0.99 ng/kg body weight	SMR = 1.2 (0.5-2.3)		
	69	≥1.00 ug/kg body weight	SMR = 1.6 (0.9-2.6)		
	<69	≥1.00 ug/kg body weight + ≥20 years latency body weight	SMR = 1.97 (1.05-3.36) Lung cancer = 3.06 (1.12-6.66)		
	127 with chloracne and erythema	≥20 years latency	SMR = 2.01 (1.22-3.15)		
Phenoxy herbicide manufacturing and preparation accident, 1963	140 exposed in accident	Current measurements mean = 96.3 ppt serum TCDD, extrapolated to 1,841.8 ppt serum TCDD max at time of accident, n =14	Malignant neoplasms RR = 1.7 (1.1-2.7)	Strengths Current in vivo TCDD serum lipid measurements. Wide range of exposure and adequate latency, dose response relationship	Bueno de Mesquita et al., 1993 Hooiveld et al., 1998
	259 exposed compared with 482 nonexposed workers	Medium exposure, extrapolated range (7.7 to 124.1 ppt) at time of accident (lipid adjusted)	Malignant neoplasms RR = 5.0 (2.2-11.5)	Weaknesses Small cohort, lack of power	
	242 exposed compared with 482 nonexposed workers	High exposure, extrapolated range (124.2 to 7,307.5 ppt) at time of accident (lipid adjusted)	Malignant neoplasms RR = 5.6 (2.5 - 12.7)		
	549 exposed compared with 482 nonexposed	Exposed but not in accident. 244.1 ppt extrapolated, n = 17	RR = 4.1 (1.8-9.0) adjusted		

Table 7-21. Standard mortality ratios (SMRs) and relative risks (RRs) of cancer in cohorts with evidence (in vivo) of exposure to dioxin

Population/industry	(N)	Exposure	Effects (95% CI)	Strengths/weaknesses	References
Chemical explosion of phenoxy herbicide factory in Seveso, Italy, July 1976	Zones A, B, and R	Exposure as measured by blood serum. TCDD ranged as high as 56,000 ppt in one child Geometry means were as follows:	Significant excess risks in males without regard for latency	<u>Strengths</u> Relatively pure exposure to TCDD. Its distribution in the environment was measured. This exposed population stable. In vivo plasma TCDD serum available on a large number of subjects. Biases and confounding not likely to explain the unusual RRs	Caramaschi et al., 1981 Bertazzi et al., 1989b, 1992, 1993, 1997, 1998, 1999, 2001a Landi et al., 1996, 1998 Pesatori et al. 1993, 1999
	A-Zone N=862 population	A-53.2 ppt (N=7) plasma TCDD current 230.0 ppt extrapolated to time of accident	No significant findings	<u>Weaknesses</u> Time lapsed since measurement of exposure. Small size of population in most heavily exposed region. Small numbers of deaths from which to measure risks. Possible misclassification of exposure. 20 year follow-up is too short	
	B-zone N=6,647 population	B-11.0 ppt (N=51) plasma TCDD current 47.5 ppt extrapolated to time of accident	*<u>Zone A and B</u> Total cancer RR = 1.10 (0.9–1.2) *Males* Total cancer RR=1.1 (1.0-1.3) Respiratory cancer RR=1.3 (1.0-1.6) Lymphohematopoietic RR=1.7 (1.0–2.8) Leukemia RR=2.1 (1.1-4.1) *Females (etc.)* Myeloma RR=3.2 (1.2–8.8)		
	R-zone N=42,831 population	R-4.9 ppt (N=52) plasma TCDD current 200 cases of chloracne were reported	**<u>Zone R</u> *Males* Esophagus RR=1.6 (1.1-2.3) **<u>Zone R</u> *Females* Bone - RR=2.5 (1.0-4.9) No separated finding yet		

*Bertazzi et al., 2001a.
**Bertazzi et al., 1997, 1998.

Table 7-22. TCDD concentrations in the blood of selected residents in the zones contaminated after the Seveso, Italy, industrial accident in 1976[a]

Study area	Lipid-adjusted plasma concentration	
	Number of Subjects	Median
Zone A	296 (1976-1977) 7 (1993-1994)	447.0 ppt 73.3 ppt
Zone B	80 (1976-1977) 51 (1993-1994)	94.0 ppt 12.4 ppt
Zone R	48 (1976-1977)	48 ppt
Reference Zone	52 (1993-1994)	5.5 ppt

[a]Adapted from Bertazzi et al., 2001a.

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PART 7B: EFFECTS OTHER THAN CANCER

7.10. INTRODUCTION

Human exposure to 2,3,7,8-TCDD has been associated with noncancer effects in most systems. The majority of effects have been reported among occupationally exposed groups, such as chemical production workers, pesticide users, and individuals who handled or were exposed to materials treated with 2,3,7,8-TCDD-contaminated pesticides, and among residents of communities contaminated with tainted waste oil (Missouri, USA) and industrial effluent (Seveso, Italy).

These effects represent a complex network of responses ranging from changes in hepatic enzyme levels which, based on current evidence, do not appear to be related to clinical disease, to observable alterations in the character and physiology of the sebaceous gland, as in chloracne (Calvert et al., 1992; Taylor, 1979). This section of Chapter 7 describes, by system , the noncancer effects associated with exposure to 2,3,7,8-TCDD. The characterization of the effects by system provides a context within which to compare the results of the various studies. However, it is important to recognize that the observed effects are not independent events but rather may be one outcome in a series of interrelated outcomes, some of which we may be incapable of measuring with the present technology or which we currently do not recognize as an outcome of exposure to 2,3,7,8-TCDD.

The information describing human effects attributed to exposure to 2,3,7,8-TCDD-contaminated materials is derived from a wide variety of sources, including clinical assessments (case reports) of exposed individuals and analytic epidemiologic studies using case-control, cross-sectional, and cohort designs. The case reports describe the acute outcomes of exposure to 2,3,7,8-TCDD and provide the basis for hypothesis generation for controlled epidemiologic studies; however, they are not suitable for testing causal relationships between exposure and related effects (Ashe and Suskind, 1950; Suskind et al., 1953; Bauer et al., 1961; Goldman, 1972).

As described in the previous section, cohort and case-control studies have been used to investigate hypothesized increases in malignancies among the various 2,3,7,8-TCDD-exposed populations (Fingerhut et al., 1991a, b; Steenland et al., 1999; Manz et al., 1991; Eriksson et al., 1990). Cross-sectional studies have been conducted to evaluate the prevalence or extent of disease in living 2,3,7,8-TCDD-exposed groups (Suskind and Hertzberg, 1984; Moses et al., 1984; Lathrop et al., 1984, 1987; Roegner et al., 1991; Grubbs et al. 1995; Sweeney et al., 1989; Centers for Disease Control Vietnam Experience Study, 1988a; Webb et al., 1989; Ott and Zober, 1994). Many of the earliest studies were unable to define exposure-outcome relationships owing to a variety of shortcomings, including small sample size, poor participation, short latency periods, selection of inappropriate controls, and the inability to quantify exposure to

2,3,7,8-TCDD or to identify confounding exposures. In more recent cross-sectional studies of U.S. chemical workers (Sweeney et al., 1989), U.S. Air Force Ranch Hand personnel (Roegner et al., 1991; Grubbs et al., 1995), and Missouri residents (Webb et al., 1989), serum or adipose tissue levels of 2,3,7,8-TCDD were measured to evaluate 2,3,7,8-TCDD-associated effects in exposed populations. The ability to measure tissue or serum levels of 2,3,7,8-TCDD for all or a large sample of the subjects confirmed exposure to 2,3,7,8-TCDD and permitted the investigators to test hypothesized dose-response relationships.

7.11. CROSS-SECTIONAL STUDIES: USES AND LIMITATIONS

Most of the studies that describe nonmalignant effects were designed as cross-sectional medical studies. These types of studies are useful for assessing the current status of the surviving study population; however, they are inherently limited by a number of factors, including survivor and participation biases, exposure and disease misclassification, recall bias, and interobserver variability. Survivor and participation biases may have occurred because the studies included only those who were living at the time of the study, and did not or could not obtain similar information on those who died or were too ill to participate. Studies of groups exposed to agents that contribute to early deaths or cause severe illnesses may exclude the populations who were at highest risk. Exclusion of the sick and deceased whose condition was associated with 2,3,7,8-TCDD may erroneously cause the risk estimate to be closer to the null than the true risk.

Disease misclassification may be introduced in a variety of ways. Medical tests in many reviewed studies were most often performed once, without follow-up. For some disorders, multiple testing is preferred to obviate normal variations in some test parameters, e.g., immunologic tests or hormone levels. In other situations, self-reported medical histories were collected and, by design, were not or could not be confirmed by medical records. When the exposed group incorrectly reports more disease than the unexposed group, recall and reporting biases may falsely raise the risk estimate.

Exposure misclassification, particularly in the early studies, was a major limitation. In the earlier studies of production workers or community residents, exposure to 2,3,7,8-TCDD was determined only by an individual's presence (residing or working) in an area that was contaminated with 2,3,7,8-TCDD (Suskind and Hertzberg, 1984; Moses et al., 1984; Hoffman et al., 1986; Poland et al., 1971; May, 1973, 1982; Martin, 1984; Bond et al., 1983, 1989; Filippini et al., 1981; Ideo et al., 1985; Mocarelli et al., 1986). The lack of a measurement to quantify exposure hindered the ability to confirm exposure and to assess the magnitude of an exposure-response relationship. If the misclassification is nondifferential, it tends to bias the measure of effect toward the null.

As described above, in studies conducted a decade later (Roegner et al., 1991; Grubbs et al., 1995; Sweeney et al., 1989; Centers for Disease Control Veterans Health Studies, 1988; Webb et al., 1989) researchers were able to confirm and quantify exposure to 2,3,7,8-TCDD in serum or adipose tissue. This breakthrough helped establish that certain previously exposed populations had 2,3,7,8-TCDD levels well above the background level of less than 20 picograms per gram of lipid (pg/g) (Patterson et al., 1989) and that the nonexposed comparison group was truly not exposed to greater than background levels. Yet, because the occupational populations were exposed to 2,3,7,8-TCDD-contaminated substances for as many as 40 years before being tested, levels attained at the time of exposure can only be estimated. It appears that for some populations with higher exposures, such as workers, the estimate reflects continuous exposure over an extended period. For example, despite the intervening period between last exposure to 2,3,7,8-TCDD and the determination of serum 2,3,7,8-TCDD levels in workers employed in the production of 2,4,5-TCP and 2,4,5-T (15 to 37 years after last occupational exposure), the duration of occupational exposure was highly correlated to serum levels of 2,3,7,8-TCDD obtained at the time of the study (1987-1988) (Pearson product moment correlation coefficient [r] = 0.7) (Sweeney et al., 1989). These data suggest a strong relationship between length of occupational exposure and serum 2,3,7,8-TCDD regardless of the length of the intervening period.

The deposition, metabolism, and excretion of high doses of 2,3,7,8-TCDD in the human system have not been fully described. A study by Pirkle et al. (1989) suggests that 2,3,7,8-TCDD decays by one-half in approximately 7.1 years, based on a one-compartment model and using a standard half-life equation. If this is true, exposures to trichlorophenol production workers may have been as high as 30,000 pg/g (Fingerhut et al., 1991a) and in excess of 50,000 pg/g in some residents of Seveso (Mocarelli et al., 1991). The data may be limited by the lack of complete information on the manner in which human metabolism handles 2,3,7,8-TCDD exposure. In a separate analysis, Michalek et al. (1996) estimated the half-life among veteran Ranch Hands to be 8.7 years (95% CI = 8.0-9.5 years). This calcuation was based on a mean decay rate of 0.0797 per year. In this analysis half-life increased with increasing body fat, but not age.

This section of Chapter 7 is a selective review of studies that, to date, provide the most information on the relationship between nonmalignant outcomes and exposure to 2,3,7,8-TCDD-contaminated materials. Animal studies have been reviewed in other chapters of this document and will not be discussed in detail. Case reports will not be reviewed, but will be used to provide support for the analytic studies. In the assessment of mortality from nonmalignant causes of death, only cohort studies in which standardized mortality ratios (SMR) or equivalent population-based risk ratios were calculated will be discussed.

7.12. DESCRIPTION OF PRINCIPAL STUDIES

In the following section, we have provided a summary of the population description and methods of the studies that reported results for two or more systems or effects. Studies that are referenced only once will be described when cited. Results of these studies will be described in subsequent sections.

7.12.1. Occupational Studies

7.12.1.1. *U.S. Chemical Workers: West Virginia*

In March 1949, an explosion of a TCP reaction kettle in a chemical plant in Nitro, West Virginia, and the subsequent cleanup exposed approximately 450 workers to 2,3,7,8-TCDD-contaminated substances. Examination of the workers in 1949 revealed a number of acute symptoms "characterized by skin, eye and respiratory tract irritation, headache, dizziness and nausea" (Suskind and Hertzberg, 1984). The acute symptoms subsided but were followed within a week or two by "acneform eruption, severe muscle pain affecting the extremities, thorax and shoulders, fatigue, nervousness and irritability, dyspnea, complaint of decreased libido and intolerance to cold" (Suskind and Hertzberg, 1984). Thirty years later, two independent, cross-sectional medical studies were conducted to evaluate the long-term consequences of exposure to 2,3,7,8-TCDD-contaminated substances among the surviving workers (Suskind and Hertzberg, 1984; Moses et al., 1984).

In a study by Suskind and Hertzberg (1984), a group of 204 (of a total of 419) active and retired white male workers exposed between 1948 and 1969 to the 2,4,5-T production process and to the reactor release were included in a clinical examination program. The control group consisted of 163 (46% participation) current or former employees of the same plant who had no self-reported exposure to 2,4,5-T production or maintenance of the facility. The study collected demographic and medical histories and performed clinical chemistries, urinalysis, pulmonary function tests, dermatologic examinations, and conduction velocities of the sural sensory and peroneal motor. Multiple linear regression analysis was used to compare the exposed and nonexposed groups.

For participation in a separate study of workers at the Nitro plant, Moses et al. (1984) invited all workers documented in union records to have worked in 2,4,5-T production and a systematic random sample of workers with no known 2,4,5-T production exposure. Fifty-five percent (N = 226) of the persons invited participated in the study. Lifetime occupational and medical histories were collected and clinical chemistries, urinalysis, and dermatologic examinations were conducted. Exposure to 2,3,7,8-TCDD could not be discerned because of irreconcilable inconsistencies in self-reported work histories and the lack of good company

records to estimate and confirm the likelihood of exposure. Although the authors recognized that absence of chloracne did not preclude exposure, they compared the results of the group with chloracne with those without chloracne. Thus, the study design was revised to explore the differences in health status in individuals with and without chloracne. Because exposed workers may have been included in the group diagnosed without chloracne, the usefulness of the data to quantify exposure-disease relationships is limited.

Two studies of this cohort also examined cancer and noncancer mortality of subsets of workers from this plant (Zack and Suskind, 1980; Collins et al., 1993).

7.12.1.2. *U.S. Chemical Workers: The NIOSH Study*

The study conducted by the National Institute for Occupational Safety and Health is a cross-sectional medical study of living workers who were previously employed for at least 1 day in one of two plants located in Newark, New Jersey, and Verona, Missouri. From 1951 to 1969, 490 workers employed at the New Jersey plant produced sodium 2,4,5-trichlorophenate (NaTCP), 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), and 2,4-dichlorophenoxy acetic acid (2,4-D). A high proportion of chloracne and other dermatologic abnormalities and cases of porphyria and hypomania were reported among the workers at the New Jersey facility (Poland et al., 1971; Bleiberg et al., 1964), which produced some of the most heavily 2,3,7,8-TCDD-contaminated NaTCP and 2,4,5-T among production facilities whose products were surveyed (Fee et al., 1975). At the Missouri plant, NaTCP and 2,4,5-T were produced intermittently for 4 months in 1968, and NaTCP and hexachlorophene were produced continuously for 22 months between April 1970 and January 1972.

For comparison, unexposed neighborhood referents were recruited using a random sampling procedure described by Sweeney et al. (1989). Referents were selected if they reported no prior history of occupational exposure to 2,3,7,8-TCDD and matched the worker by age (within 5 years), race, and gender. A total of 586 workers were eligible for inclusion in the study, of which 400 (68.3%) were living, 142 (24.2%) were deceased, and 44 (7.5%) could not be located. All 400 living workers were invited to participate in the study; 281 (70%) were examined. A description of the study population is included in the results.

Worker and referent health and exposure status were assessed in 1987-1988 through an interviewer-administered medical and occupational history and comprehensive physical and psychological examinations (Sweeney et al., 1989). A lifetime medical history was obtained from each participant by interviewers who were blind to the exposure status of the respondent. Results of the pulmonary, hepatic, gastrointestinal, porphyria, mood dysfunction, and neurologic

examinations have been published or accepted for publication (Calvert et al., 1991, 1992, 1993, 1994, 1996, 1998, 1999; Sweeney et al., 1993; Egeland et al., 1994; Halperin et al., 1995, 1998).

As a surrogate for cumulative exposure, serum 2,3,7,8-TCDD levels were measured in 237 workers and a random sample of 79 referents. Procedures for sample collection, preparation, adjustment for lipids, and statistical analysis were described in earlier reports (Fingerhut et al., 1989; Patterson et al., 1986a; Sweeney et al., 1990). The mean lipid-adjusted serum 2,3,7,8-TCDD level for workers was 220 pg/g, median 80 pg/g, ranging to 3,400 pg/g. The mean level was statistically significantly greater than that for referents (7 pg/g) (p<0.001). Analyses of other congeners of dioxins and dibenzofurans were also conducted; only the 2,3,7,8-TCDD levels were different in the two exposure groups (Piacitelli et al., 1992).

7.12.1.3. *BASF Accident Cohort*

"On 17 November 1953, an uncontrolled decomposition reaction occurred during the production of 2,4,5-trichlorophenol at a BASF AG facility in Ludwigshafen, Germany" (Ott et al., 1994). The reactor contents, which contained 2,3,7,8-TCDD, contaminated the building in which the TCP autoclave was housed. A series of studies have documented the effects and mortality experience of the workers present at the time of the decomposition reaction and exposed during the initial cleanup and equipment maintenance (May 1954 medical department list) (Cohort C1, N = 69), individuals present during subsequent clean-demolition activities between 1954 and 1969 (Cohort C2, N = 84), and a mixed group of workers identified as of December 1987 through interviews that include individuals who worked in the laboratory as safety inspectors and others who participated in the 1968-1969 demolition activities (Cohort C3, N = 101) (Zober et al., 1990; Ott et al., 1993). Two hundred forty-seven study subjects were included in a mortality study that found a significantly elevated SMR for all malignant neoplasms among workers with chloracne and 20 or more years since first exposure to 2,3,7,8-TCDD-contaminated chemicals (Zober et al., 1990).

Among 79% of the living subjects, lipid-adjusted serum 2,3,7,8-TCDD levels were measured in 138 (54%) of 254 study subjects during the period 1988-1992 (Ott et al., 1993). The geometric mean of the 2,3,7,8-TCDD levels in the entire group was 15.4 ppt (ranging from <1 to 553.0 ppt) (Ott et al., 1993) or 43 pg/g of lipid (M. G. Ott, personal communication, 1993). Geometric means for the cohorts are as follows: C1 = 1,009.5 pg/g lipid; C2 = 48.8 pg/g of lipid; and C3 = 83.7 pg/g of lipid. Background levels were determined in separate analyses of 102 unexposed individuals from Germany (Päpke et al., 1992). The geometric mean for 2,3,7,8-TCDD of the external referent group was 3.0, ranging from 0.6 to 9.1 pg/g of lipid. On the basis of regression analyses, serum 2,3,7,8-TCDD levels were highly correlated (R2=0.65) to duration

of exposure and location of exposure. Chloracne severity was positively and significantly related to 2,3,7,8-TCDD concentrations.

Comprehensive batteries of clinical chemistry measurements were also measured for the 138 subjects between 1988 and 1993 (Ott et al., 1994). Referents were selected from among BASF employees between the ages of 50 and 69 who participated in routine occupational medical examinations from 1989 to 1991. For some tests, there were as many as 6,000 referent values. For the immunologic parameters, the referent values were obtained from a group of 42 unexposed BASF employees who participated in a separate study that examined the immunologic function of 21 extruder personnel exposed to 2,3,7,8-tetrabrominated dibenzo-p-dioxin (2,3,7,8-TBDD) and -furan (2,3,7,8-TBDF) (Ott and Zober, 1996b). Cause-specific mortality and cancer incidence was also evaluated in the 243 male study subjects who were followed through 1992 (Ott and Zober, 1996a).

7.12.2. Studies of Community Residents

7.12.2.1. *The Missouri Experience*

During 1971, 2,3,7,8-TCDD-contaminated stillbottoms were removed from a hexachlorophene production facility and mixed with waste oil. This mixture was deposited on 45 residential, recreational, and industrial sites in southeastern Missouri in 1971 and 1972 (Daryl Roberts, personal communication). Waste oil mists were commonly used in the summer for dust control on roadways, horse arenas, truck depots, and other unpaved surfaces. Estimated contamination of the areas ranges from 1 to 2,200 ppb (Hoffman and Stehr-Green, 1989). A listing of potentially exposed persons was created (volunteers), and a survey was conducted to obtain baseline information to identify persons at high risk of exposure. Beginning in 1984, a series of studies were conducted to evaluate potential effects (Hoffman et al., 1986; Evans et al., 1988; Webb et al., 1989), including reproductive events, of residential exposure to 2,3,7,8-TCDD (Stockbauer et al., 1988).

The study by Hoffman et al. (1986) was conducted on 154 individuals (74% of total eligible) who were residents of the Quail Run Mobile Home Park between 1971 and 1983, because soil concentrations around the site were 2,200 ppb 2,3,7,8-TCDD. The comparison group of 155 (77% of total eligible) individuals was recruited from residents of a nearby mobile home park. The examination included tests for delayed hypersensitivity (the multitest Cornell Medical Index [CMI]; Merieux Institute, Miami, Florida) and neurobehavioral effects, blood chemistries, urinalysis, height, weight, vital signs, and examination of the skin, peripheral pulses, lymph nodes, abdomen, and peripheral nervous system. The results of this study were plagued by the exclusion of skin test results of 150 of 294 participants because of high reader error. Furthermore, information on subject exposure to 2,3,7,8-TCDD was limited because the study was based on a

minimum residence of 6 months in areas with contaminated soil. Actual contact with contaminated soil was not assessed.

In the follow-up study by Evans et al. (1988), 50 persons from the initial study who did not respond to the delayed hypersensitivity skin tests were retested. These subjects were thought to have impaired immune function. The multitest CMI was reapplied to all test subjects.

Webb and colleagues (1989) examined 41 of 51 persons with various histories of exposure to 2,3,7,8-TCDD (residential, recreational, and occupational exposure) and for whom adipose tissue levels of 2,3,7,8-TCDD were measured. Of the 41 participants, 16 had adipose 2,3,7,8-TCDD levels less than 20 pg/g (within background range), 13 had levels between $\geq$20 and 60 pg/g, and 12 subjects had levels above 60 pg/g. Standard medical examinations were conducted, and complete blood count with differential, a panel of automated chemistry tests, serum immunoglobulins, tests for porphyrins, and the multitest CMI were performed.

7.12.2.2. *Seveso, Italy*

In 1976, an explosion of a trichlorophenol reactor in a 2,4,5-T production facility in Medina, Italy, caused the contamination by 2,3,7,8-TCDD of the neighboring city of Seveso, Italy. Several reports (Biscanti et al., 1978; Homberger et al., 1979; Pocchiari, 1980a; Pocchiari et al., 1980b; Reggiani, 1978, 1980; Rehder et al., 1978; Tuchmann-Duplessis, 1977) compared four potentially affected communities (Seveso, Meda, Cesano, and Desio) to nearby unexposed communities. The contaminated area was subdivided into three zones (A, B, and R) of decreasing mean soil levels of 2,3,7,8-TCDD (Mocarelli et al., 1988). The mean 2,3,7,8-TCDD concentration in zone A was 230 $\mu g/m^2$; in Zone B, 3.0 $\mu g/m^2$; and in zone R, 0.9 $\mu g/m^2$.

Mean serum 2,3,7,8-TCDD concentrations among a sample of residents who were 13 years and older at the time of the explosion were: zone A, 443 pg/g lipid (N = 177); zone B, 87 pg/g lipid (N = 54); zone R, 15 pg/g (N = 17) (IARC, 1997). Geometric mean serum 2,3,7,8-TCDD concentrations measured were: zone A, 53.2 pg/g lipid (N = 7); zone B, 11 pg/g lipid (N = 51); zone R, 4.9 pg/g (N = 55) (Landi et al., 1997).

In 1979, Pocchiari et al. (1979) reported on initial efforts to screen residents in zones A, B, and R for 2,3,7,8-TCDD-related effects. Since then, a series of cross-sectional medical studies have reported the final results of the screening (Caramaschi et al., 1981; Ideo et al., 1985; Mocarelli et al., 1986; Assennato et al., 1989). Within 1 year of the reactor release, 193 cases of chloracne were identified among residents of zones A, B, and R, most of which resolved with time (Assennato et al., 1989). For Seveso residents, a standard diagnosis of chloracne was developed, in which all cases were stratified by severity: 0, no lesions; 1, a few comedones (up to

10, minimum stage); 2, numerous comedones and cysts (light stage); 3, comedones and cysts in specific regions (medium stage); and 4, comedones and cysts spreading from the face to other regions of the body (serious stage) (Caramaschi et al., 1981). Four studies investigated possible biochemical changes, particularly liver enzyme induction and lipid levels, among the 170 children diagnosed with chloracne and control groups (Caramaschi et al., 1981; Ideo et al., 1985; Mocarelli et al., 1986; Assennato et al., 1989).

In addition to chloracne, several other studies also evaluated peripheral neuropathy. In an early report by Pocchiari et al. (1979), tests for presence of peripheral nerve dysfunction were conducted for Seveso residents and for workers at the Icmesa production facility. Assennato et al. (1989) and Filippini et al. (1981) assessed the prevalence of peripheral neuropathy, comparing residents with and without chloracne (Assennato et al., 1989) or comparing residents having chloracne or abnormal serum hepatic enzyme levels with residents with no manifestations of 2,3,7,8-TCDD exposure (Filippini et al., 1981).

Two mortality studies, one of children ages 1-19 years and another of adults 20 years and older, examined death rates in residents of zones A, B, and R 10 years after the explosion (1976-1986) (Bertazzi et al., 1989, 1992). The comparison population was composed of approximately 100,000 inhabitants of uncontaminated areas surrounding Seveso. Follow-up for both the young and older cohorts was 99%. A third study examined the mortality of the three cohorts from July 1976 through June 1991 (Pesatori et al., 1998).

To date, although there are a few individual measurements of exposure among residents of the exposure zones, the general limitation of the studies conducted in Seveso residents is the classification of exposure of subjects by residence in zones A, B, or R, which is based on mean soil concentration of 2,3,7,8-TCDD. The weaknesses of using soil 2,3,7,8-TCDD levels to classify extent of exposure to 2,3,7,8-TCDD were aptly described by Bertazzi et al. (1989): "This (use of soil contamination) is a rather poor surrogate of exposure, and by no means an indicator of intake, since it does not take into consideration all the possible sources and ignores interindividual variability." This is the same problem encountered by some researchers investigating 2,3,7,8-TCDD-related effects among Missouri residents. One might also expand this limitation to each of the studies where environmental rather than personal levels of 2,3,7,8-TCDD contamination were used for exposure classification.

7.12.2.3. *Developmental Studies From The Netherlands*

In the early 1990s, scientists from several Dutch communities collected data on postnatal developmental outcomes and related them to total PCB-dioxin-furan TEQ from breast milk, and PCBs in cord blood and maternal blood. The results from these studies will be addressed by

system in Section 7.13. These studies are similar in design; a number come from the same study group including women and infants from Rotterdam, and from both Rotterdam and Grongenin. The outcomes studied in both communities included a neurological examination (Prechtl/Touwen) at 10 days and 18 months of age and Obstetrical Optimality score at 10 days of age. In Rotterdam only, mental and psychomotor development (Bayley Scales of Infant Development) was measured at 3, 7, and 18 months of age, and visual recognition memory (Fagan Infant test) at 3 and 7 months of age. At 42 months, these children were assessed for cognitive abilities (Kaufman Assessment Battery) and a subgroup was assessed for verbal comprehension (Reynell Language Developmental Scales). Another group in Amsterdam has also examined postnatal developmental outcomes and breast milk level; this study will be discussed at the end of this section.

The reports that covered Rotterdam, or Rotterdam and Groningen together, include the same infants. Data were collected beginning in June 1990 and continued until February 1992 or June 1992, depending on the outcome examined. Women were introduced to the project by their obstetricians or midwives, and details were explained to the women at home. First contact took place in the third trimester (32-34 weeks), and women were screened for their intentions to breast feed for at least 6 weeks ("exposed") or for their intention not to breast feed at all (comparisons). Only women with full-term deliveries to first- or second-born infants, among other characteristics, were selected for inclusion in the study. Originally 489 women who were willing to participate were identified; 71 of these were lost to the final study when they were not able to breast feed for the required 6 weeks.

Formula was supplied to those women in the study who did not intend to breast feed. In each community, the goal was to get approximately 100 in each group. The investigators did not describe the response rate, or the comparability of respondents to nonrespondents. All the reports included blood samples from the mother during the last month of pregnancy, cord blood, and breast milk collected in the second week after delivery. PCB levels (congeners 118, 138, 153, 180) were measured in the blood samples and used to estimate the prenatal exposures to the children, and PCB and dioxin-furan levels were measured in the breast milk (seventeen 2,3,7,8-substituted PCDDs and PCDFs, 3 coplanar PCBs, and 23 nonplanar PCB congeners) (Table 7-21b). These data were then used to rank exposure in the women and infants into categories to examine exposure outcome. The total breast milk values were calculated using the levels measured and multiplying this by the number of weeks of breast feeding. This approach assumes only small changes in the levels of these exposures over the duration of breast feeding when actual numbers are used, or that the relative magnitude of exposure remains consistent. As long as all the women are breast feeding, this is a useful approach to determine relative magnitude. Breast milk samples collected on the second week and about the sixth week after delivery were

compared for the following exposure groupings: dioxins-furans: IUPAC 48, 54, 66, 67, 70, 73, 75, 83, 94, 114, 118, 121, 124, 130, 131, 134, 135), coplanar PCBs (IUPAC 77, 126, 169), mono-ortho PCBs (IUPAC 105, 118, 156), di-ortho PCBs (IUPAC 170, 180), and total PCB-dioxin-furans, which includes all of the above. This terminology will be used in the descriptions of individual reports. With continued breast feeding, a drop in the levels of these would be expected as the body burden decreases. Decreases in levels were observed for a number of these; not all were statistically significant, in part because of the small number of women evaluated: decrease in dioxin-furans (no. women = 27, $p = 0.07$), coplanar PCBs (no. women = 44, $p = 0.91$), mono-ortho PCBs (no. women = 180, $p = 0.002$), di-ortho PCBs (no. women = 180, $p = 0.001$), and total PCB-dioxin-furans (no. women = 19, $p = 0.10$) (Koopman-Esseboom et al., 1994b). It seems likely that the measured levels in breast milk would continue to drop with an extended period of breast feeding. Thus, the studies' assumption of a steady-state level of dioxins, furans and PCBs in the breast milk, with the women's different lengths of breast feeding, could overestimate the actual exposure levels to varying degrees. Therefore, any effects observed might occur at a lower level of exposure than reported. Effects of exposure in these studies were assessed by analyses of the dioxin-furan TEQ or total PCB-dioxin-furan TEQ (for dioxins, furans and dioxin-like PCBs) based on levels observed in breastmilk, and $\sum PCB_{\text{cord blood}}$ or $\sum PCB_{\text{maternal blood}}$ (for IUPAC 118, 138, 153, 180), controlling for such items as sociodemographic indicators and personal habits. Because data from other sources have shown breast milk levels to be well correlated with adipose tissues, the breast milk level during the second week after delivery is a reasonable estimate for prenatal exposures (at least the relative magnitude) to these agents (Jensen, 1987).

About half the 418 mothers and infants were in Rotterdam and half in Gronginen. A comparison of a variety of demographic factors, personal habits, and health characteristics for the two communities showed no differences for a number of them (e.g. maternal age, weight, smoking status), and significantly higher parental education, maternal alcohol consumption, and birth weight of the child in Groningen; the length of gestation was one-half week longer in Groningen. A number of factors, socioeconomic status (SES) indicators, health, and exposure were different in the breast-fed versus formula-fed group (Huisman, 1995b): for example, more than 60% of both parents in the breast-fed group had higher education versus 31% or less in the formula-fed group. In addition, breast-feeding mothers were more likely to have consumed alcohol during pregnancy (37% versus 18%) and less likely to have smoked (16% versus 35%). The breast-fed pregnancies were also more highly exposed prior to breast–feeding: $\sum PCB_{\text{cord blood}}$ and $\sum PCB_{\text{maternal blood}}$ were significantly higher in this group. Analysis of breast milk levels in the Rotterdam area and in Groningen (Koopman-Esseboom et al, 1994a) showed that the dioxin-furan TEQ and some individual dioxin and congener levels (D66, D67, F83, F118, F121, F130, PCB66,

PCB118, PCB137, and PCB187) were significantly higher in the more urbanized Rotterdam area. For some of the analyses, the infants were placed into a "low" or "high" group based on the median value for the dioxin-furan TEQ (at 30.8 pg TEQ/g fat, for the total PCB-dioxin-furan TEQ (at 72.4 pg TEQ/g fat) or into "low," "medium," or "high" based on the PCB-dioxin-furan TEQ times the number of weeks breast fed. In addition, in one report different congeners were analyzed separately. These different analysis strategies make integrating the data from the various reports difficult.

Two individuals performed some of the tests (e.g., Neurologic Optimality Score in Huisman et al., 1995a and Huisman et al., 1995b; Fluency Cluster Score in Huisman et al., 1995b), one each in Rotterdam versus Grongenin. The authors reported that their comparison of the data from the two cities suggested a systematic difference between the two for some outcomes. They controlled for this potential discrepancy in the logistic regressions. As there was no direct comparison of the scoring on the same children, the above is a possible explanation, as is the possibility that there are community differences (for some unknown reason) for these specific outcomes.

A smaller series of women and their infants were studied by another research team in Amsterdam; between June 1990 and May 1991 these women were identified while still pregnant. Only women who intended to breast feed for 12 weeks were included in this study group. The reports from this group (Pluim et al., 1993; Pluim et al., 1994; Pluim et al., 1996) had a different final number of subjects (38 versus 35), but from the general description, they do appear to be from the same general group. Maternal blood was collected around the time of delivery, cord blood was collected, infant blood samples were collected at 1 and 11 weeks of age, and three weeks after delivery, two breast milk samples were collected. The authors assumed that the breast milk levels also reflected *in utero* exposures to the infants. They did not include bottle-fed children as comparisons for the following reasons: first, the SES of women who choose to breast feed tends to be different from those who choose to bottle-feed; and second, comparison of breast milk levels is not possible for the mothers of bottle-fed infants, either directly or using these levels as a surrogate for the *in utero* exposures. The 17 most toxic congeners, 7 dioxins and 10 dibenzofurans, were used to develop a dioxin-furan TEQ (see Table 7-21b for the listing of these congeners and the mean levels for the study group). The final score for consumption for each child used the amount of milk consumed (assumed to be 700 g/day while the child received only breast milk, and half that amount later), the amount of milk fat in the milk (assumed to be an average of 2.5%), and the levels of the 17 congeners. The levels determined were split at the median into "low" and "high" groups (28.0 pg dioxin-furan TEQ g/fat; high = 29.2-62.7 pg TEQ/g and low was less than 28.0 pg TEQ/g). These reports compared differences in the high

and low groups (1) with thyroid hormone concentrations (Pluim et al., 1993) (see Section 7.13.4.2); (2) with alanine aminotransferase and aspartate aminotransferase activities, and platelet count in the infants' plasma (Pluim et al., 1994) (see Section 7.13.2.5.2); and (3) against several growth measures (neonatal weight and length, liver size and quetelet index) over the first six months of life (Pluim et al., 1997) (see Section 7.13.12.8).

The Amsterdam reports are based on small groups of infants with undescribed selection procedures. Thus it is not possible to evaluate volunteer bias. These authors did attempt to more closely estimate the dioxin-furan TEQ, using changes in feeding patterns as well as the measured levels in the early sample, but did not evaluate the potential for decreasing levels with increasing length of breast feeding.

Both sets of studies split the group of breast-fed infants at the median of the TEQ into high and low exposure groups, and used these for logistic regression and other analyses. This approach for quantification of exposure is a reasonable estimation of the general magnitude of exposures. Mean levels of exposure over the total period may be somewhat lower than reported, since the breast milk evaluations occurred early in lactation (1-2 weeks after delivery), while levels were likely to decrease with longer periods of breast feeding (see Part I., Vol. II Chapter 6, of "Estimating Exposure to Dioxin-Like Compounds"). For both of these Dutch study groups, it is important to note that the levels of dioxins, furans, and PCBs were within common/background environmental ranges.

7.12.3. Studies of Vietnam Veterans

7.12.3.1. *The Vietnam Experience Study*

The Vietnam Experience Study is described by its authors as a "multidimensional assessment of the health of Vietnam veterans" (Centers for Disease Control Vietnam Experience Study, 1988a-d). This study was designed to examine effects among men who served in Vietnam.

The study population was composed of a random sample of men who enlisted in the U.S. Army from 1965 through 1971, whose military occupational status was other than "duty soldier," who enlisted for a single term with a minimum of 16 weeks active duty and who were discharged at pay grades of E-1 to E-5. The controls were selected from among veterans enlisting during the same period but whose duty station was the United States, Germany, or Korea. Participation involved completion of a telephone survey of current and past health status by 7,924 veterans who served in Vietnam and 7,364 veterans who served outside of Vietnam. A random subsample of 2,940 Vietnam and 1,972 non-Vietnam veterans participated in the health evaluation component.

In a separate study, serum 2,3,7,8-TCDD levels were measured in a subset of the examined population: 646 Vietnam veterans who served in Vietnam during 1967 and 1968 and

97 non-Vietnam veterans (Centers for Disease Control Veterans Health Studies, 1988). The mean serum 2,3,7,8-TCDD level was not different between Vietnam (mean = 4.1 pg/g lipid [standard deviation (SD) ± 2.3]) and non-Vietnam (4.2 pg/g, SD ± 2.6) veterans. Two Vietnam veterans had levels above the background level of 20 pg/g: 25 pg/g and 45 pg/g.

The overall strengths of this study are that it is a large study, with good power to detect many common disorders; participation in the questionnaire part of the study was good (87% for Vietnam veterans; 84% for non-Vietnam veterans); there was good comparability between the two cohorts in demographic characteristics, although there were differential participation rates in the examination; and validation of selected self-reported effects was conducted. This study is limited primarily by the differential participation rates in the examination (75% for Vietnam veterans; 63% for non-Vietnam veterans). The low level of 2,3,7,8-TCDD in the sample of veterans made it impossible to conduct dose-response analyses.

7.12.3.2. *U.S. Air Force Ranch Hand Study*

One of the largest epidemiologic studies of U.S. military personnel stationed in Vietnam is being conducted by the U.S. Air Force. The study population consists of Air Force personnel who served in Operation Ranch Hand units in Vietnam from 1962 to 1971 and who were employed in the dissemination of Agent Orange through aerial spraying. Comparisons included Air Force personnel who flew or maintained C-130 aircraft in Southeast Asia during the same time period.

The study design includes a series of cross-sectional medical studies conducted at 5-year intervals beginning with the baseline study in 1982 (N = 1,045 exposed, 1,224 unexposed). Two follow-up evaluations were conducted in 1985 (N = 1,016 exposed, 1,293 unexposed) and 1987 (N = 995 exposed, 1,299 unexposed). Each cross-sectional study included comprehensive physical and psychological evaluations. In the 1982 baseline and 1985 and 1987 follow-up studies, exposure was based on the comparison of the Ranch Hand group versus the comparison group. An additional analysis approximated exposure (low, medium, high) for the Ranch Hand group by using historical military data and herbicide procurement and usage records. The results of these analyses were prepared by Lathrop and colleagues (1984 and 1987). In 1988, serum 2,3,7,8-TCDD levels were measured for a sample of the 1987 Ranch Hand group (N = 866) and the 1987 comparison group (N = 804). The 1987 examination data were then reanalyzed using lipid-adjusted serum 2,3,7,8-TCDD levels as the relative measure of exposure. The median serum 2,3,7,8-TCDD level adjusted for lipids for the Ranch Hand group was 12.8 pg/g, ranging to 618 pg/g. For the comparison group, the median level was 4.2, ranging to 54.8 pg/g (Roegner et al., 1991). For later studies, veterans who refused to give serum samples in 1987 or received a nonquantifiable result were resampled in 1992.

The overall strengths of this study are that it is a large study, with good power to detect many common disorders; follow-up was very good, as is continued participation of Ranch Hand and comparison populations. The physical and psychological examinations are extensive, planned to evaluate most, if not all, outcomes hypothetically associated with 2,3,7,8-TCDD. Continued reevaluation of the subjects (every 5 years) permits investigators to monitor the development of chronic diseases and to test for additional outcomes as new biochemical and toxicological data become available. Finally, the determination of serum 2,3,7,8-TCDD levels permitted validation of the exposure matrix based on historical records and the subsequent development of disease-specific dose-response models. Repeated measures of serum 2,3,7,8-TCDD over time will also provide valuable information on its half-life in humans.

Noteworthy caveats in the study include the fact that the majority of the population had serum levels under the background level of 20 pg/g (median = 12.8 pg/g, range to 600 pg/g in 1987). These data suggest that, although there are some Ranch Hands who were exposed to very high levels of 2,3,7,8-TCDD, most of the study group had lower exposures, if any at all. In addition, serum 2,3,7,8-TCDD levels indicated that the exposure matrix used in the analysis of the baseline and 1984 studies did not appropriately describe the potential for exposure. Therefore, data described in this chapter will refer only to the baseline and 1984 results where Ranch Hands as a group were compared to the comparisons and, most often, to the reanalysis of the 1987 data (plus relevant 1992 data) using serum levels. The adjusted odds ratios for the three categories of serum 2,3,7,8-TCDD selected by Roegner and colleagues (1991) are presented and discussed. The categories are: ≤10 pg/g 2,3,7,8-TCDD; 15-≤33.3 pg/g 2,3,7,8-TCDD; and >33.3 pg/g 2,3,7,8-TCDD.

In the categorical analysis of the 1992 followup examination results (Grubbs et al, 1995), results were presented in relation to the current 2,3,7,8-TCDD concentration (current dioxin level) and to the concentration estimated since time in duty in southeast Asia (initial level) in the following categories: comparison, current dioxin level ≤10 pg/g of lipid; background (Ranch Hand), current dioxin level≤10 pg/g of lipid; low (Ranch Hand), current dioxin > 10 pg/g of lipid, 10 pg/g<initial dioxin ≤143 pg/g; high (Ranch Hand), current dioxin > 10 pg/g of lipid, 10 pg/g<initial dioxin >143 pg/g. In subsequent analyses, for the low and high categories the definitions were changed to the following: low (Ranch Hand), 10 <current and initial <94 pg/g; high (Ranch Hand), 10>current and initial >94 pg/g (Michalek et al., 1997).

A consequence of conducting a comprehensive study in which a large number of statistical tests are performed is an increased possibility of spurious findings. The reader should be cognizant of this limitation, looking for consistencies with the results of other studies and in the toxicological literature rather than statistical significance alone.

7.12.3.3. *Studies of the Effect of Ingestion of Rice Oil Contaminated With Polychlorinated Dibenzofurans, Quaterphenyls, and Biphenyls in Japan (YUSHO) and Taiwan (YU-CHENG)*

This section also briefly reviews the noncancer effects observed in Yusho (Japan) and Yu-Cheng (Taiwan) victims, individuals exposed by ingestion to large concentrations of compounds structurally related to dioxins, namely polychlorinated dibenzofurans, quaterphenyls, and biphenyls. In addition, other reviews have summarized the numerous papers dedicated to Yusho and Yu-Cheng (Lü and Wong, 1984; Kuratsune, 1989; Rogan, 1989).

Reports describing effects among individuals who ingested the contaminated rice oil both in Taiwan and Japan were generally limited descriptions of acute rather than general effects. However, because more than 25 years have passed since Yusho and 15 years since Yu-Cheng, more studies are evaluating potential chronic effects.

Recent epidemiologic studies have concentrated on the development of offspring of Yu-Cheng mothers. These children were exposed *in utero* at the time the contaminants were ingested or were conceived after the poisoning and were exposed to residual contaminants transplacentally or through breast milk (Chen et al., 1992; Lai et al., 1993, 1994; Hsu et al., 1993; Guo et al., 1992, 1993,1994a,b, 1995a,b,1996; Chao et al., 1997; Yu et al., 1994, 1998, 2000).

7.12.3.3.1. *Yusho.* The initial recognition of the effects of the ingestion of contaminated rice oil by the Yusho population occurred in 1968. As of 1983, a total of 2,060 individuals were identified as part of the affected Yusho population (Masuda et al., 1985). Five years after exposure ended, the mean concentrations of PCBs in the adipose tissue, liver, and blood of Yusho cases were 1.9 ppm, 0.08 ppm, and 6.7 ppb (Masuda et al., 1985), respectively, which were about twice the levels in the control group. Adipose tissue levels of PCDFs ranged from 6 to 13 ppb (Masuda et al., 1985). Sixteen years after exposure, mean PCQ level in adipose tissue of Yusho cases was 207 ppb, approximately 100 times the level in Japanese controls (Kashimoto et al., 1985).

7.12.3.3.2. *Yu-Cheng.* The initial recognition of Yu-Cheng occurred in 1979. As of 1983, approximately 2,000 individuals were found to have been exposed to the contaminated rice oil. Within the first year of exposure, mean serum PCB, PCDF, and PCQ levels in blood for 15 cases were 60 ppm (range 4-188 ppm), 0.14 ppb (range <0.005-0.27 ppb), and 19.3 ppb (range 0.9-63.8), respectively (Kashimoto et al., 1985). Analysis of PCB levels in blood in 1980-1981 in 165 cases (mean 38 ppb, range 10-720) (Rogan, 1989) and in 1985 in 32 cases (mean 15.4 ppb, range

0.6-86.8) (Lundgren et al., 1988) suggested that some PCBs were being eliminated. It is not clear from the reports if the samples were drawn from distinctly different individuals or included some of the same individuals.

7.13. REVIEW OF EFFECTS ASSOCIATED WITH EXPOSURE TO 2,3,7,8-TCDD

The following section contains a review of the case reports and epidemiologic studies that describe effects associated with exposure to materials contaminated with 2,3,7,8-TCDD.

7.13.1. Dermal Effects

7.13.1.1. *Chloracne*

The most widely recognized dermal effect of exposure to 2,3,7,8-TCDD-contaminated substances is chloracne. Chloracne is a persistent acneiform condition characterized by comedones, keratin cysts, and inflamed papules with hyperpigmentation and a unique anatomic distribution, occurring subsequent to acute and chronic exposure to a variety of chlorinated aromatic compounds (Crow et al., 1978; Moses and Prioleau, 1985). This acne-like condition is reported to have occurred with and without other TCDD-related health effects in at least a few workers after all reported accidents at TCP production facilities (Ashe and Suskind, 1950; Suskind et al., 1953; Goldman, 1972; May, 1973; Zober at al., 1990), among individuals involved in daily production of 2,3,7,8-TCDD-contaminated products (Bleiberg et al., 1964; Poland et al., 1971; Pazderova-Vejlupkova et al., 1981; Moses et al., 1984; Moses and Prioleau, 1985; Suskind and Hertzberg, 1984; Bond et al., 1989), among three laboratory workers exposed to pure 2,3,7,8-TCDD (Oliver, 1975), and among at least 193 (0.6%) Seveso residents, mostly children (Reggiani, 1978; Caramaschi et al., 1981; Ideo et al., 1985; Mocarelli et al., 1986; Assennato et al., 1989). Chloracne was not found among Missouri residents (Hoffman et al., 1986; Webb et al., 1989) examined 10 years after exposure or among Ranch Hand personnel (Burton et al., 1998; Roegner et al., 1991). In U.S. Army Vietnam veterans, chloracne-like skin lesions were rarely observed on examination (0.9% in Vietnam veterans versus 0.8% in non-Vietnam veterans, OR = 1.4, 95% CI = 0.7-2.9) (Centers for Disease Control Vietnam Experience Study, 1988a).

Based on reports from Seveso and studies of chemical workers, chloracne appeared shortly after exposure to 2,3,7,8-TCDD-contaminated chemicals (Caramaschi et al., 1981; Zober et al., 1990). The eruption of blackheads, usually accompanied by cysts, was observed between 2 weeks and 2 months after the reactor release (Reggiani, 1980). In Seveso, within 6 months of the explosion, 34 cases of chloracne were identified among children, whereupon a more intensive search was undertaken among schoolchildren (Caramaschi et al., 1981). In chemical workers involved in the TCP reactor release at BASF Ludwigshafen, Germany, most cases of chloracne (that were also diagnosed with cancer) developed within 2 days after first exposure (Ott et al.,

1994; Zober et al., 1990). One case of chloracne did not develop for 2 years, but the authors suggest that the etiology of this case is unclear.

For many affected individuals, the condition disappeared after discontinuation of exposure (Assennato et al., 1989) despite high serum 2,3,7,8-TCDD levels (Mocarelli et al., 1991). But for a few, the chloracne remained for many years (Suskind and Hertzberg, 1984; Moses and Prioleau, 1985). Of the 204 exposed workers in the study by Suskind and Hertzberg (1984), 52% had persistent chloracne for at least 10 years after the TCP and 2,4,5-T processes ceased, 34% reported a history of chloracne, and 14% reported no history of chloracne. Moses et al. (1984) reported that the mean duration for persistent chloracne was 26.1±5.9 years.

There are very few human data from which to determine definitively the threshold level of 2,3,7,8-TCDD at which chloracne occurs or who is at greatest risk to develop chloracne. Data from analyses of chloracne cases among chemical workers and chloracne's relationship to serum and adipose tissue levels of 2,3,7,8-TCDD and hexachlorinated (HxCDD) dioxins provide some basic yet useful information on the characteristics of chloracne cases, particularly the inter-individual susceptibility to chloracne (Bond et al., 1989; Ott et al., 1987; Beck et al., 1989; Mocarelli et al., 1991). Bond et al. (1989) described 325 cases (15%) of chloracne among 2,192 workers exposed to 2,3,7,8-TCDD and HxCDDs or octachlorinated (OCDD) dioxins between 1938 and 1982 during chemical production activities (not as a result of a reactor accident). Cases were identified through company-maintained medical records; age- and calendar year-specific incidence rates were estimated based on age- and calendar year-specific person-years of employment contributed by the cohort; and risk factors were adjusted for by logistic regression. The analysis found that risk of chloracne was highest among workers who were exposed at younger ages, among those who had the longest length of exposure to 2,4,5-trichlorophenol or pentachlorophenol production operations, and among jobs rated at the highest intensity of exposure (Ott et al., 1987). These characteristics of chloracne cases in Michigan workers are consistent with those observed in chloracne cases from the BASF accident cohort (Ott et al., 1993). Although this study may underestimate the incidence rate of chloracne owing to possible underreporting or misdiagnosis of cases, and misclassification of exposure may have occurred, this study was the first of its kind to explore analytically the risk factors associated with occupationally acquired chloracne. It is unfortunate that these exposure estimates have not been validated by serum or adipose tissue 2,3,7,8-TCDD, HxCDD, and OCDD levels.

Serum levels of 2,3,7,8-TCDD and HxCDD have been measured in chloracne cases of Seveso residents (Mocarelli et al., 1991) and German chemical workers (Beck et al., 1989; Ott et al., 1993). Mocarelli et al. (1991) described chloracne in persons from zone A who had very high serum 2,3,7,8-TCDD levels ranging from 820 to 56,000 pg/g measured within 1 year of the

reactor release (Table 7-22). The study also included other individuals from Zone A, but without chloracne, who had serum 2,3,7,8-TCDD levels that ranged from 1,770 to 10,400 pg/g. With the exception of one person with chloracne who was 16 years old at the time of the accident, all of the cases were in children under age 11. Those without chloracne, for the most part, were over age 30. It is not clear whether the children were more susceptible to the chloranegenic effects or whether they had greater exposure to 2,3,7,8-TCDD-contaminated soil or airborne effluent.

As documented by others, adult TCP production workers also developed chloracne (Beck et al., 1989; Suskind and Hertzberg, 1984; Bond et al., 1989). Adipose tissue levels of 2,3,7,8-TCDD and HxCDD measured in adult chloracne cases of German chemical production workers suggest that these cases may have been a function of the combined exposure, making it difficult to isolate the contribution of the different chlorinated compounds. All cases had estimated adipose levels of greater than 200 pg/g 2,3,7,8-TCDD and in excess of 2,000 pg/g lipid HxCDD at the time of diagnosis. Estimated levels were based on the half-life extrapolation of the adipose tissue level measured in 1986 to the date of last occupational exposure, which may have occurred between 1949 and 1984. Similarly, Ott (1993) found that 80% of the severe chloracne cases had estimated (back-calculated) lipid-adjusted serum 2,3,7,8-TCDD levels of 250 pg/g. Yet 26% of nonchloracne cases had estimated 2,3,7,8-TCDD concentrations of 250 pg/g.

Data from studies of Seveso residents conducted from 1982 to 1985 indicate that, despite high serum 2,3,7,8-TCDD levels, the chloracne resolved in all but one person by 1983 (Assennato et al., 1989). The fact that the cases of chloracne in Seveso residents resolved within 10 years may explain why no chloracne was observed in the Ranch Hand group, although some serum 2,3,7,8-TCDD levels exceeded 600 pg/g in 1988 (Roegner et al., 1991) and may have been as high as 2,400 pg/g at the time of last occupational exposure, assuming 21 years since last exposure and a 7-year half-life. Nevertheless, residual chloracne was observed 30 years after first exposure among workers from Nitro, West Virginia, which may suggest that chronic high exposure to 2,3,7,8-TCDD or exposures higher than experienced by the Ranch Hands may account for long-term persistence of chloracne.

7.13.1.2. *Dermatologic Disorders Other Than Chloracne*

Dermal effects other than chloracne attributed to 2,3,7,8-TCDD exposure include a variety of symptoms and conditions that occurred less frequently than chloracne but appeared in several groups subsequent to acute and continuous exposure to 2,3,7,8-TCDD-contaminated TCP and 2,4,5-T. Two reports indicated that after acute episodes of exposure, e.g., accidents, individuals complained of red and irritated eyes, conjunctivitis, and blepharitis (inflammation of the eyelids) (Ashe and Suskind, 1950; Baader and Bauer, 1951). Other investigators also found cases of

eyelid cysts several months after acute exposure (Suskind et al., 1953; Kimmig and Schulz, 1957a,b; Poland et al., 1971; Reggiani, 1980) and up to 25 years after exposure (Moses et al., 1984; Suskind and Hertzberg, 1984).

Hyperpigmentation and hirsutism (also known as hypertrichosis or abnormal distribution of hair) were diagnosed among chemical workers in the United States (West Virginia and New Jersey) (Ashe and Suskind, 1950; Suskind et al., 1953; Bleiberg et al., 1964; Poland et al., 1971), Germany (Bauer et al., 1961; Goldman, 1972), and Czechoslovakia (Jirasek et al., 1974) who were exposed to 2,3,7,8-TCDD-contaminated TCP during manufacturing processes or industrial accidents and among laboratory workers in England exposed while synthesizing pure 2,3,7,8-TCDD (Oliver, 1975). Upon reexamination 25 years later, hypertrichosis was observed in exposed workers (5.4% exposed vs. 1.8% unexposed) from the West Virginia plant, particularly among workers with persistent chloracne on clinical examination (10.3% with persistent chloracne vs. 0% with history of chloracne only) ($p<0.001$) in one of two independent studies (Suskind and Hertzberg, 1984). A second study by Moses et al. (1984) found no evidence of hypertrichosis, although 31% of the exposed workers had evidence of residual chloracne (Moses et al., 1984). Studies of Vietnam veterans have reported no significant increase in the prevalence of either hyperpigmentation or hypertrichosis (Roegner et al., 1991; Centers for Disease Control Vietnam Experience Study, 1988a). Three cases of hypertrichosis but not hyperpigmentation were observed among Missouri residents, one with serum levels less than 20 pg/g and two with levels between 20 and 60 pg/g (Webb et al., 1989). Neither disorder was noted on examination among residents of the Quail Run Mobile Home Park (Hoffman et al., 1986).

Actinic or solar elastosis was found to be more prevalent among West Virginia workers diagnosed with active chloracne at the time of their examinations in 1979 (Suskind and Hertzberg, 1984) (exposed = 59.1% vs. unexposed = 30.1%, $p<0.01$). No significant difference was observed in the age-adjusted prevalence of actinic elastosis in workers with or without chloracne in the study by Moses et al. (1984). Actinic elastosis is known to be directly related to sun exposure; however, the amount of sun exposure, skin type, or other factors contributing to the sensitivity of the skin to sunlight were not assessed in the report. No other studies of TCP production workers, the Ranch Hands, or U.S. Army Vietnam veterans have found an increase in the prevalence of actinic elastosis.

Among the group of workers studied by Suskind and Hertzberg (1984), three cases of Peyronie's disease were noted. Peyronie's disease is a rare condition characterized by progressive scarring of the penile membrane. No explanation for this finding was expressed, nor has the condition been noted (or perhaps looked for) in other studies (Bond et al., 1989; Moses et al., 1984; Roegner et al., 1991).

In 1984, a statistically significant excess of nonmelanotic skin cancer was reported among Ranch Hand personnel involved in the aerial spraying of herbicides over Vietnam compared with a matched comparison group (Lathrop et al., 1984). The comparison group was composed of Air Force personnel assigned to cargo missions outside the sprayed areas of Vietnam. A follow-up study of the same cohorts in 1987 confirmed the excess of basal cell carcinoma and attributed the increase to sunlight exposure (Lathrop et al., 1987). However, in the reanalysis of the 1987 examination data, skin neoplasms of any kind were not related to serum 2,3,7,8-TCDD level (Roegner et al., 1991).

7.13.1.3. *Comment*

From an epidemiologic perspective, chloracne is a common consequence of exposure to chemicals contaminated with 2,3,7,8-TCDD and some other polyhalogenated hydrocarbons. Available data on serum or adipose tissue levels of 2,3,7,8-TCDD have not determined the threshold at which a case of chloracne occurs. Evidence from Bond et al. (1989) suggests that for chemical production workers the risk of chloracne may be related to the part of the process in which the workers were engaged, the amount of time spent in the contaminated region, and the intensity of the exposure while in the area. Chloracne is also related to short-term high-intensity exposures, as observed in Seveso residents (Reggiani, 1980) and occupational cohorts (Ott et al., 1993). Few studies have been successful in evaluating the relationship between history of chloracne and long-term nonmalignant effects. However, Zober et al. (1990) noted that the SMR for all malignant neoplasms for workers with chloracne and who had at least 20 years of latency (time since first exposure) was statistically significantly elevated (SMR 201; 90% CI = 122, 135). Future studies that are able to evaluate the association between history of chloracne and effects would provide useful information in this regard.

Other conditions, such as hyperpigmentation and hypertrichosis, may be more acute effects of 2,3,7,8-TCDD exposure that resolve over time, because they were not observed in studies where the cohorts were examined years after the cessation of exposure. Actinic keratosis, Peyronie's disease, and basal cell carcinoma may not be due to 2,3,7,8-TCDD because actinic keratosis and Peyronie's disease have been observed in a single cohort. Likewise, the excess basal cell carcinoma was noted only in one study group, and the results could not be replicated when a better indicator of personal exposure to 2,3,7,8-TCDD, serum 2,3,7,8-TCDD, was used as a surrogate for exposure in the statistical models.

7.13.2. Gastrointestinal Effects

7.13.2.1. *Hepatic Effects*

Changes in liver function and structure after exposure to 2,3,7,8-TCDD are commonly observed in experimental animals (Greig et al., 1973; Vos et al., 1974; Jones and Greig, 1975; McConnell et al., 1978a,b; Jones et al., 1981; Zinkl et al., 1973; Kociba et al., 1976, 1978; Gasiewicz et al., 1980; DeCaprio et al., 1986). The changes are not always consistent from one species to another, but they have prompted examination of hepatic effects among exposed human populations. As with animals, there is wide variation in the type and degree of hepatic effects reported in humans after exposure to 2,3,7,8-TCDD-contaminated materials. This section describes selected hepatic effects associated with 2,3,7,8-TCDD exposure observed in humans, including hepatomegaly and hepatic enzyme changes.

7.13.2.2. *Liver Size*

Increased liver size is consistently reported in treated animals after exposure to 2,3,7,8-TCDD (Vos et al., 1974; Allen et al., 1977; McConnell et al., 1978a,b; Kociba et al., 1978; Gasiewicz et al., 1980). Among exposed human populations, four case reports in three populations, but not controlled epidemiologic studies, described evidence of enlarged livers or hepatomegaly. Liver size was reportedly increased among two TCP production workers in West Virginia within a few months after a TCP reactor explosion (Ashe and Suskind, 1950; Suskind et al., 1953) and among "several" production workers in Czechoslovakia exposed to TCP, the butyl ester of 2,4,5-T, and sodium pentachlorophenol (Jirasek et al., 1974). Temporary liver enlargement was observed in 5 of 22 Seveso residents who had severe chloracne (Reggiani, 1980). The hepatomegaly lasted "several" months without concomitant elevation in hepatic enzymes. Fortunately, the effect appeared to be transient. Cross-sectional medical studies of TCP production workers (Bond et al., 1983; Suskind and Hertzberg, 1984; Moses et al., 1984; Calvert et al., 1992), Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991), and Missouri residents (Webb, 1989; Hoffman et al., 1986) have found little evidence of excess hepatomegaly in the exposed populations. Additionally, no dose-response relationship was observed between serum levels of 2,3,7,8-TCDD and physical findings of an enlarged liver for the 1987 or 1992 examinations of Ranch Hands (≤10 pg/g 2,3,7,8-TCDD, RR = 0.39, 95% CI = 0.11-1.33; 15-≤33.3 pg/g 2,3,7,8-TCDD, RR = 1.47, 95% CI = 0.57-3.79; >33.3 pg/g 2,3,7,8-TCDD, RR = 1.69, 95% CI = 0.60-4.75) (Roegner et al., 1991) (Background: RR = 0.51 95% CI = 0.19, 1.38; Low: RR = 0.26, 95% CI = 0.06, 1.09; High: RR = 1.02, 95% CI = 0.43, 2.44) (Grubbs et al., 1995) or the NIOSH study of TCP production workers (two workers; four referents; OR = 0.46, 95% CI = 0.09, 2.43) (Calvert et al., 1992).

One Missouri resident was found to have hepatomegaly, but he also was suffering from diabetes mellitus. His adipose tissue 2,3,7,8-TCDD level was 430 pg/g (Webb et al., 1989). The differences in findings between the case reports and the controlled epidemiologic studies suggest that hepatomegaly may be a resolvable, acute effect as a result of exposure to high levels of 2,3,7,8-TCDD.

7.13.2.3. *Enzyme Levels*

Laboratory studies have demonstrated changes in hepatic enzyme levels after 2,3,7,8-TCDD exposure, although there is considerable interspecies variation in the observed effect (Zinkl et al., 1973; Kociba et al., 1976, 1978; Gasiewicz et al., 1980; Olson et al., 1980). Epidemiologic studies and case reports describe elevated liver enzymes among exposed TCP production workers, Ranch Hand veterans (Roegner et al., 1991), and among Seveso residents (Mocarelli et al., 1986; May, 1982; Martin, 1984; Moses et al., 1984; Calvert et al., 1992; Ott et al., 1994).

7.13.2.4. *GGT*

Increased levels of gamma glutamyl transferase (GGT) may suggest activity such as cholestasis, liver regeneration, or drug or xenobiotic metabolism (Table 7-23). The studies of Seveso children demonstrate an increase in GGT levels occurring shortly after the explosion and then a gradual decline to near normal levels within 5 years. In one of the earliest studies of Seveso children with (N = 141) and without chloracne (N = 138), 2.8% of the children with chloracne had out-of-range GGT levels, but none of the children without chloracne had an out-of-range level ($p<0.001$) (Caramaschi et al., 1981). These results were echoed in a study of children from zones A, B, and R of Seveso, in which enzyme levels were measured yearly between June 1977 and June 1982 (Mocarelli et al., 1986). GGT levels were elevated in children of zone A, particularly in boys, during the first 2 years after the explosion (1977: exposed = 9.73 U/L; unexposed = 7.28 U/L; $p<0.01$; 1978: exposed = 9.88 U/L; unexposed = 8.26 U/L; $p<0.05$) (Mocarelli et al., 1986). Levels in girls during the same years were elevated but did not achieve statistical significance. For the next 4 years of the study, GGT levels remained elevated in boys and girls from zone A compared to unexposed children, but the values declined to normal levels with time.

GGT was found to be elevated among TCP production workers from one plant in Great Britain and in workers from West Virginia, Missouri, and New Jersey up to 30 years after last occupational exposure to 2,3,7,8-TCDD-contaminated chemicals (May, 1982; Martin, 1984; Moses et al., 1984; Calvert et al., 1992). The findings of two studies of British workers were

similar. Mean GGT levels were increased, but not statistically elevated, in workers with chloracne compared to unexposed controls tested 10 years after exposure to 2,3,7,8-TCDD-contaminated chemicals as a result of a TCP reactor explosion (chloracne, GGT = 39 U/L; controls, 27.7 U/L [May 1982]) (chloracne, GGT = 32 U/L; controls, 32 U/L [Martin, 1984]). Similarly, a statistically significant excess in the proportion of individuals with abnormally high GGT levels was found among West Virginia workers with chloracne who were examined as many as 30 years after exposure (Moses et al., 1984) (chloracne, mean GGT = 26.3 U/L, 23% abnormal; no chloracne, mean GGT = 17.4 U/L, 9% abnormal; $p<0.003$). Yet, compared to controls, GGT was not elevated in another study of West Virginia workers (Suskind and Hertzberg, 1984).

In a study by Calvert et al. (1992), the mean GGT level and the proportion of workers with out-of-range levels were statistically significantly elevated among TCP workers from New Jersey and Missouri (workers, mean GGT = 58.5 U/L; unexposed referents, mean GGT = 47.4 U/L, $p<0.03$; workers, 11% abnormal; referents, 5% abnormal, OR = 2.27, 95% CI = 1.17-4.39). Based on the logistic regression model in Table 7-24, the increases in GGT were limited to workers with high serum 2,3,7,8-TCDD levels (>100 pg/g) and high lifetime alcohol consumption (>30 alcohol years) (alcohol year = 1 alcoholic beverage/day for 1 year). The contribution of other potentially confounding exposures that may have affected GGT levels was not explored in this study. Other studies of TCP production workers in Michigan and West Virginia or the BASF accident cohort did not report elevations in GGT levels (Bond et al., 1983; Suskind and Hertzberg, 1984; Ott et al., 1994).

Both the Vietnam Experience Study and the U.S. Air Force Ranch Hand Study found statistically significant elevations in GGT levels (Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991). In Army Vietnam veterans, mean GGT levels were 43.2 U/L compared with 41.1 U/L in non-Vietnam veterans (OR for out-of-range value = 1.3, 95% CI = 1.0-1.8) (Centers for Disease Control Vietnam Experience Study, 1988a). In the 1987 follow-up study, the comparison of the adjusted mean GGT level in the comparison group and in each of the three Ranch Hand groups defined by 2,3,7,8-TCDD level found statistically significant increases in the Ranch Hand population (≤10 pg/g 2,3,7,8-TCDD, $p<0.017$; 15-≤33.3 pg/g 2,3,7,8-TCDD, $p<0.043$; >33.3 pg/g 2,3,7,8-TCDD, $p<0.001$) (Roegner et al., 1991). In the 1992 followup, significant increseases were noted in Ranch Hands classified as either low or high exposure (Grubbs et al., 1995).

7.13.2.5. *AST and ALT*

7.13.2.5.1. ***Adult measures*****.** Abnormal levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may indicate liver cell damage from a number of causes, including

hepatic necrosis, metastatic carcinoma, or obstructive jaundice (AST and ALT) or infectious or toxic hepatitis and cirrhosis (AST). Elevated levels of these enzymes may also be due to nonhepatic origins, such as myocardial infarction, acute pancreatitis (AST and ALT), or skeletal, cerebral, or renal necrosis (AST).

With respect to exposure to 2,3,7,8-TCDD, elevations in serum ALT and AST appear to be transient effects of acute exposure (Table 7-25). Case reports note that some populations have increased serum ALT levels shortly after exposure (Seveso children, British and Czechoslovakian TCP production workers) (May, 1973; Jirasek et al., 1974; Caramaschi et al., 1981; Mocarelli et al., 1986). Whereas epidemiologic studies conducted 10 to 30 years after last exposure reported no effects in exposed workers, Vietnam veterans, and Missouri residents compared to unexposed control groups (Table 7-25) (Suskind and Hertzberg, 1984; May, 1982; Martin, 1984; Bond et al., 1983; Calvert et al., 1992; Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991; Grubbs et al., 1995; Hoffman et al., 1986; Webb et al., 1989; Ott et al., 1994), or workers with and without chloracne (Moses et al., 1984). Furthermore, it appears from a single study that current exposure to 2,3,7,8-TCDD-contaminated substances must exceed some threshold to produce detectable enzyme elevations (Poland et al., 1971). Normal levels of AST (AST = 10.6 U/L) were found in workers who volunteered to participate in a medical study conducted concurrently with their employment in a New Jersey chemical facility producing TCP and 2,4,5,-T (Poland et al., 1971). This was the same plant included in a later cross-sectional medical study of workers that found, in 1988, a high mean serum 2,3,7,8-TCDD level for the group (220 pg/g) but no elevations in AST or ALT (Calvert et al., 1992; Fingerhut et al., 1991a). Similarly, no increases in AST were noted in the BASF accident cohort (Ott et al., 1994).

Several reports illustrate the probable transiency of ALT and AST elevations after heavy 2,3,7,8-TCDD exposure. Both enzymes were reported to be elevated among TCP production workers employed in Czechoslovakia who were described as exhibiting symptoms of “chemical intoxication” (Jirasek et al., 1974). The authors reported that AST and ALT levels were “different” in 11 (20%) of the 55 examined workers. These workers were exposed to 2,3,7,8-TCDD-contaminated chemicals, pentachlorophenol, and its production by-products, which include hexa-, hepta-, and octachlorinated dioxins and dibenzofurans. The exposures occurred between 1965 and 1968, with the ensuing effects beginning shortly thereafter. The observation period lasted from 1967 to 1973. In a follow-up report of the same population conducted in approximately 1977, Pazderova-Vejlupkova et al. (1981) did not report liver enzyme levels but suggested that the levels were not abnormal.

Similarly, ALT was increased in 5 of 14 TCP workers from Great Britain who were in the manufacturing building at the time of a TCP reactor explosion in 1968 (May, 1973). Levels for

AST were not reported. In 1977, workers from the same facility were reevaluated. No elevations in AST or ALT were found in production and laboratory workers with chloracne (May, 1982).

Finally, during the first year after the TCP reactor explosion, Caramaschi et al. (1981) evaluated AST and ALT among Seveso children with and without chloracne. Only ALT was statistically significantly elevated in children with chloracne. In a larger study, Mocarelli et al. (1986) tested liver enzyme levels yearly from 1977 to 1982 in male and female children from Seveso and from the unexposed surrounding area. In the 1977, 1979, 1980, and 1981 test series ALT, but not AST, was statistically significantly ($p<0.05$) elevated among male children in Seveso compared with unexposed comparisons. Female children had normal levels compared with controls for all years. In 1982, ALT levels in the exposed boys returned to normal.

None of the studies reporting elevations in ALT or AST identified clinical evidence of liver disease in the study populations. Therefore, in the absence of reports of hepatic or nonhepatic diseases related to changes in ALT or AST levels among exposed individuals, it is possible that the increases in ALT and AST are related to high-level, acute exposure to 2,3,7,8-TCDD-contaminated chemicals and that, barring additional exposure, the enzyme levels decrease with time.

7.13.2.5.2. ***Developmental measures*****.** One report (Pluim et al., 1994) has examined blood measures in 35 babies (the study and exposure groupings are described in detail in Section 7.12.2.3.). Four blood samples were taken: maternal blood around delivery, cord blood, and the infant's blood at 1 and 11 weeks of age. These samples were used to measure leucocytes (WBC), platelets, and differential, along with plasma, activity of gamma glutamyltransferase (GGT), AST, and ALT, and levels of cholesterol and bilirubin. Dioxin and furan levels were measured in breast milk collected about 3 weeks post-delivery. None of the maternal blood measurements were outside the normal range. A statistically significant inverse correlation was observed in an uncorrected comparison of the number of polynuclear neutrophils and dioxin-furan levels in breast milk $r = -0.53$, $p = 0.022$); this disappeared when regression analysis compared these and controlled for gestational age. None of the other factors compared in the cord blood or at 1 week or 11 weeks of age were statistically significant. The next set of analyses used the estimated cumulative dioxin-furan intake from breast feeding at 11 weeks of age; the PCDD/PCDF TEQs ranged from 5.7 to 123.7 pg TEQ/g fat, with a mean of 44.7 pg. The statistically significant correlations are presented in Table 7-26. These results are unadjusted, but remain significant after adjusting for maternal age, gestational age, and birth weight (regression coefficients were not presented). The author proposed that the changes in ALT and AST suggest an effect on the liver, associated with the cumulative exposure to dioxin-furans, and notes that all but three of the

children had ALT and AST within "normal" ranges, but the distribution of some of these findings (e.g., an increase in platelets) did vary. From this study, it is not possible to determine the reversibility of these changes.

7.13.2.6. *D-Glucaric Acid*

In five studies of Seveso residents, TCP production workers, and Vietnam veterans, urinary excretion of D-glucaric acid was measured to determine if exposure to 2,3,7,8-TCDD induced hepatic microsomal activity (Table 7-27). D-glucaric acid excretion is an indirect but valid indicator of enzyme induction.

Ideo and colleagues (1985) measured urinary D-glucaric acid in adults and children from all zones of Seveso and from nearby uncontaminated towns. Of adults tested in 1978, D-glucaric acid excretion was significantly elevated in adults residing in Seveso, Italy, at the time of the reactor explosion compared with residents of unexposed communities (Seveso = 27.1 μmol/g of creatinine vs. unexposed = 19.8 μmol/g of creatinine, $p<0.05$). No further studies of adults have been published. A series of studies evaluated D-glucaric acid excretion in Seveso children (Ideo et al., 1985) (Table 7-27). In 1976, the levels in children from zone A with chloracne (39 μmol/g of creatinine) were significantly greater than in children without chloracne (20.5 μmol/g of creatinine). Additional studies, conducted until 1981, found significant yearly decreases in urinary D-glucaric acid excretion. By 1981, levels were within normal range.

These early analyses of D-glucaric acid levels were conducted without the benefit of individual exposure measurements. In 1989-1994, serum 2,3,7,8-TCDD concentrations were analyzed in blood samples collected in 1976-77 from the original study group. In a comparison of D-glucaric acid levels and serum 2,3,7,8-TCDD concentrations, Cassaniga et al. (1999) found the median D-glucaric acid levels of the 26 controls and of the 11 exposed children with 2,3,7,8-TCDD concentrations below 1,000 pg/g lipid were similar (Controls = 22.8 μmol/g creatinine; <1,000 pg/g lipid TCDD = 21.6 μmol/g creatinine); the median D-glucaric acid levels of the five children with 2,3,7,8-TCDD concentrations above 1,000 pg/g were twice as high (59.2 μmol/g creatinine). These data suggest that D-glucaric acid levels may be a useful marker of recent, very high exposure to 2,3,7,8-TCDD because within 5 years after exposure, D-glucaric acid levels returned to normal.

D-glucaric acid-creatinine ratios were used to assess urinary excretion in TCP production workers tested within a year of suspension of TCP production and 10 years after a TCP reactor explosion. For exposed workers with or without chloracne at the time of the study, the D-glucaric acid-creatinine ratio was significantly higher than that of the unexposed controls (exposed = 2.09; unexposed controls = 1.59; $p<0.05$) (Martin, 1984).

Other studies of Air Force Ranch Hands or TCP production workers that examined D-glucaric acid excretion did not find increases in exposed populations 10 to 37 years after last exposure to 2,3,7,8-TCDD-contaminated chemicals (Roegner et al., 1991; Calvert et al., 1992).

7.13.2.6.1. ***Comment.*** The evidence presented by the large number of case reports and epidemiologic studies of groups exposed to 2,3,7,8-TCDD-contaminated chemicals suggests that hepatic enzyme induction occurred in some populations within a short time after high-level 2,3,7,8-TCDD exposure. In most cases, enzyme levels decreased as the time from exposure increased. However, even after more than 15 years since last exposure, levels of GGT continue to be significantly elevated in relation to serum 2,3,7,8-TCDD in TCP production workers with above-average alcohol consumption (Calvert et al., 1992) and in Air Force Ranch Hands (Roegner et al., 1991; Grubbs et al., 1995). Other Vietnam veterans (U.S. Army ground troops) also have significantly increased GGT levels compared with non-Vietnam veterans, but this increase in the Army veterans is probably not due to exposure to high levels of 2,3,7,8-TCDD. In the population of Army Vietnam veterans studied, the mean serum 2,3,7,8-TCDD was approximately 4 pg/g (Centers for Disease Control Veterans Health Studies, 1988), compared to a mean of 220 pg/g (range to 3,400 pg/g) in the production workers and a median of 12 pg/g (range to 600 pg/g) in the Ranch Hands.

The finding of continued elevation of GGT in the NIOSH and Army veterans may be a spurious result or it may reflect activity related to the continued presence of above-background levels of 2,3,7,8-TCDD in exposed individuals.

7.13.2.7. ***Porphyrin Metabolism***

In rats and mice, exposure to 2,3,7,8-TCDD has been clearly shown to produce alterations in porphyrin metabolism (Goldstein et al., 1973, 1982; Smith et al., 1982; Jones et al., 1981; DeVerneuil et al., 1983; Cantoni et al., 1981). Whether 2,3,7,8-TCDD is associated with porphyrin changes in humans, particularly porphyria cutanea tarda (PCT), is a subject of some debate. PCT is a form of acquired or inherited porphyria caused by a deficiency of the enzyme uroporphyrinogen decarboxylase and the resulting overproduction and excretion of uroporphyrin (Sweeney, 1986). The predominant characteristics of PCT include skin fragility, blistering upon sun exposure, dark pigmentation, excess hair growth, hepatomegaly, reddish-colored urine, and urinary excretion of uro- and heptacarboxylicoporphyrins (Strik, 1979). PCT has been associated with excessive alcohol intake, oral estrogens, iron overload, hepatomas, and exposure to polyhalogenated hydrocarbons (Strik, 1979). A particularly large outbreak of PCT occurred after consumption of grain treated with hexachlorobenzene (HCB) (Cam and Nigogosyan, 1963).

Cases of PCT were described in two populations of TCP production workers (Bleiberg et al., 1964; Jirasek et al., 1974) and among members of a family with inherited uroporphyrin decarboxylase deficiency who were living in Seveso at the time of the reactor explosion (Strik, 1979).

In 1964, Bleiberg reported that based on the Watson-Schwartz test, 11 of 29 New Jersey TCP production workers with chloracne had PCT as a result of increased urinary uroporphyrins, coproporphyrins, and urobilinogen. In a later study of 73 workers from the same plant in New Jersey, including four of the individuals that Bleiberg et al. (1964) found to have elevated urinary porphyrins, Poland et al. (1971) identified one individual with uroporphyrinuria. The report did not explain if this individual was one of the four described by Bleiberg et al. (1964). In the NIOSH study that examined workers from the same plant in New Jersey, the pattern of urinary porphyrin excretion for each participant was assessed to determine the presence of PCT (Calvert et al., 1994). No difference in the prevalence of PCT was found between workers and an unexposed control group (OR = 0.93, 95% CI = 0.19, 4.54). Furthermore, there were no differences in the risk between workers and the control group for an out-of-range uroporphyrin concentration or an out-of-range coproporphyrin concentration. Because this study was conducted at least 15 years after last occupational exposure to TCDD, it was not possible to determine whether porphyrinuria occurred during the years more proximal to occupational 2,3,7,8-TCDD exposure.

Jirasek et al. (1974) found 11 of 55 Czechoslovakian TCP production workers to have elevated urinary uroporphyrins that decreased during the observation period; the authors did not describe the test used to measure urinary uroporphyrins or coproporphyrins. Ten years later in a follow-up study, Pazderova-Vejlupkova et al. (1981) found no evidence of increased excretion of uroporphyrins or dermatological indications of PCT in the same group of workers.

There is some question that the porphyria noted in the New Jersey (Bleiberg et al., 1964) and Czechoslovakian workers was due to 2,3,7,8-TCDD exposure. Jones and Chelsky suggest that the observed cases of PCT in both plants may be due to exposure to HCB or a combination of both 2,3,7,8-TCDD and HCB (Jones and Chelsky, 1986). HCB was manufactured at the New Jersey plant from 1951 until 1960 and was produced at the facility in Czechoslovakia during the production of pentachlorophenol and TCP (Jirasek et al., 1973). In addition, there is some question as to the appropriateness of the clinical test Bleiberg et al. (1964) used to measure porphyrin levels. The Watson-Schwartz test was capable of measuring only the presence of porphobilinogen. The test was rarely positive in cases of exposure to hepatotoxins. Bleiberg's findings suggest that either other unspecified tests were used to measure uro- and coproporphyrin levels or the authors misinterpreted the function of the Watson-Schwartz test.

Evidence of porphyria in other studies of individuals exposed to 2,3,7,8-TCDD-contaminated substances is minimal. Although Suskind and Hertzberg (1984) sampled urine for porphyrins in the examination of West Virginia TCP workers, the authors report that the data are not valid. However, there was no dermatologic evidence of porphyria identified among the exposed workers. Moses et al. (1984) found no difference in porphyrin levels when comparing TCP workers with and without chloracne. Finally, no PCT was reported among three laboratory workers exposed to pure 2,3,7,8-TCDD (Oliver, 1975), the only humans known to have documented unintentional exposure to uncontaminated 2,3,7,8-TCDD.

In 1977, 60 Seveso residents were tested for elevated porphyrins, exclusive of the family with inherited deficiency of uroporphyrinogen decarboxylase. None of the 60 residents developed PCT; however, 13 (22%) exhibited secondary coproporphyrinuria, 5 of whom showed a slight increase of urocarboxyporphyrins, heptacarboxyporphyrins, and coproporphyrins classified as a "transition constellation to CHP type A" (Doss et al., 1984). Porphyrin levels were retested in 1980. Porphyrin levels returned to normal in 12 individuals. In three of those with transition CHP, porphyrin levels were higher than those in 1977 and were attributed to liver damage and alcohol consumption. Doss et al. (1984) suggested that in the Seveso family with uroporphyrinogen dicarboxylase deficiency, the exposure to 2,3,7,8-TCDD-contaminated effluent caused an exacerbation of a preexisting enzyme deficiency.

7.13.2.7.1. ***Comment.*** It is possible that the PCT and elevated urinary porphyrins observed in the New Jersey and Czechoslovakian workers were a direct result of exposure to hexachlorobenzene. In the follow-up studies, urinary porphyrin levels in workers were not elevated (Pazderova-Vejlupkova et al., 1981; Poland et al., 1971) or did not differ from levels in the control group (Calvert et al., 1992). The transient elevations in coproporphyrins among 22 Seveso residents described by Doss et al. (1984) may be a direct result of acute exposure to 2,3,7,8-TCDD.

The association is not clear. However, 2,3,7,8-TCDD is a potent porphyrigen in rats and mice and, therefore, high acute exposures may have contributed to the observed changes in porphyrin levels in these populations.

7.13.2.8. *Lipid Levels*

Animal studies provide conflicting evidence on the relationship between exposure to 2,3,7,8-TCDD and serum lipid levels. Some studies suggest that short-term high exposure to 2,3,7,8-TCDD increases serum cholesterol (Greig et al., 1973; Zinkl et al., 1973; Poli et al., 1980; Gasiewicz et al., 1980; Schiller et al., 1986; Gasiewicz and Neal, 1979; Olson et al., 1980) and triglyceride fractions (Schiller et al., 1986; McConnell et al., 1978a,b; Gasiewicz and Neal, 1979),

whereas other studies suggest a decrease (Gasiewicz et al., 1980; Olson et al., 1980) or no change in triglyceride levels (Poli et al., 1980). The human data appear to be similarly confusing. A number of case reports and epidemiologic studies have described increases in the levels of serum lipid fractions, particularly total cholesterol and triglycerides, in TCP production workers, laboratory workers, Seveso and Missouri residents, and Vietnam veterans. Others report no differences between subject and reference levels. A summary of the reported levels is included in Tables 7-28 and 7-29.

7.13.2.9. *Total Cholesterol*

Two case reports of workers with presumably high exposures to 2,3,7,8-TCDD-contaminated chemicals described elevations in total cholesterol. In 50% of 55 Czechoslovakian TCP production workers examined between 1968 and 1969 who exhibited signs of "chemical intoxication," total cholesterol was noted as elevated (Jirasek et al., 1974). In a follow-up study 10 years later, lipid levels among workers removed from exposure were not significantly different from referent levels, but total cholesterol levels remained significantly increased (Pazderova-Vejlupkova et al., 1981). In a separate report, three laboratory workers who were exposed during the synthesis of pure 2,3,7,8-TCDD developed serum cholesterol levels in excess of 7.7 mmol/L (Oliver, 1975). No information on pre-exposure cholesterol levels was provided in either report.

The results of epidemiologic studies conflict. Among British TCP production workers whose last exposure to 2,3,7,8-TCDD-contaminated chemicals was less than 1 year at the time of the study, total cholesterol levels in exposed workers with (6.02 mmol/L) and without (6.14 mmol/L) chloracne were significantly elevated compared to unexposed controls (5.6 mmol/L) (Martin, 1984) (Table 7-28), whereas May (1982) found unexposed workers (6.6 mmol/L) to have cholesterol levels higher than those of exposed workers with chloracne (5.97 mmol/L). Martin (1984) also found reduced, but not significantly, HDL cholesterol among exposed workers with chloracne (1.19 mmol/L) compared to unexposed controls (1.25 mmol/L). The differences in the results may be due to differences in the control groups and inclusion of different workers in the exposed groups.

Cholesterol levels in West Virginia TCP production workers were compared with unexposed workers from the same plant (Suskind and Hertzberg, 1984). No difference was identified in mean cholesterol levels between workers and controls. However, when lipid fractions were examined, there was a larger but nonsignificant percentage of exposed workers with elevated LDL cholesterol (7.7%) compared to unexposed controls (6.3%). A comparison of workers with persistent chloracne, no chloracne, or a history of chloracne found a significant

association (p<0.05) between the proportion of out-of-range LDL cholesterol values and persistent chloracne. An out-of-range LDL was defined as above the 90th percentile of the total range of values. In a second study that compared West Virginia workers with and without chloracne, no difference was found in mean cholesterol levels (Moses et al., 1984). In the NIOSH study, there was little difference between the adjusted mean total cholesterol levels for workers (5.7 mmol/L) and referents (5.6 mmol/L) and no relation to increasing serum 2,3,7,8-TCDD levels (Calvert et al., 1996). The mean levels were adjusted for age, body mass index, age, and gender.

Mean cholesterol levels were no different between workers in the BASF accident cohort (6.14 mmol/L) and the referent population (6.37 mmol/L) and were not related to current or log TCDD back-calculated levels (Ott et al., 1994). In addition, no significant differences were noted between the exposed and unexposed populations for HDL and LDL levels.

In general, cholesterol levels among exposed community residents were not increased. Despite their high exposure to 2,3,7,8-TCDD-contaminated TCP, neither children nor adults from Seveso were found to have elevated serum cholesterol levels compared to controls (Mocarelli et al., 1986; Assennato et al., 1989). Evaluated from 1976 through 1985, cholesterol levels in this population remained constant throughout the study period (Table 7-28). Similarly, among Missouri residents, serum cholesterol was not related to residence in the Quail Run Mobile Home Park (Hoffman et al., 1986) or to adipose tissue 2,3,7,8-TCDD levels (Webb et al., 1989).

Among U.S. Army veterans, there was no difference in total cholesterol levels between groups serving in Vietnam or other arenas (Centers for Disease Control Vietnam Experience Study, 1988a). In contrast, there was a statistically significant positive relationship between Ranch Hands with serum 2,3,7,8-TCDD levels above 33.3 pg/g and total cholesterol in Air Force Ranch Hands (Roegner et al., 1991). The total cholesterol-HDL ratio was also highest in this serum 2,3,7,8-TCDD category. In the 1992 analysis, although cholesterol concentrations remained higher in the High Ranch Hand category compared to the Low, Background and Comparison group, the difference was not great enough to achieve statistical significance (Grubbs et al., 1995).

7.13.2.10. *Triglycerides*

Elevated triglyceride levels were reported in only three of the studied populations. Among British TCP workers, triglycerides were significantly higher in exposed workers with (1.97 mmol/L) and without (1.90 mmol/L) chloracne compared to unexposed controls (1.41 mmol/L) (Martin, 1984). TCP production workers from West Virginia who had chloracne had a statistically nonsignificant increase in mean triglyceride levels (chloracne = 1.69 mmol/L; without chloracne = 1.46 mmol/L) (Moses et al., 1984). In addition, compared to the unexposed

Comparison population, triglyceride levels in Air Force Ranch Hands were significantly elevated for all serum 2,3,7,8-TCDD categories (Table 7-29). Among workers in the NIOSH study there appeared to be a small rise in triglyceride levels with increasing serum 2,3,7,8-TCDD (Calvert et al., 1996). The mean adjusted triglyceride levels and the percent of abnormal triglyceride values increase with increasing serum 2,3,7,8-TCDD level (<158 femtograms/liter [fg/L], mean = 1.04 mmol/L, % abnormal = 5.7; 158-520 fg/L, mean = 1.26 mmol/L, % abnormal = 6.1; 521-1,515 fg/L, mean = 1.23 mmol/L, % abnormal = 6.1; 1,516-19,717 fg/L, 1.35 mmol/L, % abnormal = 1.7, $p<0.05$ compared to referents [1.15 mmol/L]). Odds ratios and 95% confidence intervals for the quartiles are OR = 0.7 (95% CI = 0.2, 1.9), OR = 1.1 (95% CI = 0.4, 3.2), OR = 0.9 (95% CI = 0.3, 2.9), and OR = 1.7 (95% CI = 0.6, 4.6), respectively. The authors suggest that despite this small rise with 2,3,7,8-TCDD level, the influence of factors such as gender, body mass index, use of beta-blocker medication, and smoking had far greater effects on lipid concentration than did 2,3,7,8-TCDD level. Likewise, triglyceride levels in the BASF accident cohort were similar to those in the referent cohort and not related to 2,3,7,8-TCDD level (Ott et al., 1994).

Triglyceride levels were not elevated in Missouri (Hoffman et al., 1986; Webb et al., 1989) or Seveso residents (Mocarelli et al., 1986; Assennato et al., 1989) or in U.S. Army Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988a). However, in the 1987 examination, mean adjusted triglyceride concentrations were statistically significantly higher among Ranch Hands whose serum 2,3,7,8-TCDD levels were above 15 pg/g of lipid (Roegner et al., 1991). In the 1991 examination, mean adjusted triglyceride concentrations only in the high group were significantly different from the comparison group (Grubbs et al., 1995).

7.13.2.10.1. ***Comment.*** The effect of exposure to 2,3,7,8-TCDD-contaminated chemicals on cholesterol or triglyceride levels is not consistently well defined in the available studies. It is possible the transient elevations in total cholesterol and triglyceride levels may have occurred after high 2,3,7,8-TCDD exposure, as in the experience of the British and Czechoslovakian TCP workers and British laboratory workers. However, this scenario does not concur with the evidence from Seveso or among Ranch Hands. Despite their very high exposure to 2,3,7,8-TCDD-contaminated chemicals, neither adults nor children from Seveso had lipid levels above the referent level. In contrast, Ranch Hands continue to have elevated lipid levels despite the extended length of time between exposure and testing. Other factors, such as dietary fat intake, familial hypercholesterolemia, alcohol consumption, and exercise, which also affect cholesterol and other lipid levels, may be factors that were not considered in many of these studies.

7.13.3. Other Gastrointestinal Disorders

A variety of gastrointestinal disorders other than liver conditions were reported among TCDD-exposed groups. After heavy, acute, or chronic exposure, chemical workers in West Virginia (Ashe and Suskind, 1950), West Germany (Baader and Bauer, 1951; Bauer et al., 1961), and Czechoslovakia (Jirasek et al., 1974) consistently reported transient episodes of right upper quadrant pain, loss of appetite, and nausea. None of the reports suggest an etiology for these symptoms, nor were the symptoms reported in later follow-up studies of any cohorts (Suskind and Hertzberg, 1984; Moses et al., 1984; Pazderova-Vejlupkova et al., 1981).

Three investigations of TCP production workers reported an increased prevalence of a history of upper gastrointestinal tract ulcer across all age strata of West Virginia workers (exposed = 20.7% vs. unexposed = 5.5%) (Suskind and Hertzberg, 1984) and all digestive system diseases (type not specified) among workers employed in a plant in Midland, Michigan (prevalence: exposed = 1.5% vs. unexposed = 0.5%) (Bond et al., 1983). The factors contributing to these conditions have not been examined fully. Neither the Ranch Hand study (Roegner et al., 1991; Grubbs et al., 1995) or the NIOSH study (Calvert et al., 1992) found increased risk of upper gastrointestinal tract ulcers with increasing serum TCDD level.

7.13.4. Thyroid Function

7.13.4.1. *Adult Effects*

The thyroid plays an essential role in the maintenance of metabolic rate, food intake, and differentiation and maturation of various cell types. Because many of the toxic effects of 2,3,7,8-TCDD noted in animals resemble the signs of thyroid dysfunction, researchers considered the role of the thyroid in 2,3,7,8-TCDD toxicity (Neal et al., 1979). Some studies found a single high dose of 2,3,7,8-TCDD resulted in decreased levels of serum thyroxine (T4), indicating hypothyroidism, but no consistent findings were reported for alterations in 3,5,3′-triiodothyronine (T3); researchers report decreases, no change, and increases in levels of T3 (Bastomsky, 1977; Potter et al., 1983; Pazdernik and Kozman, 1985; Potter et al., 1986; Henry and Gasiewicz, 1987; Roth et al., 1988; Muzi et al., 1989). Furthermore, hypothyroidism induced in rats was protective against 2,3,7,8-TCDD-induced weight loss, immunotoxicity, and mortality (Rozman et al., 1984; Pazdernik and Kozman, 1985). This protective effect was reversed when T4 supplements were given to these animals (Rozman et al., 1985). Henry and Gasiewicz (1987), however, found that in hamsters serum T3 and T4 levels increased after 2,3,7,8-TCDD administration, putting in question the role of the thyroid in 2,3,7,8-TCDD-induced toxicity.

These animal findings suggest that if the thyroid plays a role in human toxicity, hypothyroidism would be manifested as a reduction in serum T4; in extreme cases of 2,3,7,8-

TCDD toxicity, however, one may experience hyperthyroidism. Only three studies of production workers examined this issue (Suskind and Hertzberg, 1984; Ott et al., 1994; Calvert et al., 1999). Suskind and Hertzberg (1984) performed T4 radioimmunoassay and thyroxine-binding globulin (TBG) tests and found no significant differences between exposed and unexposed workers. Quantitative results were not presented. Similarly, thyroid stimulating hormone (TSH), T4, and TBG levels were within normal range in the BASF accident workers and the means were not statistically different (Table 7-30). However, TGB and T4 levels were positively related to 2,3,7,8-TCDD levels in regression analyses (Ott et al., 1994). In the NIOSH study, TSH, total T4, and thyroid binding resin were measured. Overall, workers had a significantly higher adjusted mean free T4 index; however, there was no trend with serum 2,3,7,8-TCDD concentrations (Calvert et al., 1999). TSH was not different between workers and referents.

The 1987 Ranch Hand study indicated a nonsignificant reduction of T3% uptake but this was not measured in the 1991 study (Table 7-31). A slight increase in the mean level of TSH (Table 7-32) with increasing serum 2,3,7,8-TCDD level was noted in both 1987 and 1991; these results, however, did not reach statistical significance (Roegner et al., 1991; Grubbs et al., 1995). Among Army Vietnam veterans, mean TSH levels, but not mean free thyroxine index (FTI) levels, were statistically significantly higher than among non-Vietnam veterans, after adjustment for the six entry characteristics of age and year of enlistment, race, enlistment status, general technical test score, and primary military occupation (Table 7-31) (Centers for Disease Control Vietnam Experience Study, 1988a). However, the percent of values that were out of reference range did not differ significantly for TSH (Vietnam veterans, 1.0%; non-Vietnam veterans, 0.6%, OR = 2.0, 95% CI = 0.9-4.3) and FTI (Vietnam veterans, 5.4%; non-Vietnam veterans, 4.6%, OR = 1.2, 95% CI = 0.9-1.5). The exposure levels were low, based on the sample for which 2,3,7,8-TCDD was measured.

7.13.4.1.1. ***Comment.*** Few human studies examined the relationship between 2,3,7,8-TCDD exposure and thyroid function, and the results of present research are equivocal. These studies examined individuals with lower exposure to 2,3,7,8-TCDD than the animals, and exposure was chronic. The data from the Ranch Hand and the NIOSH studies, which measured serum 2,3,7,8-TCDD concentrations, suggest that in adults there are few long-term effects on adult thyroid function.

7.13.4.2. *Developmental Effects*

Two series of studies, both in The Netherlands but conducted in different communities, examined thyroid function in infants and related this to dioxin, furans and/or PCB levels in breast milk, cord blood, or third-trimester materal serum samples.

The first study, among infants in Amsterdam (Pluim et al., 1992; Pluim et al, 1993), examined thyroid function among 38 full-term breast-fed infants in relation to the total toxic equivalents per kg of breast milk fat (TEQ/kg) of dioxins and furans (listed in Table 7-21b and described in detail in Section 7.12.2.3) . The authors measured total T4, thyroxine-binding globulin (TBG), and thyroid stimulating hormone (TSH) levels sequentially in cord blood, infants at 1 week of age, and infants at 11 weeks of age (Tables 7-30 and 7-33). Total T3 was measured in cord blood and at 11 weeks, and free T4 was measured in cord blood. Infants were classified into "high" and "low" groups at the median of the range. At 1 week and 11 weeks postnatally, total T4 and total T4/TBG ratios were significantly higher among infants in the high group. At 11 weeks, TSH was also significantly higher for the high group. The authors suggest that exposure to high levels of dioxins and furans, either *in utero* or through breast milk, modulates the hypothalamic-pituitary-thyroid regulatory system of the infant (Pluim et al., 1992; Pluim et al., 1993).

A study conducted over approximately the same time period in Rotterdam, The Netherlands, examined thryoid function in 105 mother-infant pairs (Koopman-Esseboom et al., 1994c). Exposure was estimated using breast milk collected in the 1-2 weeks after delivery. As in the other study, the mother-infant pairs were split into two groups at the median dioxin-furan TEQ based on the congeners listed in Table 7-21b (see details in Section 7.12.2.3.). The authors measured total T4, total T3, free T4, and TSH levels in the mother during the last month of pregancy and 9-14 days post delivery, in cord blood, and in infants at 9-14 days and three months after birth (Tables 7-30 and 7-33). Of those enrolled in the study, 78 mother-infant pairs met all criteria and were included in the final analyses. All the thyroid measures were within normal ranges, with the exception of TSH for one woman. All of the TEQs (dioxin-furan TEQ, coplanar PCB TEQ, nonplanar PCB TEQ, and total PCB-dioxin-furan TEQ) were significantly correlated with infant plasma levels of TSH at the second week and third month, and inversely correlated with total T3 pre-delivery and with total T3 and total T4 post-delivery for the mothers. The only exception is that the nonplanar PCB TEQ was not significantly correlated with the mothers total T4 after delivery and the infants' third month TSH. Measures from the infants during their second week of life showed a significant increase in TSH (Table 7-33) and a significant decrease for total T4 and free T4 (Table 7-30) for infants in the "high" group.

7.13.4.2.1. ***Comment.*** Two studies of nursing infants suggest that ingestion of breast milk with a higher dioxin-furan TEQ may alter thyroid function (Pluim et al., 1993; Koopman-Esseboom et al., 1994c). Both studies had similar exposure groupings and some findings in common: both had significant increases in TSH at about 3 months of age with higher TEQs, and in one report, significant increases at about 2 weeks of age and in the cord blood. Significant changes were found with high TEQ for total T4, but they were in opposite directions, increased in neonates at 1 and 11 weeks of age (Pluim et al., 1993) and decreased for infants during the second postnatal week (Koopman-Esseboom et al., 1994c). Koopman-Esseboom and her colleagues also noted a significant increase in T4/TBG and a significant decrease in free T4. Both studies covered a short observation period, which limits the examination of persistent or long-term changes in thyroid status, and analyses did not control for other factors that might affect thyroid status. These findings suggest a possible shift in the distribution of thyroid hormones, and point out the need for collection of longitudinal data to assess the potential for long-term effects associated with developmental exposures.

These two developmental studies investigated relatively small numbers of individuals with thyroid parameters in the normal range. However, the high group, at about 3 months of age, had increased TSH levels in comparison to the low group. Total T4 levels and total T4 to thyroid binding globulin (TBG) ratio were generally elevated in the high infants.

The exact processes accounting for these observations in humans are unknown, but when put in perspective of animal responses, the following might apply: dioxin-furan increases the metabolism and excretion of thyroid hormone, mainly T4, in the liver. Reduced T4 levels stimulate the pituitary to secrete more TSH, which enhances thyroid hormone production. Early in the disruption process, the body can overcompensate for the loss of T4, which may result in a small excess of circulating T4 to the increased TSH. In animals, given higher doses of dioxin, the body is unable to maintain homeostasis, and TSH levels remain elevated and T4 levels decrease.

7.13.5. Adult Reproductive System

7.13.5.1. *Hormones*

In laboratory rats, high doses of 2,3,7,8-TCDD have been related to decreased testosterone levels, with evidence that dioxin decreases testosterone synthesis (Kleeman et al., 1990; Mebus et al., 1987; Moore and Peterson, 1988; Moore et al., 1985).

A reported symptom of men who were exposed to 2,3,7,8-TCDD-contaminated materials as a result of daily exposure and industrial accidents is reduced libido (Baader and Bauer, 1951; Bauer et al., 1961; Suskind et al., 1953). Two independently conducted studies of West Virginia TCP workers noted that exposed study subjects also reported this condition approximately 50%

more often than either the unexposed controls or individuals without chloracne (Moses et al., 1984; Suskind and Hertzberg, 1984). Endocrine studies or evaluations of conditions or situations that may lead to a reduction in libido were not conducted.

In the NIOSH study of TCP production workers, questions regarding libido were not asked; however, reproductive hormone levels were measured and related to serum 2,3,7,8-TCDD levels. In linear regression analyses, serum 2,3,7,8-TCDD was positively and significantly related to serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and inversely related to total testosterone after adjustment for potential confounders ($p<0.05$) (Egeland et al., 1994). The prevalence of abnormally low testosterone was two to four times higher among workers with serum 2,3,7,8-TCDD levels of 20-75 pg/g (OR = 3.9, 95% CI = 1.3, 11.3), 76-243 pg/g (OR = 2.7, 95% CI = 0.9, 8.2), or ≥244 pg/g (OR = 2.1, 95% CI = 0.8, 5.8) than among unexposed referents (4.8%) (mean serum 2,3,7,8-TCDD = 7 pg/g). Workers in these same serum 2,3,7,8-TCDD quartiles had a higher prevalence of abnormally high LH than workers with serum 2,3,7,8-TCDD levels of 244 pg/g to 3,400 pg/g, but the differences between each serum 2,3,7,8-TCDD category and referents were not significant.

The Ranch Hand veterans study provides the only other human data available that evaluate the relationship between serum 2,3,7,8-TCDD and testosterone (Roegner et al., 1991). Ranch Hand veterans with current serum dioxin levels exceeding 33.3 pg/g were reported to have a lower mean total serum testosterone level (515.0 ng/dL) than the nonexposed comparison group (525.2 ng/dL), but the difference was statistically nonsignificant. No association was observed with FSH and LH. In additional analysis by Henriksen et al. (1997) no association was found between abnormally high or abnormally low testosterone level and dioxin exposure category. Testicular abnormality was assessed by physician palpation at the 1987 physical examination (Roegner et al., 1991). Because of this finding, testicular volume was measured by ultrasound at the 1992 physical examination (Grubbs et al., 1995). No association was found between testicular volume measured by ultrasound and dioxin exposure category in 1992 (Grubbs et al., 1995).

Testosterone, FSH, and LH were also measured in U.S. Army veterans and non-Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988a). No significant differences in hormone means were noted between the two groups. Additionally, the proportions of values outside the reference range were also similar.

7.13.5.1.1. ***Comment.*** The human data offer some evidence of alterations in male reproductive hormone levels associated with substantial occupational exposure to 2,3,7,8-TCDD. The results support the animal literature, in which dioxin-related effects have been observed on the hypothalamic-pituitary-Leydig-cell axis and on testosterone synthesis.

7.13.5.2. ***Endometriosis***

After noting the prevalence and severity of endometriosis in rhesus monkeys chronically exposed to 2,3,7,8-TCDD (Rier et al. 1993), investigators started looking at endometriosis in humans. The first reported effort was a case-control study (Mayani et al., 1997) comparing 79 women, all treated in an infertility clinic during 1991-1995, some with endometriosis (N = 44), and the comparisons with tubal infertility (N = 35). All women underwent laparoscopic examination for diagnosis and scoring of endometriosis. Altogether, 9 women had 2,3,7,8-TCDD above the limits of detection: 2.9% of the controls (N = 1 of 35), 12.5% of those women with Stage I-II endometriosis (N = 3 of 24), and 25% of those with Stage III-IV endometriosis (N = 5 of 20). Logistic regression was used to control for potential effects of the different racial/ethic compositions of the cases and controls. The results of this analysis, compared to other unadjusted analyses, are not explicitly identified, but are probably OR = 7.6 (95% CI = 0.87-169.7). The authors did not present sufficient information on their data analyses to evaluate them (for example, whether actual levels of 2,3,7,8-TCDD were entered, or whether detectable levels were observed), but did note the limited power of this effort. An exposure-severity relationship was not observed. However, the frequency of exposure increased with increasing severity (not statistically tested).

A recent report (Pauwels et al., 1999) examined 101 infertile women treated at a collaborating Center for Reproductive Medicine in Belgium between 1995 and 1998. The couple were defined as infertile after attempting pregnancy for at least 1 year without success. Using laproscopic examination, 42 women were diagnosed with endometriosis; 25 women had mechanical infertility (e.g., tubal disease), 8 husbands of 20 without diagnosis were found to be infertile. Fourteen women were excluded from analysis because of ovulatory dysfunction. CALUX TEQs were generated using serum (N = 101), adipose tissue (N = 46) and follicular fluid (N = 8) based on major PCB congeners and chlorinated pesticides. In preliminary analyses and using a cut point of 100 pg TEQ/g serum lipid weight, the investigators observed proportionately more women with endometriosis with high TEQs (17%) compared to the controls (4%) (OR = 4.0, NS).

Finally, a study of endometriosis looked at each woman's history of breast milk consumption (Ikezuki et al., 1999). The authors hypothesized that women who were breast fed as infants would have higher dioxin levels and subsequently higher rates of endometriosis than would those who had been formula fed. A total of 2,848 women were queried: 2,281 from 8 companies participating in the project, and 567 women in the Japanese Endometriosis Association or who had surgery at Tokyo University Hospital. The proportions observed were the reverse of those hypothesized: more controls had been breast fed (68%) than had women with endometriosis

(51%). These data are of questionable use because of limited ascertainment of exposure, lack of knowledge about potential cases missed by the recruitment methods, and lack of detail about the comparability of the case and comparison groups.

7.13.5.2.1. ***Comments.*** The first two reports of infertility patients (Mayani et al., 1997; Pauwels et al., 1999) raised the potential for an association between endometriosis and 2,3,7,8-TCDD or TEQ exposure. These studies are small and of limited power. Studies currently underway will greatly add to the database on this outcome. The study comparing breast-fed women to those who were bottle-fed contained little concrete data on exposure and, most likely, incomplete and potentially biased selection of cases, and thus are of limited use for examining the relationship of dioxin to endometriosis.

7.13.6. Diabetes

Diabetes and fasting serum glucose levels were evaluated in cross-sectional medical studies because of the apparently high prevalence of diabetes and abnormal glucose tolerance tests in one case report of 55 TCP workers (Pazderova-Vejlupkova et al., 1981). In this group, evaluated 10 years after exposure ended, approximately 50% of the subjects had either confirmed cases of diabetes or abnormal glucose tolerance tests.

The results of later medical studies are mixed. Cross-sectional studies of workers from Nitro, West Virginia (Suskind and Hertzberg, 1984; Moses et al., 1984), found no difference in glucose levels between the exposed and control populations, although no quantitative values were presented in either study. Similarly, the adjusted odds ratio for out-of-range fasting glucose levels comparing Vietnam veterans to non-Vietnam veterans was not statistically significant (OR = 1.0, 95% CI = 0.4-2.2) (Centers for Disease Control Vietnam Experience Study, 1988a). But a comparison of the adjusted mean fasting glucose levels between the two groups was marginally significant (Vietnam veterans, 5.2 mmol/L; non-Vietnam veterans, 5.1 mmol/L, $p<0.05$). Mean fasting glucose levels in the BASF accident cohort were marginally elevated compared to the referent population and were associated with current levels of 2,3,7,8-TCDD ($p = 0.062$), but not the back-extrapolated level (Ott et al., 1994). In the NIOSH study, 9.3% of workers and 7.0% of age-matched comparisons met the case definition for diabetes. Although 60% of workers with serum 2,3,7,8-TCDD concentrations above 1,500 pg/g lipid met the case definition for diabetes, prevalence of diabetes mellitus was not related to serum 2,3,7,8-TCDD concentrations (Calvert et al., 1999). However, adjusted mean serum glucose levels (5.45 mmol/l, $p<0.03$) were significantly elevated for workers with half-life extrapolated 2,3,7,8-TCDD concentrations between 1,860 and 30,000 pg/g lipid.

Results from the Ranch Hand study (Henriksen et al., 1997) suggest that serum 2,3,7,8-TCDD levels may be positively and significantly related to diabetes and 2-hour postprandial glucose levels. Every participant who underwent at least one examination (1982-1992) was considered for inclusion in this analysis. Diabetic status was assessed by measuring 2-hour postprandial glucose and by using a case definition of diabetes. Diabetes was defined as having a verified history of diabetes mellitus by diagnosis or an oral glucose tolerance test of $\geq$11.1 mmol/L (200 mg/dL). In this analyses, the cohort was categorized by current and half-life extrapolated serum 2,3,7,8-TCDD concentrations (in pg/g lipid): Comparisons current < 10; Ranch Hands—background current < 10, low 10 < current and half-life extrapolated < 94, high 10 < current and half-life extrapolated > 94. Median serum 2,3,7,8-concentrations in pg/g lipid for the Ranch Hand groups are: low: 15.0 (range 10.0 - 26.6); high: 46.2 (range 18.0 - 617.8). Risk of diabetes mellitus was moderately increased for both low (RR = 1.3, 95% CI = 1.0-1.7) and high (RR = 1.5, 95% CI = 1.2-2.0) groups but not for the background group. For Ranch Hands participating in the 1992 examination, the risk for being classified as having an impaired fasting glucose level (140 mg/dl-200 mg/dl based on the 2-hour postprandial glucose test) was also moderately increased for the high group (RR = 1.6, 95% CI = 1.2-2.2). The data also suggest that Ranch Hands in the high group have a shorter time to diabetes onset and are more likely to use some kind of control for their diabetes, with a greater percentage using oral medication.

The outcome measures used in the Ranch Hand study, presence of diabetes, 2-hour postprandial, and fasting, did not permit a determination of the type of diabetes involved. However, it shows that nondiabetic Ranch Hands with higher current (>10 pg/g lipid) or past (>94 pg/g lipid half-life extrapolated) serum 2,3,7,8-TCDD concentration may be at a slightly greater risk for developing diabetes than individuals with background levels of 2,3,7,8-TCDD. These individuals also appear to have a greater prevalence of elevated fasting glucose levels, which may be a precursor to conversion to a diabetic state.

Mortality from diabetes was assessed in the NIOSH and IARC occupational cohorts (Steenland et al., 1999; Vena et al., 1998) and among adult residents of zones A, B and R in Seveso, Italy (Pesatori et al., 1998). In the NIOSH cohort, mortality due to diabetes was slightly but nonsignificantly elevated when considering diabetes only as an underlying cause of death (SMR = 118, 95% CI = 77-173) or if there was any mention of diabetes on the death certificate (multiple causes of death analysis) (SMR=89, 95% CI = 87-133). The results were the same in a cohort of 608 workers with chloracne (SMR=106, 95% CI = 29-271). When compared to an internal control group, there was a inverse dose-response relationship between mortality from diabetes and exposure score.

In the subset of workers in the IARC cohort exposed to 2,3,7,8-TCDD or chlorophenols N=13,831), there were modest, nonsignificant elevations in the risk of death from diabetes controlling for any workplace exposure to TCDD/HCDD (RR = 2.25, 95% CI = 0.53-9.50 N = 33) for duration of exposure (RR = 2.52, 95% CI = 0.89-7.11, N = 10 for 10-19 years), time since first exposure (latency) (RR = 2.34, 95% CI = 0.56-9.83, N = 14 for 10-19 years) and year of first exposure (1955-1964, 1965+) (RR = 1.76, 95% CI = 0.58-5.31, N = 10 for 1965+) using Poisson regression analysis.

In the Seveso cohort, very modest, statistically significant elevations in mortality from diabetes were observed only in females of zones B (RR = 1.9, 95% CI = 1.1-3.2, N = 13) and R (RR = 1.2, 95% CI = 1.0-1.6, N = 74) but not in females of zone A or males from any zone (Pesatori et al., 1998). Among males, statistically nonsignificant increased mortality was seen in zone B (RR = 1.3, 95% CI = 0.6-2.9) and in zone R (RR = 1.1, 95% CI = 0.8-1.6). No deaths from diabetes occurred in males of zone A. Given the small number of individuals in zone A, there is little power to detect an effect of TCDD exposure on mortality from diabetes.

Analysis of the risk of alteration in glucose metabolism among individuals exposed only to environmental levels of 2,3,7,8-TCDD was conducted using subjects who participated as comparisons in the 1992 examination phase of the Ranch Hand study (Longnecker and Michalek, 2000). Diabetes prevalence and serum insulin and glucose levels were compared to serum 2,3,7,8-TCDD concentration. Median serum 2,3,7,8-TCDD concentration was 4.0 ng/kg (or 4 pg/g) lipid, which included 108 subjects with levels below the limit of detection and who were assigned a level of 0.625 mg/kg. Multivariate regression analysis (adjusted for age, race, body mass index, waist size, family history of diabetes, body mass index at the time the dioxin was measured, military occupation, and triglycerides) suggests a slight increase in prevalence of diabetes with increasing 2,3,7,8-TCDD serum concentration; however, the risk did not rise monotonically with increasing serum concentration. All odds ratios calculated were compared to subjects in Quartile 1 who had < 2.8 ng/kg [Quartile 2, 2.8 - <4.0 ng/kg, OR 0.91, 95% CI = 0.50-1.68; Quartile 3, 4.0 - <5.2 ng/kg, OR 1.77 95% CI = 1.04-3.02; Quartile 4, < 5.2 ng/kg OR 1.56, 95% CI = 0.91-2.6]. Similar results were found when comparing serum 2,3,7,8-TCDD level and the estimated change in level of insulin: [Quartile 2, 2.8 - <4.0 ng/kg, 0.13, 95% CI = 0.00-0.25; Quartile 3, 4.0 - <5.2 ng/kg, 0.11 95% CI = -0.02 - 0.24; Quartile 4, < 5.2 ng/kg 0.14, 95% CI = 0.01-0.27].

7.13.6.1. *Comment*

Results of the available epidemiologic studies provide a patchwork of evidence that limits a conclusion of a strong causal relationship between occupational or environmental exposure to

2,3,7,8-TCDD and alterations in glucose metabolism. Diabetes is a particularly difficult outcome to study using the designs described above. Although the cross-sectional studies attempted to limit methodologic biases by using standard case definitions for diabetes and eliminating cases that occurred prior to exposure, cases that did not participate in the study or died prior to the study were lost to the analysis. This may have the effect of depressing the outcome measure, which may have been the case in the NIOSH study (Calvert et al., 1999). Mortality studies commonly miss diabetes as a cause of death because the many potentially fatal conditions manifested as a result of the diabetes are recorded as the primary cause of death. This should not introduce differential bias into the study because it is assumed that the death certificates of both the worker and comparison populations are treated in the same way. Steenland et al. (1999) attempted to remedy this problem by including in the analysis all recorded causes of death, yet they did not find excess mortality from diabetes among workers, even the group thought to be more highly exposed. This approach, called "multiple cause of death analysis" was not used in the analysis of the IARC or Seveso cohorts. In addition, it appears that in none of the above mentioned mortality studies was onset of diabetes in relationship to exposure considered in the analysis. Therefore, workers whose onset of diabetes occurred prior to exposure were included in the analysis, potentially overestimating the risk of exposure.

Furthermore, the patchwork of findings may also be attributed, in part, to the heterogeneous etiology of diabetes and, perhaps, the interrelationship between the intrinsic factors and exposure to 2,3,7,8-TCDD .

In addition, the National Academy of Sciences' Institute of Medicine (IOM) conducted a review of the scientific evidence on the relationship between exposure to 2,3,7,8-TCDD and Type 2 diabetes (IOM, 2000). In this review, the committee examined the results of four mortality studies of chemical workers (Steenland et al, 1999; Vena et al, 1998) and Seveso residents (Pesatori et al., 1998) and also morbidity studies of chemical workers (Calvert et al., 1999), Ranch Hands (Longnecker and Michalek, 2000; Air Force Health Study, 2000) and Vietnam veterans from Australia (Commonwealth Department of Veterans' Affairs, 1998a,b). The committee concluded that based on the collective evidence of the data and not on a single study that ". . . there is limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type 2 diabetes." They also noted that the observed increased risk of Type 2 diabetes in Vietnam veterans related to herbicide exposure was small and that, in this population, known risk factors, including family history, obesity and physical inactivity were more strongly related to the prevalence of diabetes.

7.13.7. Immunologic Effects

7.13.7.1. *Adult Effects*

Animal toxicologicalal studies have demonstrated numerous immunologic effects after exposure to 2,3,7,8-TCDD (see Chapter 4 for a more comprehensive review). In humans, the information with which to assess the immunologic consequences of exposure is sparse. A number of epidemiologic studies and one case report have described the immunologic function of populations exposed to 2,3,7,8-TCDD (Evans et al., 1988; Hoffman et al., 1986; Webb et al., 1989; Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991; Jennings et al., 1988; Reggiani, 1978; Ott et al., 1994; Tonn et al., 1996; Ernst et al., 1998; Halperin et al., 1998; Jung et al., 1998; Michalek et al., 1999). One study of extruder personnel exposed to brominated dioxins and furans was also reported (Zober et al., 1992).

Evaluation of the immunologic status in exposed residential populations has not found a relationship between exposure and impaired status. Immunocompetence was tested twice in 44 children who were residents of the region of Seveso with the highest 2,3,7,8-TCDD contamination and in 43 age-matched children who did not reside in the contaminated area (Reggiani, 1978). Twenty of the exposed children had chloracne and 24 had no skin lesions. The tests included serum immunoglobulins, complement levels, lymphocyte subpopulations, and lymphocyte activity analysis. Although no data were presented, the authors reported that the various measures were within normal range and that there was no difference between the two groups.

Initial studies of Missouri residents who had the potential for exposure to 2,3,7,8-TCDD-contaminated soil suggested that 2,3,7,8-TCDD caused depression in cell-mediated immunity (delayed hypersensitivity), as demonstrated by a statistically significant increase in anergy (exposed vs. nonexposed: 11.8% vs. 1.1%) (Hoffman et al., 1986). This study, however, was limited by the exclusion from test results of 61% and 32% of the exposed and unexposed groups, respectively. A follow-up study confirmed the presence of substantial bias in the first study. Evans et al. (1988) retested 28 of the 50 exposed residents and 15 of the 27 unexposed residents who did not respond (anergic) or responded weakly (relatively weakly) to an antigen challenge in the first study. A follow-up study could not confirm the presence of anergy. Both studies found in the exposed residents increased frequencies in CD4/CD8 ratio of less than 1.0 (Table 7-34). No other abnormalities were noted by Hoffman et al. (1986) (Tables 7-35 to 7-40).

In a later study of Missouri residents, Webb et al. (1989) found no clinical evidence of immunosuppression in 40 individuals whose adipose 2,3,7,8-TCDD levels ranged from under 20 pg/g to over 430 pg/g (top of range not given). Tests included serum immunoglobulins, T-cell surface markers OKT3, OKT4, OKT8, OKT11, Leu11c, CD4/CD8 ratio, (CD4 + CD8)/CD3, and B1 and B2 cells. In logistic regression, significant (p<0.05) relationships were noted for IgG,

%CD3, %T11, %CD8, and %CD4 + LEU8 POS, controlling for age and sex (Tables 7-35 to 7-40).

The effect of past occupational exposure on immunologic function was examined in 18 British workers who were evaluated 17 years after accidental industrial exposure to chemicals contaminated with 2,3,7,8-TCDD (Jennings et al., 1988). It is not clear from the article when occupational exposure to 2,3,7,8-TCDD ended for these workers. Exposed workers and unexposed controls were matched for age, race, sex, smoking habits, alcohol consumption, and percent of ideal body weight. There were no significant differences in the levels of immunoglobulins, T and B lymphocytes, responsiveness to phytohemagglutinin A, and in the number of CD4 and CD8 counts. Three measures were found to be statistically significantly ($p<0.05$) higher in workers than in controls: antinuclear antibodies (ANA) (8 workers vs. 0 controls, $p<0.01$) (when Hep2 cells were used as substrate but not when rat liver cells were used), immune complexes (workers = 11 vs. 3 controls, $p<0.05$), and natural killer cells (NK) (workers = 0.21×10^6/L vs. controls = 0.59×10^6/L, $p<0.002$) identified by the monoclonal antibody Leu-7 (Table 7-41). No evidence of a consistent relationship between dioxin exposure and immune system alteration, as indicated by antinuclear antibodies, were found in the Ranch Hands Study (Michalek at al., 1999). In the discussion, the authors could not explain the physiologic basis of their findings and suggested that further research was needed.

Among participants in the BASF accident study cohort, with the exception of natural killer cells and helper-inducer cells, the proportions of some lymphocyte populations (B cells, T-cells, T helper cells, T suppressor cells) were lower among workers, but the distribution of cells in referents and workers was equivalent (Ott et al., 1994). Levels for IgA, IgG, IgM, and complement C4 and C3 were slightly higher in workers than in the unexposed referent population. There also appeared to be slight dose-related increases in IgA, IgG, and complement C4 with 2,3,7,8-TCDD levels measured in October 1988 and February 1992. IgA and IgG were related to the half-life extrapolated 2,3,7,8-TCDD levels. It must be noted, however, that the statistically significant relationship between IgA and 2,3,7,8-TCDD is most likely due to a case of liver cirrhosis and the association with IgG due to a liver carcinoma.

Eleven German workers, exposed to chemicals contaminated with 2,3,7,8-TCDD and other polychlorinated dioxins between 1966 and 1976 during production of 2,4,5-T or maintenance activities were studied by Tonn et al. (1996). Between 1989-1992, serum 2,3,7,8-TCDD concentrations were measured. The levels ranged from 43 to 874 pg/g lipid. No differences were noted between the exposed and control groups for the lymphocyte subsets tested or response to mitogen stimulation. However, in TCDD-exposed workers, the response of T-cells to irradiated stimulator cells or IL-2 was statistically significantly decreased.

In the NIOSH study, measures of immunologic status and function were evaluated (Halperin et al., 1998). Of all the parameters examined, only a slight decrease in the number and

proportion of activated T-cells appeared to be related to 2,3,7,8-TCDD serum concentration: CD3/Ta1 k/mm^3 (number of activated cells) (TCDD 52-125 pg/g, OR = 2.7, 95% CI = 1.4-1.5; TCDD 126-297 pg/g, OR = 2.6, 95% CI = 1.4-4.9; TCDD 298-3389 pg/g, OR = 2.4, 95% CI = 1.3-4.6), and CD3/Ta1 (%) (TCDD 52-125 pg/g, OR = 2.5, 95% CI = 1.3-4.8; TCDD 126-297 pg/g, OR = 2.3, 95% CI = 1.2-4.3; TCDD 298-3389 pg/g, OR=2.4, 95% CI = 1.3-4.5).

Jung et al. (1998) and Ernst et al. (1998) evaluated the immunologic status and function of workers exposed to PCDDs and PCDFs during production of 2,4,5-T and other chlorophenols. The cohort of exposed workers was previously described by Flesch-Janys et al. (1992). Jung et al. (1998) included all 192 workers in their analysis. The median serum TCDD concentration of this group was 36.1 pg/g lipid, with a range from 1.2 to 893.2 pg/g lipid. With the exception of a significant negative correlation between $CD3^+/CD8^+$ cells and logTEQ, no other parameters were found to be exposure-related.

Workers included in the analysis by Ernst et al. (1998) had a median serum TCDD level of 217 pg/g lipid, ranging from 33.6 to 2,732 pg/g lipid. The serum TCDD concentrations in the 28 age-matched control approximated normal at 4 pg/g lipid. Exposed subjects worked a minimum of 7 years in the tricholorophenol and 2,4,5-T departments. Compared to controls, the exposed group had significantly increased proportions of $CD8^+CA45R0^+$ (cytotoxic memory T-cells) and activated $CD8^{dim}CA57^+$, and a significantly lower number of lymphocytes with naive phenotype $CD45R0^+$. The authors also report that interferon release in diluted whole-blood cultures, but not in isolated peripheral blood mononuclear cells, was statistically significantly decreased in TCDD-exposed workers.

Among the 21 extruder personnel exposed to both 2,3,7,8-TBDD and 2,3,7,8-TBDF, of the 16 parameters tested, only complement C4 was statistically significantly ($p<0.01$) associated with concentrations of 2,3,7,8-TBDD and 2,3,7,8-TBDF (Zober et al., 1992). Borderline associations were noted between 2,3,7,8-TBDF and decreases in total lymphocyte count ($p = 0.056$), T-cell count ($p = 0.045$), T-helper cell count (CD4) ($p = 0.045$) and an increase in complement C3 (0.054), and between 2,3,7,8-TBDD and a decreased percent lymphocyte count ($p = 0.054$). However, with the exception of complement C3, the associations appear to be driven by a single individual with the highest 2,3,7,8-TBDD levels (478 pg/g of lipid) who, at the time of the study, exhibited no evidence of clinical immunodeficiency.

Two studies extensively evaluated immunologic function in Vietnam veterans. No significant differences were noted among U.S. Army ground troops and the comparison population in lymphocyte subset populations, T-cell populations, or serum immunoglobulins (Tables 7-34 to 7-40) (Centers for Disease Control Vietnam Experience Study, 1988a). Comprehensive immunologic profiles were developed for each participant of the U.S. Air Force Ranch Hand Study (Tables 7-34 to 7-40) (Roegner et al., 1991). Significant positive associations

were found between IgA and serum 2,3,7,8-TCDD. The authors suggest that the rise in IgA is consistent with a subclinical inflammatory response, but the authors could not explain the source of the inflammatory response. In analysis of the 1992 examination round, Michalek et al. (1999) found no relationship between category of serum TCDD concentration and immunologic changes. The study population was classified by median serum TCDD concentration: Comparison: 4.0 pg/g lipid, range 1-10 (current level); Ranch Hand background: 5.7 pg/g lipid, range 1-10 (current level); Ranch Hand low: 52.8 pg/g lipid, range 28-94 (half-life extrapolated); Ranch Hand high: 194.7 pg/g lipid, range 94-3,290 (half-life extrapolated). Of all the tests performed, only prevalence of an abnormal skin test, represented as a composite score and the proportion of CD20 cells in the background group, and the absolute count for $CD16^{+}CD56^{+}CD3^{-}$ were significantly different than the referent population.

7.13.7.1.1. ***Comment***. The information on immunologic function in humans, children or adults, relative to exposure to 2,3,7,8-TCDD is scarce. All but one of the epidemiologic studies are restricted to adults and do not describe a consistent pattern of effects among the studies. Natural killer cells (NK) were increased among one population of 2,3,7,8-TCDD chemical workers examined 17 years after exposure ended (Jennings et al., 1988). These findings were not corroborated in Ranch Hands (Roegner et al., 1991; Michalek et al, 1999), the BASF accident cohort (Ott et al., 1994), the NIOSH cohort (Halperin et al., 1998), the Hamburg cohort (Jung et al., 1998; Ernst et al., 1998), or workers exposed to 2,3,7,8-TBDD and TBDF (Zober et al., 1992). Dose-related elevations in IgA were observed in Ranch Hands in relation to current levels and in the BASF accident cohort with respect to both current and half-life extrapolated 2,3,7,8-TCDD levels. Yet, IgA was not higher in adult Missouri residents with adipose 2,3,7,8-TCDD levels above background (Webb et al., 1989). IgG was also significantly related to 2,3,7,8-TCDD in the BASF accident cohort but not in Ranch Hands (Michalek et al., 1998). While complement C3 and C4 were elevated in both the BASF accident cohort and the extruder personnel, no other study examined these endpoints.

The effect of acute, high exposure to 2,3,7,8-TCDD among children from Seveso was reportedly negative within 2 years after exposure (Reggiani, 1978). Although no data have been published illustrating the values obtained from the tests of immunologic function in these children, the author indicates that the measured parameters were no different in the exposed and unexposed children after two series of tests.

More advanced functional analyses have been conducted relating to the ability of T-cells to respond to intercellular stimulators such as the interleukins and interferon (Tonn et al., 1996; Ernst et al., 1998). These studies are suggestive of a decreased ability of T-cells to respond in individuals more heavily exposed to PCDDs and PCDFs. More work needs to be done in

similarly exposed populations to confirm these findings and to determine the mechanism of action.

More comprehensive evaluations of immunologic function with respect to 2,3,7,8-TCDD exposure are necessary to assess more definitively the relationships observed in nonhuman species. Longitudinal studies of the maturing human immunologic system may provide the greatest insight, particularly because animal studies have found many of their significant results in immature animals and breast milk is a source of 2,3,7,8-TCDD and other related compounds. Additional studies of highly exposed adults may also shed light on the effects of long-term chronic exposures. Therefore, there appears to be too little information to suggest definitively that 2,3,7,8-TCDD, at the levels observed, is an immunotoxin in humans.

7.13.7.2. *Developmental Effects*

One report (Weisglas-Kuperus et al., 1995) has examined direct and surrogate measures of immune status in 207 babies in Rotterdam (study described in detail in Section 7.12.2.3.). The surrogate measures were derived from questionnaires given to the mothers, covering incidence of rhinitis, bronchitis, tonsillitis, and otitis in children up to 18 months of age. Almost all of the children (205) were immunized against measles, rubella, and mumps; the children's antibody levels to these were used to assess humoral antibody production. For the purposes of this report, cord bloods from 48 of these children were analyzed to assess prenatal TEQ levels; at age 3 months, 47/48 bloods were drawn from the original group, with another child, randomly selected, added to this group. At 18 months, 37 of the original children gave blood, and 6 other children, randomly selected, were added to this group. In these samples, the following were measured: monocytes, granulocytes, and lymphocytes in whole blood; lymphocyte subpopulations were determined using monoclonal antibodies. No relationship was found between pre- and postnatal total TEQ levels and respiratory tract symptoms (i.e., number of periods with rhinitis, bronchitis, tonsillitis, and otitis) or humoral antibody production at 18 months to vaccination against mumps, measles, and rubella at 14 months. A higher prenatal exposure, estimated by cord blood levels, was associated with alterations in T cell subsets, with an increased number of $TcR\gamma\delta^+$ T cells; increased total numbers of T cells, $CD8^+$ cells, and $TcR\gamma\delta^+$ T cells at 18 months of age were associated with higher TEQ levels (Table 7). Higher TEQ levels were also associated with a decreased number of monocytes (Total TEQ, Dioxin-furan TEQ, mono-ortho PCB TEQ, and Di-ortho PCB TEQ) and granulocytes (Total TEQ only) at 3 months. All values were found to be within clinically "normal" ranges. The authors suggested that the subtle changes in the number of blood leukocytes do not necessarily mirror alterations in the cell composition of lymphoid and nonlymphoid organs, nor do they necessarily reflect functional defects (Weisglas-Kuperus et al., 1995).

In an update to the report described above (Weisglas-Kuperus et al. 2000), 193 children were examined at 42 months of age. Questionnaires were completed for 175, including questions on infection and allergic disease in the children. Blood samples were collected on a subsample of 85 children, limiting data on concurrent PCB levels (PCBs 118, 138, 153, 180) in plasma and immunologic marker analyses in lymphocytes. Examination of questionnaire reports of infectious diseases and allergies, only reduced levels of "attacks of shortness of breath with wheeze was associated with prenatal PCB exposure (n=175; OR=0.44; 95% CI: 0.18-0.99); more associations were observed with current PCB levels (n=85): increases in recurrent middle ear infections (OR=3.05; 95% CI: 1.17-7.98); chicken pox (OR=7.63; 95%CI:1.21-48.54); and reduced allergic reactions (OR=0.01; 95%CI:0.01-0.37). Dioxin-furan TEQ at birth was associated with increased coughing, chest congestion, and phlegm (OR=1.06; 95%CI:1.00-1.11). Total PCB levels at 42 months were significantly lower for formula fed children (0.21 ug/l versus 0.75 ug/l, $p<0.05$); however, no significant differences were observed for recurrent middle ear infections, chicken pox or allergic reaction. Interestingly, when these were examined by duration of breast feeding, infections and chicken pox were lower and allergic reactions were higher with longer breast feeding (all were borderline non-significant at p=0.06 or 0.07), even though the total PCB levels at 42 months were over 70% higher (not significant). Positive associations were observed between the total PCB levels at birth (cord blood, maternal blood or both) and lymphocytes, CD3+, CD3+CD8+, CD4+CD45RO+, and CD3+HLA-DR+ T-cells; no associations were observed with the current PCB levels or with the dioxin-furan TEQ at birth. The authors concluded that effects of perinatal exposures persist, and are associated with a greater likelihood of infectious disease but less likelihood of allergic conditions. In addition, they concluded that the benefits of longer periods of breast feeding helped to counteract the effects of exposure.

7.13.7.2.1. ***Comment***. These data suggest some long term effects are occurring. Repeating these investigations in other groups would be informative.

7.13.8. Neurologic Effects

Although there are few studies reporting neurologic abnormalities related to 2,3,7,8-TCDD exposure in adult animal models, neurologic effects are reported to have occurred shortly after exposure in occupationally exposed individuals (Ashe and Suskind, 1950; Baader and Bauer, 1951; Bauer et al., 1961; Goldman, 1972; Jirasek et al., 1974; Oliver, 1975; Pocchiari et al., 1979) (Table 7-43) and in Seveso residents (Filippini et al., 1981) (Table 7-44). Previous case reports and studies found symptoms referable to the central (CNS) and peripheral (PNS) nervous systems among workers and community residents exposed to 2,3,7,8-TCDD-contaminated materials. Although human studies reveal a wide spectrum of effects due to 2,3,7,8-TCDD

(Sweeney et al., 1989), very few toxicological studies have focused on the nervous system. Singer et al. (1982) reviewed the following animal studies, which examined the relationship of CNS dysfunction and 2,3,7,8-TCDD exposure: Elovaara et al. (1977) found anomalous CNS function in some rats exposed to a single dose of 2,3,7,8-TCDD, and Creso et al. (1978) reported CNS symptoms of irritability, restlessness, and increased aggression in rats administered 2,3,7,8-TCDD.

7.13.8.1. *Adult Neurobehavioral Assessments*

Numerous case reports cite symptoms referable to the nervous system occurring after acute exposure among occupationally exposed individuals (Creso et al., 1978; Ashe and Suskind, 1950; Suskind et al., 1953; Goldman, 1972), as well as chronic exposure to 2,3,7,8-TCDD-contaminated materials (Oliver, 1975; Baader and Bauer, 1951; Kimmig and Schulz, 1957a,b; Bauer et al., 1961; Poland et al., 1971). Symptoms include headache (Ashe and Suskind, 1950; Bauer et al., 1961; Jirasek et al., 1974; Oliver, 1975; Kimmig and Schulz, 1957a,b; Poland et al., 1971), insomnia (Ashe and Suskind, 1950; Suskind et al., 1953; Oliver, 1975; Kimmig and Schulz, 1957a,b), nervousness or irritability (Ashe and Suskind, 1950; Suskind et al., 1953; Bauer et al., 1961; Oliver, 1975), depression and anxiety (Bauer et al., 1961; Jirasek et al., 1974), loss of libido, and encephalopathy (Jirasek et al., 1974; Kimmig and Schulz, 1957a) (Table 7-43).

Some reports indicate that symptoms referable to the CNS and PNS may persist in some exposed individuals for as long as 25 years (Suskind et al., 1953; Poland et al., 1971; Jirasek et al., 1973; Jirasek et al., 1974; Creso et al., 1978; Ashe and Suskind, 1950; Suskind et al., 1953). In 1953, Suskind et al. reported a variety of CNS-related symptoms in 36 workers from a plant in Nitro, West Virginia, who had developed chloracne and other symptoms after exposure to contaminants subsequent to a TCP reactor explosion in March 1949 (N = 11) or during normal production process of TCP and 2,4,5-T (N = 25) between 1948 and 1953 (Suskind et al., 1953). Such symptoms reported among this relatively young group (average age = 36 years, range = 22-63 years) included fatigue (N = 21), nervousness and irritability (N = 17), and decreased libido (N = 13). No attempt was made to determine whether these symptoms also occurred among exposed individuals without chloracne or among the nonexposed plant population.

Between 1968 and 1969, Jirasek et al. (1974) “observed very closely” (by clinical evaluation) a group of 55 workers exposed to 2,3,7,8-TCDD in the production of 2,4,5-T, hexachlorobenzene, and pentachlorophenol. As described in the report, intoxication with 2,3,7,8-TCDD “occurred gradually from 1965 to 1968,” although further quantification of exposure is not described. Psychiatric examination revealed the following: severe neurotic symptoms (64%), neurasthenia syndrome with depressive component (11%), depressive syndromes (8%), pseudoneurasthenia syndromes in patients with arteriosclerosis of the CNS

(14%), and normal psychiatric examination (3%). One patient died at age 57 years with rapidly progressive dementia secondary to an atypical arteriosclerosis involving brain and other organs.

Ten years after the initial examination, Pazderova-Vejlupkova et al. (1981) evaluated the health status of 44 of the original 55 workers. They found the following on psychiatric examination: 58% continued to have neurotic symptoms without depressive or anxiety components, 18% developed severe neurasthenia syndromes with signs of dementia, and 24% were normal.

Poland et al. (1971) administered the Minnesota Multiphasic Personality Inventory (MMPI) to 52 male production workers who were exposed at that time to TCP, 2,4,5-T, 2,4-D, and other chemicals. Severity of acne correlated significantly with a high score on the hypomania scale of the MMPI. When production workers were compared with 17 presumably unexposed administrative workers, the two groups differed on only one MMPI symptom scale; exposed production workers scored higher on the hypochondriasis scale.

Table 7-45 describes the results of neurologic and neurobehavioral assessments of TCP production workers, Ranch Hands, and U.S. Army Vietnam veterans.

Moses et al. (1984) found a significant excess among workers with chloracne compared to those without lesions for the following symptoms: insomnia, decreased libido, and difficulties with ejaculation or erection. There was no difference between the two groups for the symptoms of fatigue, irritability, nervousness, depression, or personality changes.

In the study by Suskind and Hertzberg (1984), psychological symptoms were evaluated by interview and peripheral nerve function by nerve conduction velocity of the peroneal motor and sural sensory nerve fibers. The complaint of loss of libido was more frequent among exposed than unexposed, even after stratification by age. The complaint of nervousness, depression, or anxiety was not significantly related to exposure (16.3% vs. 11.7%) in the crude analysis, even though the sample size was sufficient to detect a twofold increase. However, in the group over 50 years old there was a significant exposure effect (19% vs. 6.4%) for the complaint of nervousness, depression, or anxiety. The complaint of impotence was significantly related to exposure in the crude analysis, but after stratification by age this effect disappeared.

The effects of exposure to 2,3,7,8-TCDD on measures of current symptoms of depression were evaluated (Alderfer et al., 1992) as part of the NIOSH cross-sectional medical study (Sweeney et al., 1989). Symptoms of depressed mood were measured by the Beck Depression Inventory and the depression subscale of the Self-Report Symptom Checklist-90-Revised (SCL-90-R). Neither serum 2,3,7,8-TCDD levels nor status as a worker was associated with depressed mood as assessed by either the Beck Depression Inventory or the SCL-90-R depression subscale (Alderfer et al., 1992). This finding supports the conclusion that current serum levels of 2,3,7,8-TCDD are not associated with current depression among a population of workers that was highly

exposed to TCDD. However, because this cross-sectional study was conducted many years after 2,3,7,8-TCDD exposure, this analysis could not address the question of whether 2,3,7,8-TCDD is associated with past depression that resolved before the study was performed. These findings are consistent with those of the U.S. Air Force study (Roegner et al., 1991) of personnel who applied Agent Orange during the Vietnam War: serum 2,3,7,8-TCDD was not associated with the depression subscale score of the SCL-90-R after controlling for covariates.

The Air Force study conducted neurologic and psychological assessments of the participating Ranch Hands and comparisons (Lathrop et al., 1984). In the first examination series published in 1984 (baseline), the psychological assessment included a self-report of psychological or emotional illness, the Diagnostic Interview Schedule (DIS), Cornell Medical Index (inventory of psychophysiologic symptoms), MMPI, Halstead-Reitan Battery (HRB), and Wechsler Adult Intelligence Scale (WAIS). In the 1987 follow-up examination, the psychological assessment included an interviewer-administered questionnaire in which each participant was asked about the occurrence of mental or emotional disorders and sleep disorders. The presence of posttraumatic stress disorder was based on a subset of questions from the MMPI; the WAIS IQ assessment was deleted and the Millon Clinical Multiaxial Inventory (MCMI) and the Symptom Checklist-90-Revised (SCL-90-R) were added (Lathrop et al., 1987).

Results of the 1984 baseline study revealed no difference between Ranch Hands and the comparison group for self-reported psychological or emotional illness. The DIS revealed significantly more fatigue, anger, erosion, and anxiety for high school-educated but not college-educated Ranch Hands. These outcomes were highly related to education. The Cornell Medical Index found 4 of 10 parameters abnormal for Ranch Hands: startle, psychosomatic, gastrointestinal nervousness, and anxiety. These parameters were inversely related to education level. On the MMPI, high school-educated Ranch Hands showed significant differences (more deficits) on subscales for hypochondria, masculinity/femininity, and mania/hypomania, but comparisons scored higher on the subscale for denial, a finding that might undermine the deficits noted for Ranch Hands. Again, MMPI scores were influenced by education level ($p<0.01$) but not exposure level. For both the HRB and WAIS, there was no difference between Ranch Hands and comparisons, and the scores were related to education level.

In the 1987 reanalysis with serum 2,3,7,8-TCDD (Roegner et al., 1991), there was no significant difference between groups or relationship with serum 2,3,7,8-TCDD levels on reported (and verified) data on lifetime psychological illness or sleep disorders or any SCL-90-R. Some of the MCMI parameters appeared to be related to serum 2,3,7,8-TCDD levels (significantly higher mean schizoid and schizotypal scores and significantly lower mean histrionic score in the group above 33.3 pg/g than in comparisons). However, these findings were inconsistent with similar variables in the SCL-90-R and the self-reported histories.

Comprehensive neurologic and psychological assessments were conducted on participants of the Vietnam Experience Study (Centers for Disease Control Vietnam Experience Study, 1988a, b). The neurobehavioral tests evaluated aptitude, concept formation and problem-solving, memory, manual dexterity, verbal skills, visuomotor skills, attention, and mental control. Among Vietnam veterans there was a significantly greater prevalence of alcohol abuse or dependence (Vietnam veterans, 13.7%; non-Vietnam veterans, 9.2%; OR = 1.5, 95% CI = 1.2-1.8), depression (Vietnam veterans, 4.5%; non-Vietnam veterans, 3.2%; OR = 2.0, 95% CI = 1.4-2.9), and a higher prevalence of poor psychological status (Centers for Disease Control Vietnam Experience Study, 1988b). The poor psychological status tended to be most prevalent in Vietnam veterans who were not white, who enlisted before their 19th birthday, and whose enlistment test scores fell below the group median.

In the study of residents of the Quail Run Mobile Home Park, neurobehavioral tests evaluated reaction time, mood, memory, visuo-motor coordination, intelligence, and indicators of psychological stress (Hoffman et al., 1986). Differences between Quail Run residents and controls were observed in the vocabulary subtest of the WAIS (Quail Run = 34.7, controls = 41.1, raw scores; $p<0.01$), tension/anxiety raw score (Quail Run = 13.7, controls = 11.1; $p<0.01$), and anger/hostility scale (Quail Run = 11.6, controls = 8.9; $p<0.05$) of the POMS inventory, and for the depression/dejection and fatigue/inertia scales (no data provided).

7.13.8.2. *Adult Neurologic Status*

On neurologic examination, 11 of 60 West Virginia workers with chloracne exhibited decreased sensitivity to pinprick, whereas none of the 34 subjects without chloracne had decreased pinprick sensation ($p<0.01$) (Moses et al., 1984). There were no other differences in performance of the neurologic examination noted in the text. When examined by Suskind and Hertzberg (1984), no significant differences were noted in the conduction velocities of either nerve fiber (sural sensory: exposed workers, mean = 42.06±0.49; unexposed workers, mean 41.49±0.54; peroneal motor: exposed workers, mean = 41.77±0.47; unexposed workers, mean = 42.62±0.52).

Among New Jersey and Missouri TCP workers, the overall neurologic status and peripheral nerve function were assessed for all 281 workers and 260 referents by self-reported medical history; neurologic examination; electrophysiologic tests of nerve conduction velocity, amplitude, and latency; and vibratory and thermal threshold (Sweeney et al., 1993). No differences in neurologic status or nerve function between workers or referents were detected. Additionally, although the mean serum 2,3,7,8-TCDD level in the workers was 220 pg/g, there was no relationship between neurologic function and levels of serum 2,3,7,8-TCDD.

The neurologic examination in the 1987 follow-up study evaluated cranial, CNS, and PNS function in participating Ranch Hands (Lathrop et al., 1987). In general, there was no difference in the prevalence of neurologic abnormalities in Ranch Hands and comparisons. However, Ranch Hands with serum 2,3,7,8-TCDD levels above 33.3 pg/g tended to have a higher proportion of individuals with abnormal coordination than the comparisons (Ranch Hands, 2.7%; comparisons, 0.4%; adjusted RR = 18.3, $p<0.001$) (Roegner et al., 1991).

Overall neurologic status of Army Vietnam veterans did not differ from that of non-Vietnam veterans (Vietnam veterans, 1.0%; non-Vietnam veterans, 0.8%; OR = 1.2, 95% CI = 0.6-2.3) (Centers for Disease Control Vietnam Experience Study, 1988b). Only self-reported symptoms related to nerve disorders were significantly more prevalent among Vietnam veterans than non-Vietnam veterans (Vietnam veterans, 8.2%; non-Vietnam veterans, 6.5%; OR = 1.2, 95% CI = 1.0-1.6).

Table 7-44 describes the results of neurologic and neurobehavioral studies of Seveso and Missouri residents. While three studies evaluated the neurologic status of residents of Seveso (Pocchiari et al., 1979; Filippini et al., 1981; Assennato et al., 1989), no studies evaluated neurobehavioral changes. In an effort to quantify exposure-related neurologic disorders among Seveso residents and among workers from the Icmesa plant, two government-sponsored screenings were conducted in 1977 and 1978 on 308 residents of Seveso and 200 workers. Among these workers, approximately 4% (N = 8) were found to have damage to nerve fibers of multiple (unspecified) nerves, controlling for confounding factors such as alcohol abuse, diabetes, kidney disease, and neurotoxic medication use (Pocchiari et al., 1979). The report did not describe the extent of worker exposure to 2,3,7,8-TCDD. Other potential neurotoxic occupational exposures do not appear to have been considered. Three workers were described as having polyneuropathies of the lower limbs.

In 1981, prevalence risk ratios (PRR) for neuropathy were calculated separately for the 308 Seveso residents (Filippini et al., 1981). PRRs for neuropathy were determined for residents who exhibited clinical indication of 2,3,7,8-TCDD exposure, defined as the presence of elevated liver enzyme levels (GGT, ALT, AST) (which are also indicative of nonspecific insults to the liver) or chloracne, and for those who exhibited conditions that are risk factors for neuropathy, e.g., alcoholism, inflammatory disease, diabetes, or potential occupational exposure to neurotoxins. Seveso residents who had clinical indication of 2,3,7,8-TCDD exposure (chloracne or elevated liver enzymes GGT, AST, ALT) or who had risk factors for neuropathy were found to have significantly greater prevalence of neuropathy than residents without either manifestation (PRR exposure = 2.8, 95% CI = 1.2-6.5; PRR for possible 2,3,7,8-TCDD-predisposing factors = 2.6, 95% CI = 1.2-5.6) (Filippini et al., 1981). Additional analysis showed that individuals who

met the definition for chloracne or abnormal levels of hepatic enzymes were significantly more at risk than residents without either condition.

Residents of Seveso who developed chloracne after the reactor release (N = 193) were invited to a series of three follow-up screenings in 1982-1983, 1983-1984, and 1985 (Assennato et al., 1989). A control group from a nearby but uncontaminated area was also examined. Conduction velocities of the median motor, peroneal motor, and sural sensory fibers were conducted in 1982-1983 and 1985 (Assennato et al., 1989). No increases in the prevalence of abnormal electrophysiologic measures were observed in the chloracne group when compared with controls without chloracne. In addition, there was no change in the conduction velocities for each fiber from the 1982-1983 to 1985 studies.

Quail Run residents reported significantly more "numbness" or "pins and needles" in the hands or feet (28.6%) than the controls (18.1%) ($p<0.05$), but there were no differences in mean threshold scores for the more objective neurosensory tests. Residents also reported more persistent severe headaches (Quail Run, 26.0%; control, 14.2%; $p<0.05$).

Participants in the study by Webb et al. (1989) did not complete neurobehavioral tests, but they were examined by a neurologist. The results were unremarkable. Of the 38 participants, two with levels above background had abnormal pinprick sensitivity ($\leq$20 pg/g, N = 2; 20-60 pg/g, N = 1; $\geq$60 pg/g, N = 1), three had abnormal vibration thresholds ($\leq$20 pg/g, N = 2; 20-60 pg/g, N = 1; $\geq$60 pg/g, N = 2), and four had abnormal reflexes ($\leq$20 pg/g, N = 2; 20-60 pg/g, N = 2; $\geq$60 pg/g, N = 2). The results of other components of the neurologic examination were not reported and are assumed to be normal.

7.13.8.2.1. ***Comment on adult studies.*** The overall results of these case reports and epidemiologic studies demonstrate that exposure to 2,3,7,8-TCDD-contaminated materials is associated with symptoms referable to the central and peripheral nervous systems shortly following exposure and, in some cases, lasting many years (Tables 7-44 and 7-45). Symptoms include fatigue, nervousness, anxiety, and decreased libido (Ashe and Suskind, 1950; Suskind et al., 1953; Oliver, 1975; Kimmig and Schulz, 1957a,b; Bauer et al., 1961; Jirasek et al., 1974). One case report found mania/hypomania on the MMPI (Poland et al., 1971). These symptoms are consistent with mood disorder. Although one study reported neurasthenia with signs of dementia lasting 10 or more years following exposure (Jirasek et al., 1974), the U.S. Air Force study of Vietnam veterans used neurobehavioral testing but was unable to demonstrate cognitive or other functional CNS deficits. However, this negative study did not investigate the relationship between serum 2,3,7,8-TCDD levels and neurobehavioral deficits. NIOSH investigated measures of depressed mood many years after exposure to 2,3,7,8-TCDD among production workers and

found no relationship between depressive symptoms and serum 2,3,7,8-TCDD levels (Alderfer et al., 1992).

Overall neurologic status of workers, community residents, and Vietnam veterans exposed to 2,3,7,8-TCDD and evaluated from 5 to 37 years after last exposure appears to be normal. These data suggest that, although exposure to 2,3,7,8-TCDD may have been extensive, as in the case of the exposed workers, Ranch Hands, and Seveso residents, and case reports describe many related symptoms, the effects may have been transient. If so, studies conducted years after the last exposure would not detect such changes. These results suggest that, in adults, no long-term neurologic effects were caused by even high exposure to 2,3,7,8-TCDD-contaminated materials. However, there is very little information with which to examine the effects of exposure on the developing human neurologic system.

7.13.8.3. *Developmental Neurobehavioral Effects*

Five recent reports from The Netherlands have examined neurologic/behavioral outcomes. Outcomes are summarized in Table 7-46. The overall design of these studies and the classification of biological exposure data are described in detail in Section 7.12.2.3.

A pair of studies examined the same group of children from Rotterdam (Table 7-46). These infants were tested for (1) psychomotor and mental development indices (PDI and MDI) based on the Dutch standardized verion of Bayley Scales of Infant Development (Koopman-Esseboom et al., 1996) at ages 3, 7, and 18 months; (2) Visual Recognition Memory Scores based on the Fagan Test of Infant Intelligence (Koopman-Esseboom et al., 1995b) at ages 3 and 7 months; and (3) use of the Prechtl neonatal neurologic examination (Koopman-Esseboom et al., 1995a) to classify infants (about 2 weeks of age) as to neurologic normality.

The first study (Koopman-Esseboom et al., 1995b) demonstrated a significant increase in the visual recognition memory test (Fagan Test of Infant Intelligence) for breast feeding and length of breast feeding when examined with maternal serum PCB levels. Neither the prenatal PCBs nor the non-dioxin-like PCBs in breast milk were associated with the Fagan outcome at either time period. In this report and another (Koopman-Esseboom et al., 1996), reported below, a cumulative score was developed for “low,” “medium,” and “high” exposure which multiplied the pg total PCB-dioxin-furan TEQ/g fat times weeks breast feeding (see Table 7-46). In the final regression analyses, significant differences were not observed for total PCB-dioxin-furan TEQ with outcomes at 3 months of age. However, at 7 months, there was a dose-related increase in scores with “medium” and “high” total PCB-dioxin-furan TEQ (Table 7-46). The authors suggested that these benefits resulted from (1) increased breast-feeding and (2) the high total PCB-dioxin-furan TEQ being an artifact of its correlation with the higher level of lipids or

lipophilic factors (e.g. hormones, long-chain polyunsaturated fatty acids [LCPUFAs]) beneficial to this aspect of development.

The second study (Koopman-Esseboom et al., 1996) observed a beneficial effect on PDI at 7 months of age (PDI-7) for breast feeding versus formula when the total PCB-dioxin-furan TEQ was low (Table 7-46). There were statistically significant deficits observed for PDI-7 in the regression analysis of "medium" levels of total PCB-dioxin-furan TEQ, and for medium and high levels of total PCB-dioxin-furan TEQ combined. MDI-7 showed a significant increase with duration of breastfeeding, but the total PCB-dioxin-furan TEQ did not have a significant effect. The other endpoints (MDI-3, PDI-3, MDI-18 and PDI-18) were not significantly associated with either duration of breast feeding or total PCB-dioxin-furan TEQ. In the analysis of prenatal PCB (using maternal blood levels collected late in pregnancy), PDI scores were lower at 3 months with higher PCB levels. The authors also examined thyroid hormone levels because they are necessary for brain development, and found no significant effects of thyroid hormone levels on PDI or MDI.

The third study (Koopman-Esseboom et al., 1995a) used the Prechtl neonatal neurologic examination to classify infants (about two weeks of age) as to neurologic normality: "normal," "mildly abnormal" (e.g., mild hypotonia or tremor), or "definitely abnormal" (e.g., hyper-excitability, hypotonia, hypertonia, or a hemisyndrome). Two infants in each location were classified as "definitely abnormal," and 20 total were classified as "mildly abnormal" (11 in Groningen and 9 in Rotterdam). One "definitely abnormal" child was eliminated from further analyses because of a birth trauma. Because of the small numbers, the remaining 23 children were grouped together and termed "neurologically abnormal." These groups were examined for obstetric optimality scores and thyroid levels (these thyroid levels were discussed in Section 7.13.4.2) and no significant findings were observed. The categorization of neurologically normal or abnormal, as expected, was highly correlated with the neurologic optimality scores (postural tone cluster and reflex cluster) (see Huisman et al., 1995a,b). The levels of coplanar PCB TEQ and total PCB-dioxin-furan TEQ were different in the two groups (Table 7-46). Only free T4 was significantly different in the two groups (total T3, total T4, free T4, and TSH were tested). The authors concluded that there was no signficant relationship of dioxins, furans, and PCBs with these "clinically relevant" outcomes and recommended follow-up of these children as they aged.

Two more studies examined the Rotterdam children and the Groningen children together (Table 7-46). These studies covered (1) neonatal neurologic development at 10-21 days post-birth (Huisman et al. 1995a) and (2) neurological condition at 18 months (Huisman, 1995b).

In the first report (Huisman et al., 1995a), infants were examined 10-21 days after birth, and several evaluations were made: (1) neonatal neurological condition (394 infants were normal, 20 suspect, and 4 abnormal); (2) Prechtl's Neurologic Optimality Scores (NOS), based on 21

items; and (3) these 21 items grouped to develop postural tone cluster scores and reflex cluster scores. The NOS and the cluster scores were then dichotomized for use in the statistical analyses: the NOS was divided at the median (a score of 57), the postural tone cluster score (less than or equal to 9 (43% of the children) versus greater than 9, and the reflex cluster score (less than or equal to 10 (22% of the children) versus greater than 10. Prenatal PCB measures (maternal blood and cord blood) were not associated with NOS or the clusters. Many individual PCBs, dioxins and furans in breast milk were associated with NOS (Table 7-46), as were most of the summary measures based on breast milk (total PCB-dioxin-furan TEQ, dioxin-furan TEQ, $\sum PCB_{breast\ milk}$, mono-ortho PCB TEQ, and di-ortho PCB TEQ.) Coplanar PCB TEQ was associated with hypotonia (measured through the postural tone cluster score): OR:1.64 (1.03-2.63). Because the data suggested observer differences in the two communities (by a shift in the distribution between them), analyses controlled for community. However, the scoring of the two observers was not compared for some common subjects.

The second report (Huisman et al., 1995b) examined the same groups of infants at 18 months of age. The infants were assessed during an observation of motor functions using techniques described by Touwen, Hempel, and colleagues (1992-3). Of the 418 children scored, 408 were considered "normal" and the remainder were "mildly abnormal" (9) or "abnormal" (1). Only the prenatal PCB exposure (estimated by either $\sum PCB_{cord}$ or $\sum PCB_{maternal\ blood}$) was associated with it at 18 months (Table 7-46) The authors observed an interaction with paternal smoking, so that the adverse outcome with exposure was observed only in children with nonsmoking fathers. The authors noted that maternal smoking was only collected during pregnancy, and so the association of maternal postnatal smoking could not be evaluated. None of the measures of PCB, dioxin, or furans were associated with the fluency cluster score, but breast-fed children in general did have a higher score than did formula -fed children.

These children were again assessed at 42 months of age (Patandin et al., 1999). In this round, 395 children (94% of the original study group) were assessed for cognitive abilities using the Kaufman Assessment Battery for Children (K-ABC), and a subgroup of 193 (the Rotterdam children) were assessed for verbal comprehension using the Reynell Language Developmental Scales (RDLS). $\sum PCB$ was calculated using PCBs (IUPAC numbers 118, 138, 153 and 180) from the mother's blood, cord blood, and plasma from the 42-month-old children. PCB, dioxin, and furan levels were available for the breast milk samples collected 2 weeks after delivery from breast-feeding mothers. Exposure metrics included $\sum PCB$, total TEQ (dioxin, furan and PCB), and the sum of 20 non-dioxin-like PCBs. Statistically significant deficits were associated with the natural log of the $\sum PCB_{maternal\ blood}$ for K-ABC for the entire group, and for those children who were formula fed. Significant deficits for the RDLS were noted only in the formula-fed children.

Analyses of the current body burden in the children were not associated with any cognitive deficits. Statistically significant changes were not observed in the breast-fed children, possibly because of the higher SES status, parental education, and parental verbal IQs. Another possibility is the beneficial effects of breast feeding in general.

7.13.8.4. *Comment on Developmental Studies*

One factor demonstrated in this series of studies is the benefit derived from breast feeding. Even though the level of environmental toxicants reaching the child through early dietary exposure may be greater with breast feeding, formula-fed children did not do as well overall on many behavioral and neurological measures in these studies. This may not be true with environmental "accidents," which could result in much higher levels to the child. These differences could also be attributed to the association of breast feeding with socioeconomic status of the households, parental education levels, etc.

A large number of dioxins, furans, and PCBs were evaluated at different developmental stages. Given the smaller volume in the collection of third-trimester blood from the mother and cord blood at birth, only four PCBs were measured (IUPAC 118, 138, 153, 180). Thus, prenatal dioxin-furan levels can only be approximated in these data. The statistically significant correlations between the different agents and biological sources suggest that it would be difficult to sort out effects of any individual group or class of agents.

In some of these studies, total breast-feeding time and breast milk levels were used to estimate the total exposure via breast feeding. This model is a reasonable relative estimate of broad categories, but may be problematic for estimation for women with widely different lengths of breast feeding. The levels in breast milk are likely to decrease over time, and the consumption of breast milk is likely to drop gradually as other food sources are increased. Thus the general levels of the broad groupings are useful, but the individual estimates should be used with caution.

Several of these studies based their results on crude (unadjusted) analyses. Given that there were significant differences between the breast-feeding parents and the bottle-feeding parents as to socioeconomic status (e.g., education, profession) and other lifestyle factors (e.g., smoking and drinking patterns), these results could change with a more in-depth analysis. The observation of hypotonia and prenatal PCB exposures is consistent with another study from the 1980s (Rogan et al., 1986). This study found effects of prenatal exposure (but not postnatal through breast feeding) on hypotonia, as did one of the Dutch studies (Huisman et al., 1995a). These associations with prenatal exposure have persisted up to 42 months of age (Patandin et al., 1999). These findings are consistent with findings of cognitive deficits in 11-year old children

exposed prenatally to PCBs in Michigan; as with the Dutch studies, deficits were not associated with exposures through breast feeding (Jacobson and Jacobson, 1996).

7.13.9. Circulatory System

The relationship between human exposure to 2,3,7,8-TCDD-contaminated chemicals and disorders of the circulatory system has been explored. A number of early case reports have described effects on the cardiovascular system among individuals reportedly exposed to chemicals contaminated with 2,3,7,8-TCDD. Myocarditis (Goldman, 1972), myocardial infarctions (Walker and Martin, 1979; Bauer et al., 1961), ectasia of the coronary arteries (England, 1981), and rapidly progressive atherosclerosis (Jirasek et al., 1974; Pazderova-Vejlupkova et al., 1981) have been reported.

Some of the earliest studies described mortality from diseases affecting the circulatory system among worker populations exposed to 2,3,7,8-TCDD (Bond et al., 1987; Coggon et al., 1991; Fingerhut et al., 1991b; Zober et al., 1990; Bueno de Mesquita et al., 1993; Bertazzi et al., 1989, 1992; Collins et al., 1993) (Table 7-47). The circulatory system includes ICD-9 codes 390-459 (International Classification of Diseases 9). Most early studies were designed primarily to test hypotheses relating to cancer and, secondarily, to characterize mortality compared to the general population from causes other than cancer, and without detailed characterization of confounders related to the circulatory system.

In many of the earlier studies, mortality from all diseases of the circulatory system among TCP production workers was similar to or less than mortality in the general population, as described by an SMR of 100 (Table 7-47). Examples include The Netherlands (Plant A) (SMR = 98, 95% CI = 65-142) (Bueno de Mesquita et al., 1993); the United States (Nitro, West Virginia) (SMR = 90, 95% CI = 80-100) (Collins et al., 1993); and Great Britain (SMR = 116, 95% CI = 91-146) (Coggon et al., 1991). In studies of workers with chloracne, mortality from circulatory diseases was decreased in U.S. workers (SMR = 95, 95% CI = 79-113 (Bond et al., 1987), and moderately increased in German workers, SMR = 121, 90% CI = 83-170 (Zober et al., 1990). In the follow-up study of the same cohort of German workers with chloracne —data not presented— this excess disappeared (Ott and Zober, 1996a).

More recent studies, many of which are updates of earlier reports (Flesch-Janys et al., 1995, Ott and Zober, 1996a; Hooiveld et al., 1998; Vena et al., 1998; Steenland et al., 1999), more thoroughly examined mortality from noncancer endpoints, including diseases of the circulatory system. In these studies, researchers employed more sophisticated analytical methods, such as adjustment for confounders, use of internal control groups, and measurement or estimation of

exposure to 2,3,7,8-TCDD or related compounds to refine calculated risk estimates for mortality from diseases of the circulatory system and other outcomes.

In a cohort of German chemical workers (Hamburg) who manufactured 2,4,5-TCP, and 2,4,5-T and chemicals contaminated with higher chlorinated PCDDs and PCDFs (Flesch-Janys et al., 1995), mortality for all circulatory diseases was positively related to estimated 2,3,7,8-TCDD concentrations and significantly related to estimated total TEQ concentrations above 39 ng/kg, lipid adjusted. Lipid-adjusted 2,3,7,8-TCDD concentrations and total TEQ estimates for the cohort were based on PCDD and PCDF measurements of 190 male workers.

In contrast, Ott and Zober (1996a) found no dose-dependent relation between estimated 2,3,7,8 -TCDD dose and mortality from diseases of the circulatory system (Conditional risk ratio = 0.93, 95% CI = 0.70, 1.24) when adjusted for cigarette smoking, body mass index, and age in workers from Ludwigshafen, Germany. Similarly, Vena et al. (1998) found significant deficits in mortality from circulatory diseases (SMR = 94, 95% CI = 88, 99) among workers in the expanded IARC international cohort exposed only to phenoxy herbicides and chlorophenols when compared to country-, gender-, age-, calendar period-, and cause-specific national death rates using the World Health Organization Mortality Data Bank. However, when compared to an internal control group of workers not exposed to TCDD/HCDD, mortality from all circulatory diseases among workers exposed to TCDD or HCDD was statistically significantly elevated (RR = 1.51, 95% CI = 1.17, 1.96). This significant increase occurred for workers exposed for 5-9 years and 10-19 years, but not for periods over 20 years.

In an update of the Dutch cohort, when compared to the general population (SMR = 100, 95% CI = 80, 140) or to an internal comparison group (adjusted RR = 1.4, 95% CI = 0.8, 2.5), little risk for mortality from circulatory disease was observed among the 549 workers exposed between 1955 and 1991 to 2,4,5-T; 2,4,5-TCP; and contaminants, or among the 140 workers exposed in a 1963 reactor release (SMR =110, 95% CI = 60, 170) (Hooiveld et al., 1998).

Mortality from more specific endpoints, such as ischemic heart disease, all heart diseases, and cerebrovascular disease, was noted in a few studies. The SMR from ischemic heart disease was decreased (SMR= 96, 95% CI = 51-164) in U.S. workers (Midland, Michigan) (Bond et al., 1987) and in German workers from Ludwigshafen (SMR = 70, 95% CI = 40-110) (Ott and Zober, 1996a). Overall mortality from ischemic heart disease was not elevated in a cohort of chemical workers from Hamburg, but it was significantly increased in workers only in the highest 2,3,7,8-TCDD quintile (RR = 2.48, 95% CI = 1.32-4.66). In an update of the Dutch cohort study through 1991, mortality from ischemic heart disease was elevated but did not achieve statistical significance (SMR = 190, 95% CI = 90-360) (Hooiveld et al., 1998). For the 29 workers with a

history of chloracne who were also exposed as a result of the 2,4,5-TCP reactor release, mortality was significantly elevated (SMR = 3.7, 95% CI = 1.4-8.1, N = 6).

For workers included in the IARC cohort exposed to phenoxy herbicides or chlorophenols, mortality from ischemic heart disease was decreased relative to the WHO comparison population (SMR = 97, 95% CI = 90-104) but significantly increased relative to an internal control group using Poisson regression (RR = 167, 95% CI = 123-226) (Vena et al., 1998). Using estimated cumulative exposure scores (Piacitelli et al., 1997), Steenland et al. (1999) found mortality from ischemic heart disease moderately increased with increasing exposure score, with an SMR = 93 in the lowest septile to an SMR = 123 for workers in the highest septile ($P_{\text{test for trend}} = 0.14$). In an analysis using Cox regression and an internal control group, only the rate ratio for the category with the highest exposure score (7^{th} septile) was statistically significantly elevated, the test for trend overall exposure score categories was statistically significant ($p = 0.5$). In the subcohort with chloracne mortality from ischemic heart disease was marginally increased (SMR = 117, 95% CI = 94-144).

Cerebrovascular disease mortality was increased by more than twofold in Michigan TCP production workers with chloracne (SMR = 208, 95% CI = 57,539) (Bond et al., 1987).
In an update of the 1993 study of Dutch TCP production workers (Bueno de Mesquita et al., 1993), mortality from cerebrovascular disease remained slightly elevated when compared both to the national population (SMR = 140, 95% CI = 60-260) and to an internal control group (SMR = 140, 95% CI = 40-510) (Hooiveld et al., 1998). Steenland et al. (1999) found a deficit of mortality from cerebrovascular disease in an update of the NIOSH cohort (SMR = 96, 95% CI = 74-121), as did Vena et al. (1998) in his study of nonneoplastic mortality in the IARC expanded cohort (SMR = 84, 95% CI = 71-98, international comparison population). When compared to the internal reference population, mortality was significantly elevated in the IARC expanded cohort (RR = 1.55, 95% CI = 0.83-2.28).

Mortality from IHD was lower than expected (SMR = 82, 95% CI = 0.67-1.02) in a cohort of 1,909 herbicide sprayers followed from 1972 through 1989. Workers eligible for study applied a mixture of 2,4-D and 2,4,5-T for 2 weeks or longer anytime during the period 1951-1971 (Asp et al., 1994). Similar trends were observed for other diseases of the circulatory system.

In veteran populations, among 1,261 Ranch Hand personnel, mortality from circulatory disease was nonsignificantly elevated (SMR = 110, 95% CI = 60-150) compared with that of a comparison population of 19,101 other Air Force veterans who were not exposed to herbicides (Michalek et al., 1990). These results were repeated in an updated mortality analysis (SMR = 105, 95% CI = 96-142) (Wolfe et al., 1994). After 15 years of followup, overall mortality from circulatory disease was as expected (SMR = 100, 95% CI = 70-130); only the SMR for enlisted

ground personnel, the subgroup with the highest dioxin levels, was greater than expected (SMR = 100, 95% CI = 90-150) (Michalek et al., 1998). Of the 118 total deaths, 3 were due to cerebrovascular disease (SMR = 2.7, 95% CI = not calculated). Similar nonsignificant increases in the relative mortality ratio (RMR) were observed for circulatory diseases (RMR = 1.6, 95% CI = 0.8-3.2) in Australian Vietnam veterans (N = 19,205; 260 deaths) compared to 25,677 (263 deaths) non-Vietnam veterans who served only in Australia (Fett et al., 1987). In contrast, the unadjusted relative risk of 0.49 (95% CI = 0.25-0.99) for all circulatory diseases suggested a deficit of deaths from this cause among 9,325 Vietnam Army veterans (246 deaths) compared to 8,989 non-Vietnam veterans (200 deaths) (Centers for Disease Control Vietnam Experience Study, 1988c).

Bertazzi and colleagues examined the mortality experience of Seveso residents ages 1-19 years (Bertazzi et al., 1992) and ages 20-74 years (Bertazzi et al., 1989) 10 years after the TCP reactor release. In the younger population, two deaths from circulatory diseases occurred only in female residents (RR = 1.63, 95% CI = 0.3-8.1). In the older population, circulatory disease mortality of residents from zone A (the most highly contaminated region) was elevated in both males (RR = 1.75, 95% CI = 1.0-3.2) and females (RR = 1.89, 95% CI = 0.8-4.2). In males, the highest death rate occurred during the first 5 years after the release, 1976-1981 (RR = 2.04, 95% CI = 1.0-4.2), and in females, the highest death rate occurred during the second 5 years post release, 1982-1986. As the authors suggest, the study was limited by a small number of subjects, a crude measure of 2,3,7,8-TCDD exposure, and a short followup period. The authors could not attribute the increased mortality from circulatory disease to 2,3,7,8-TCDD exposure, but suggested that the "high stress and pollution" imposed on the residents of zone A may have been a contributing factor.

An update of the 15-year (1976-1981) mortality experience of the cohorts of zones A, B and R was conducted by Pesatori et al. (1998). In zone A males, moderate increases in mortality from all circulatory diseases combined was observed (RR = 1.6, 95% CI = 1.1-2.5, N = 21) due, in part, to the threefold increase in mortality from chronic ischemic heart disease (RR = 3.0, 95% CI = 1.2-7.3, N = 5). Among females in zone A, rheumatic heart disease (RR = 15.8, 95% CI = 4.9-50.4, N = 3) and hypertension (RR = 3.6, 95% CI = 1.2-11.4, N = 3) were in excess. No significantly increased risks were observed for circulatory disease among residents of zone B, however, in zone R males and females, small but statistically significant elevations occurred for all circulatory diseases (RR = 1.1, 95% CI = 1.0-1.2, N = 719 males; RR = 1.1, 95% CI = 1.0-1.2, N = 759 females). Among males, chronic ischemic heart disease was 40% higher than expected (RR = 1.4, 95% CI = 1.1-1.7, N = 126) and 30% higher in females (RR = 1.3, 95% CI = 1.0-1.5, N = 133). Only in zone R was the risk for mortality from cerebrovascular disease increased.

Many cross-sectional medical studies also examined the association between 2,3,7,8-TCDD exposure and effects on the cardiovascular system (Suskind and Hertzberg, 1984; Moses et al., 1984; Bond et al., 1983; Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991; Grubbs et al., 1995; Calvert et al., 1998). In the NIOSH morbidity study cohort, after controlling for important confounders, no associations were observed between serum 2,3,7,8-TCDD concentrations and increased risk for myocardial infarction, angina, arrhythmia, hypertension, systolic or diastolic hypertension at the time of the study, or abnormal peripheral arterial flow (Calvert et al., 1998).

Statistically significant associations relative to 2,3,7,8-TCDD exposure were found in the Ranch Hand study only for diastolic blood pressure, arrhythmias detected on the electrocardiogram (ECG), and peripheral pulse abnormalities (Roegner et al., 1991). However, there is some doubt that the significant findings are dose related because significant increases in the mean diastolic blood pressure were found in Ranch Hands with serum 2,3,7,8-TCDD levels from 15 to 33.3 pg/g but not in the Ranch Hands with higher serum levels. The adjusted odds ratios for ECG-diagnosed arrhythmias among Ranch Hands were not entirely consistent with a dose-response relationship. For each serum 2,3,7,8-TCDD category the odds ratios were: serum 2,3,7,8-TCDD levels $\leq$10 pg/g, OR = 1.33 (95% CI = 0.68-2.58, p = 0.40); 15-33.3 pg/g, OR = 0.83 (95% CI = 0.31, 2.23, p = 0.71); and for serum 2,3,7,8-TCDD levels above 33.3 pg/g the OR was 2.34 (95% CI = 1.00-5.51, p = 0.051). The proportion of individuals in this group with arrhythmias (5.2%) was not much higher than in Ranch Hands whose serum levels were $\leq$10 pg/g (4.7%). Finally, relative to the comparison group, the proportion of abnormal peripheral pulses in all Ranch Hands, regardless of serum level, was elevated.

In the 1995 followup analysis, the findings closely reflect those of the 1992 analysis, although some results did vary (Grubbs et al., 1995). The prevalence of hypertension of hypertension continued to be significantly related to serum 2,3,7,8-TCDD levels, although there was no evidence for a dose-response association for either diastolic or systolic blood pressure. Overall ECG abnormalities were not different between Ranch Hands and comparisons. However, dose-related increases in risk were noted for RBBB, nonspecific ST and T-waves, and arrhythmias. Finally, no consistent evidence was found for a dose-related increase in the prevalence of abnormal peripheral pulses; however, the prevalence was statistically significant when Ranch Hands were compared to the comparisons.

No excess abnormalities or disorders of the circulatory system or heart were found in several groups of TCP production workers, although their potential for exposure to 2,3,7,8-TCDD-contaminated chemicals was high (Suskind and Hertzberg, 1984; Moses et al., 1984; Bond et al., 1983). The prevalence of hypertension or coronary artery disease (both self-reported),

abnormal ECG findings, atherosclerotic changes (not specified) on chest X-ray, or blood pressure elevation was not elevated in West Virginia TCP production workers (Suskind and Hertzberg, 1984). Similarly, when Moses et al. (1984) examined TCP production workers with chloracne and compared them with workers not affected by chloracne, they found no increased risk for self-reported abnormal ECG, self-reported angina, or self-reported myocardial infarction and no difference in the physical examination of the cardiovascular system. Finally, Bond et al. (1983) found no increased risk for self-reported hypertension among workers involved in the production of trichlorophenol and 2,4,5-T.

7.13.9.1. *Comment*

The SMRs for circulatory system diseases reported in the studies occupational are close to 100, suggesting that the "healthy worker effect" is diminished in these cohorts. Because employed workers are healthier than the general population, the SMR for cardiovascular disease in employed populations tends to be less than 100 (McMichael, 1976; Fox and Collier, 1976). It is also possible that because most of the cohorts exposed to TCDD and related compounds are composed mainly of retired or deceased workers, the healthy worker effect is reduced.

The picture relating exposure to 2,3,7,8-TCDD and diseases of the circulatory system is mixed. Animal data indicate that high doses of 2,3,7,8-TCDD affect cardiac and vascular integrity (Allen and Carstens, 1967; Allen et al., 1977; Norback and Allen, 1973). Data from a few animal studies suggest that relatively high doses of 2,3,7,8-TCDD cause damage to the myocardium and heart valves in rats (Kociba et al., 1978; Buu-Hoï, 1972) and to the arterial walls in rabbits (Brewster et al., 1987). Other research found that 2,3,7,8-TCDD may alter cardiac function in rats and guinea pigs (Hermansky et al., 1988; Kelling et al., 1987; Canga et al., 1988), causing reduced spontaneous and isoproterenol-induced heart contractility; this suggests that 2,3,7,8-TCDD may increase the risk of arrhythmias among the dosed animals. The authors postulate that 2,3,7,8-TCDD alters cyclic-AMP concentrations, altering the responsiveness of cardiac cells to β-adrenergic stimuli (Brewster et al., 1987). In contrast, histopathologic changes were not observed in the cardiovascular system of hamsters, which appear to be resistant to the effects of 2,3,7,8-TCDD at levels of 3,000 μg/kg of (Olson et al., 1980). Other experimental studies suggest an association between 2,3,7,8-TCDD and alterations in lipid levels (Poli et al., 1980; Albro et al., 1978; Bombick et al., 1984; Swift et al., 1981).

Findings from mortality and morbidity studies of production workers are not definitive, and suggest the need for analyses more specifically examining possible effects on the circulatory system and heart. The outcomes examined in the animal and human studies are different. Animal studies describe morphologic and chemical changes in the vascular and cardiac cells caused by

2,3,7,8-TCDD. On the other hand, the diseases and causes of death in the human studies assessed the possible consequences of exposure on long-term pathologic changes to the tissues, which cause cell and, sometimes, organ and system failure. Using the animal data, it is possible to project the long-term consequences of exposure to the organ or system. However, the animal studies do not account for the possibility of intervening events, such as the repair of tissue after exposure ends, or other events that reduce the hypothesized endpoint to a much less drastic outcome.

In recent studies, circulatory diseases and diseases of the heart were investigated as hypothesized health outcomes of exposure to 2,3,7,8-TCDD. A few mortality studies considered the possible confounding effect of other variables, including smoking, lipid levels, and other conditions that influence circulatory diseases and disorders of the heart. However, a general limitation of mortality studies is that only those conditions that ultimately caused the death of the individual are enumerated. Events such as myocardial infarctions, which may debilitate the individual but not cause death, may be missed if death is caused by another circumstance. Therefore, the effect of 2,3,7,8-TCDD on the coronary arteries might be missed because it was not coded as the underlying cause of death on the death certificate.

With the exception of the studies of the Ranch Hand and NIOSH cohorts (Roegner et al., 1991; Michalek et al., 1998; Calvert et al., 1999), cross-sectional analyses of other more highly exposed groups were limited by a lack of good exposure data and an inability to examine the relationship between serum 2,3,7,8-TCDD levels and diseases of the circulatory system or heart. Such studies may also be limited by the fact that they include a survivor population, as described in the introduction.

Further research would be useful to define the relationship between the pathologic endpoints observed in animals after high single doses of 2,3,7,8-TCDD and the disease outcomes observed in humans after high long-term exposure. To identify whether 2,3,7,8-TCDD has an effect on the human vasculature, additional work is needed to determine whether certain doses of 2,3,7,8-TCDD cause changes in the human vascular system; to determine whether there are changes in the action of chemicals associated with human cardiac muscle contraction caused by 2,3,7,8-TCDD exposure; and to assess mortality and morbidity in individuals with potential for 2,3,7,8-TCDD exposure while carefully controlling for other risk factors and using more accurate measures of exposure.

7.13.10. Pulmonary Effects

Studies of long-term exposure to 2,3,7,8-TCDD in Sprague-Dawley rats (Kociba et al., 1979; van Miller et al., 1977), B6C3F1 mice (NTP, 1982a), Swiss-Webster mice (NTP, 1982b),

and rhesus monkeys (Allen et al., 1977) have reported changes in bronchiolar or alveolar tissue ranging from epithelial hyperplasia and metaplasia to squamous cell carcinomas. The hyperplastic and metaplastic changes observed in exposed animals are similar to the pathologic picture of chronic bronchitis in humans (American Thoracic Society, 1962).

Case reports have described temporary respiratory irritation (Zack and Suskind, 1980) and tracheobronchitis (Goldman, 1972) among chemical workers exposed to 2,3,7,8-TCDD-contaminated herbicides following industrial accidents. In addition, Baader and Bauer (1951) reported chronic bronchitis in seven workers involved in pentachlorophenol production, which resolved in all but two workers within 2 weeks after production was discontinued.

There is conflicting evidence from controlled epidemiologic studies regarding an association between chronic respiratory system effects and human exposure to substances contaminated with 2,3,7,8-TCDD. One study of workers involved in the production of TCP and 2,4,5-T suggested that 2,3,7,8-TCDD exposure increases the risk for abnormal ventilatory function (Suskind and Hertzberg, 1984). This study found a statistically significantly increased risk for an abnormal forced expiratory volume at 1 second (FEV_1) ($p<0.01$), an abnormal forced vital capacity (FVC) ($p<0.001$), and an abnormal FEV_1/FVC ratio ($p<0.05$) among workers who were smoking at the time of the study. For workers, the percent predicted spirometric parameters for FEV_1, FVC, and FEV_1/FVC were 99.4%, 92.7%, and 76.5%, and for referents, 104.4%, 97.6%, and 79.9%, respectively. The only other study of TCP and 2,4,5-T production workers that reported ventilatory function findings found no association between serum 2,3,7,8-TCDD levels and declines in ventilatory function (Calvert et al., 1991). The disparity in results between the two studies may be related to the age of the unexposed populations and potential exposures of the exposed. In the Suskind and Hertzberg study, the exposed workers were, on average, 10 years older than the unexposed workers. Although the authors indirectly adjusted for age by analyzing age-adjusted ventilatory measures, it is not clear if these adjustments can completely control for a 10-year difference in age. In the study by Calvert et al. (1991), the difference in mean age between the exposed and unexposed groups was 0.6 years. The second difference involves the potential for exposure to 2,4,5-T acid dust at the plants studied. The 2,4,5-T acid that was produced at the plant studied by Suskind and Hertzberg was finished as a powder. At the plants studied by Calvert et al. (1991), the 2,4,5-T acid was finished as a liquid. Therefore, the potential for exposure to 2,4,5-T acid dust was greater at the plant studied by Suskind and Hertzberg (1984). Although we are not aware of any published reports supporting an association between ventilatory function and 2,4,5-T acid exposure, a respiratory burden of particles, in the absence of a specific toxic agent, can be a probable cause of ventilatory function declines (Becklake, 1985).

The Ranch Hand study also examined the association between serum 2,3,7,8-TCDD level and respiratory system effects (Roegner et al., 1991). This study found significant declines in the mean FEV_1 and the mean forced expiratory volume (FVC) for Ranch Hands with serum 2,3,7,8-TCDD levels above 33.3 pg/g (adjusted mean FEV_1 = 91.3%; mean FVC = 87.4) compared to a nonexposed comparison group (adjusted mean FEV_1 = 93.5%; mean FVC = 91.7) (Roegner et al., 1991). The 2,3,7,8-TCDD-related declines were small and were interpreted by the authors to be "subtle" and "not clinically significant." As expected, smoking appeared to have the greater influence on lung function although this has not been considered by the Air Force in their interpretation. In the followup examination conducted in 1992, no consistent relationship was found between serum 2,3,7,8-TCDD concentrations and respiratory parameters (Grubbs et al., 1995).

Mortality from respiratory diseases among the various exposed populations as is mixed. In productions workers, no excess mortality was observed from all diseases of the respiratory system among subcorhort of workers in the IARC study exposed to phenoxy herbicides or chlorophenols (SMR = 86, 95% CI = 73-101, N = 151) (Vena et al., 1999) or among German accident workers (N = 1) (Ott and Zober, 1996a).

7.13.10.1. *Other Mortality Studies of Production Workers*

Overall mortality from respiratory diseases among the Seveso population was less than expected for all exposure zones except males in zone A (Pesatori et al., 1998). However, chronic obstructive lung disease was twofold higher than expected in females in zone B (N = 7) and threefold higher in males of zone A (N = 4).

7.13.10.2. *Comment*

In conclusion, case reports indicate that intense acute exposure to 2,3,7,8-TCDD can produce respiratory irritation. However, the findings from controlled epidemiologic studies do not support an association between 2,3,7,8-TCDD exposure and chronic noncancer effects on the respiratory system.

7.13.11. Renal Effects

There is little evidence in the animal or human data to suggest that exposure to 2,3,7,8-TCDD is related to renal or bladder dysfunction. In a single case report, a child exposed to 2,3,7,8-TCDD after contact with soil sprayed with contaminated waste oil was diagnosed with focal pyelonephritis (Kimbrough et al., 1977). After diagnosis and treatment, the condition resolved with no reported recurrence. No major renal or bladder dysfunctions were noted among

Air Force Ranch Hands (Lathrop et al., 1984, 1987; Roegner et al., 1991) or among TCP production workers from West Virginia (Suskind and Hertzberg, 1984) or New Jersey (Poland et al., 1971).

7.13.12. Developmental/Reproductive Effects

Animal studies of reproductive effects have focused primarily on maternal 2,3,7,8-TCDD exposure and developmental toxicity. Prenatal exposure to 2,3,7,8-TCDD has been associated with increased pre- and postnatal mortality, cleft palate and kidney abnormalities, altered sexual development, and reduced fertility in studies of maternal exposure in a number of species. Fewer studies have focused on the effects of dioxin on the male reproductive system or on the results of matings in which only the males were exposed to dioxin. Studies of male exposures have not provided evidence of paternally mediated effects on the offspring. (Chapter 5 contains a detailed account of the animal literature.)

Thus, experimental research has emphasized maternally mediated developmental effects of 2,3,7,8-TCDD, while in humans, studies of paternal exposures have predominated. Moreover, assessment of exposed male animals has most commonly examined the effects of 2,3,7,8-TCDD on spermatogenesis, fertility, and sex organ development (Theobold and Peterson, 1984), whereas studies of human males have mainly targeted studies of congenital malformations and recognized spontaneous abortions. Experimental research designed to corroborate human investigations may provide critically needed data to plug the gaps in our understanding of the mechanisms through which 2,3,7,8-TCDD exposure may operate to produce adverse reproductive events in humans.

The origin of concerns regarding a potential link between exposure to chlorinated dioxins and adverse developmental events can be traced to early animal studies reporting increased incidence of developmental abnormalities in rats and mice exposed early in gestation to 2,4,5-T (Courtney and Moore, 1971). This was of grave concern, as the U.S. military's most widely used herbicide during the Vietnam conflict, Agent Orange, was composed of approximately equal proportions by weight of the n-butyl esters of 2,4-D and 2,4,5-T. The latter is contaminated by 2,3,7,8-TCDD during manufacture.

One dilemma encountered when attempting to review the epidemiologic literature dealing with dioxins and reproductive effects is the categorization of studies of sufficient similarity to allow for comparative analysis. These studies vary greatly in the nature (occupational, environmental) and route (inhalation, ingestion, absorption) of exposure; in the reproductive and developmental outcomes examined (often multiple endpoints were considered, and case definition differed across studies); in the assessment of parental exposure (maternal, paternal, or both); and in the timing of exposure relative to the pregnancy.

The examination of reproductive and developmental disorders poses several challenges to the researcher compared to other health outcomes. First, to understand both normal and pathologic reproduction, evaluation should include paternal and maternal, and sometimes fetal, contributions. Increased interest in male-mediated reproductive toxicity emphasizes the need to consider the couple as the unit of analysis in many reproductive study settings (Olshan and Mattison, 1994).

The second challenge to researchers is the interrelatedness of the spectrum of reproductive endpoints available for study. Fecundity (the joint potential to conceive), fertility (the production of live children), and very early pregnancy loss (those conceptions that do not survive to be recognized by usual diagnostic methods) as related to 2,3,7,8-TCDD exposure have not been evaluated in the same population. Clearly, these endpoints affect the rates of reproductive outcomes occurring later in the reproductive spectrum.

Another feature of developmental effects is the changing vulnerability of the developing organism throughout gestation. Exposure to a single developmental toxicant throughout pregnancy may result in different effects at various stages of gestation. The window of susceptibility varies; therefore, knowledge of the timing of exposure is critical in these studies.

Finally, although not restricted to studies of developmental events, care must be given to the collection and analysis of data on potential confounders. These factors may need to be obtained for both mother and father, with attention to the timing of specific characteristics, such as changes in smoking or occupation during pregnancy.

The reproductive effects of dioxins in humans were succinctly and elegantly reviewed by Hatch in 1984 (Hatch, 1984b). In her review, Hatch employed type of exposure, i.e., populations that were exposed occupationally, environmentally, or through industrial accident or military service, as the classification scheme for the research presented. The same approach has been followed in this review. The earlier investigations of 2,3,7,8-TCDD and reproductive effects, i.e., those conducted prior to 1984, are presented separately from the more recent studies. The development of assays in the mid-1980s to quantitate 2,3,7,8-TCDD in serum and adipose tissue, allowing individual measurements of exposure, warrants this dichotomy of the research.

Review of the Literature Prior to 1984

7.13.12.1. *Occupational Studies*

Epidemiologic studies of occupational dioxin exposure and reproductive effects have focused on paternally mediated effects, with exposures occurring at varying intervals relative to conception. Townsend et al. (1982) interviewed 370 wives of employees exposed to dioxins at the Dow Michigan Division in Midland, Michigan (63% of those eligible for the study), and 345

control wives of Dow employees who were not exposed to dioxin (62% of the eligible control pool). Exposure classification was determined by an industrial hygienist familiar with the processes performed at the plant. Employees were considered exposed to dioxin if they had been assigned for at least 1 month to specific jobs associated with chlorophenol processes between 1939 and 1975. All outcomes were reported by the employee's spouse.

There was no systematic attempt to ascertain the reason(s) for the high refusal rate in both cohorts. "Unsolicited reasons" for refusal included divorce, death of spouse, or no pregnancies; no breakdown by cohort was provided. The possibility of differential rates of infertility or early pregnancy loss, as reflected by the reported absence of pregnancy, was not addressed in this study.

For the multiple endpoints of spontaneous abortion, stillbirth, birth defects, infant mortality, and childhood morbidity, no significant association between dioxin exposure and any adverse event was identified (Table 7-48). This study had a very long interval during which the exposure and event could have occurred, and a minimum requirement for paternal exposure of 1 month at any time during that interval. This exposure definition essentially assumes "irreparable" damage that would persist long after the father's active occupational exposure had terminated or a very long half-life, resulting in an elevated biological level up to 35 years later. Thus, an effect of exposure, if one existed, would have been diluted by this approach. The authors do not discuss whether time since last exposure was considered in the analysis.

In another study of occupational exposure to 2,4,5-T, Smith et al. (1982) identified 616 male chemical applicators from a list maintained by New Zealand's Agricultural Chemicals Board and 531 comparison workers at small agricultural contracting companies. Of these, 548 sprayers and 441 agricultural contractors and their spouses participated, with impressive response rates of 89% and 83%, respectively. Mailed questionnaires ascertained spraying activities from the males and reproductive histories from their spouses. The investigators noted that wives of the chemical sprayers anecdotally reported assisting their husbands in spraying activities, some performing this task during their pregnancy.

The questionnaires were completed in 1980 and elicited information on spraying activities and reproductive events that occurred between 1969 and 1980. Reported pregnancy outcomes were categorized into three groups based on whether the fathers had sprayed any chemicals at any time during, or prior to, the calendar year in which the pregnancy occurred and whether 2,4,5-T had been used. There were 1,122 births reported among the 441 control spouses and 1,172 among the 548 spouses of the exposed sprayers. If all other factors were comparable in both cohorts (maternal age, socioeconomic status, and maternal smoking histories were shown to be similar), then there appear to be 220 fewer births observed in the exposed group than might be expected. No associations between herbicide exposure and spontaneous abortion (OR = 0.89, 95% CI = 0.6-

1.3) or congenital malformations (OR = 1.2, 95% CI = 0.6-2.4) were identified. Other risk factors did not appear to be controlled in the analysis of these data: for example, the analysis of miscarriages did not appear to control for maternal age or occurrence of prior fetal loss. Multiple pregnancies per family unit were studied; however, the authors did not address the problem of nonindependent events.

This study is limited by the high probability of exposure to chemicals other than 2,4,5-T. Although exposure levels were not quantitated in this study, a later study of a subset from this same population was conducted to estimate 2,3,7,8-TCDD exposure.

In 1988, Smith and colleagues selected nine pesticide applicators from the above group with the greatest number of years and months per year of pesticide application and evaluated their serum 2,3,7,8-TCDD levels (Table 7-49). The mean serum 2,3,7,8-TCDD level, adjusted for total lipids, among the cases (53.3 pg/g) was 10 times that of age-matched controls (5.6 pg/g). However, exposure in this study was based on self-reports of pesticide application, and research has demonstrated that self-reports do not correlate with documented serum 2,3,7,8-TCDD levels (Needham et al., 1991). Therefore, it would be helpful if serum levels could be obtained from a subset of those applicators with lower self-reported exposures.

A clinical epidemiology study conducted in 1979 examined workers involved with the manufacture of 2,4,5-T between 1948 and 1969 in Nitro, West Virginia (Suskind and Hertzberg, 1984). All active and retired plant employees exposed to the 2,4,5-T process during that 22-year interval comprised the eligible pool of "exposed" subjects. The control group consisted of current and former plant employees who were never associated with the 2,4,5-T process, according to company records. The response rates for these cohorts were 61% (N = 204) and 46% (N = 163), respectively.

A reproductive history was obtained from these male employees during an interview and clinical examination. No attempt was made to verify reports of live births, infant deaths, miscarriages, birth defects, and stillbirths with the spouses or through medical records. There were no significant differences in rates of any adverse outcome by exposure status. Given the poor response rates, crude measure of exposure, and lack of verification of paternally reported reproductive histories, this study was not likely to detect an association between 2,3,7,8-TCDD and reproductive events if one existed.

7.13.12.2. *Environmental Studies*

The problem of documentation of exposure is perhaps of even greater concern in studies of subjects environmentally exposed to dioxins but lacking individual 2,3,7,8-TCDD measures. The route of exposure (inhalation, ingestion, absorption), length and intensity of exposure, and the

timing of the exposure are more difficult to estimate in free-living populations compared with workers in an occupational setting.

Selection bias is also a critical concern in environmental studies because there is no environmental equivalent to company records for defining the exposure status of the study group. Proximity of residence to a source (e.g., a toxic waste site or an industrial source) was generally the best option available for identifying the population at risk of exposure. Issues such as length of time living at that residence, the amount of time spent in the home, other potential sources of exposure (e.g., occupational), and the timing of the contamination episode relative to the outcome of interest may have greatly affected the degree of exposure.

The potential for volunteer bias, which is likely in studies that rely on subjects recruited through publicized requests for participation, is an additional concern in studies of this nature. Moreover, it is extremely difficult to conduct epidemiologic investigations under crisis situations such as the industrial accident that occurred in Seveso, Italy. Given these limitations, the efforts of these investigators have provided valuable impetus to the refinement of study designs and the development of more sophisticated techniques to explore this issue.

7.13.12.2.1. ***The Seveso, Italy, dioxin accident of 1976***. In 1976, during the production of trichlorophenol at the ICMESA plant in Seveso, Italy, a runaway reaction resulted in an explosion that ultimately contaminated 700 acres in the surrounding community. Environmental levels of 2,3,7,8-TCDD were determined by using wipe tests, evaluating toxic effects in small animals, and analyzing grass samples. Approximately two weeks later, more than 200 families were evacuated from high-contamination areas. Exposures were sufficiently high for chloracne to be observed in this environmentally exposed population. Following the reactor release, an extensive surveillance system was initiated to monitor the health of the exposed population. Changes in fetal loss rates occurring during the last quarter of 1976 and first quarter of 1977 were found in both exposed and unexposed communities. An estimated 150 women were in the first trimester of pregnancy at the time of the accident (Rehder et al., 1978); of these, 125 women wished therapeutic abortions by October 1976. Therapeutic abortions were approved for 30. Another estimate (Tuchmann-Duplessis, 1980a,b) reports a total of 108 (50 in 1976 and 58 in 1977) therapeutic abortions in the four affected communities. Several reports (Biscanti et al., 1978; Pocchiari, 1980; Pocchiari et al., 1980) suggested that a large number of women obtained unapproved, and therefore not reported, therapeutic abortions. This supposition was supported by a steep decrease in birth rates in the first 6 months of 1977, that was primarily observed in the exposed communities. (All communities had had decreases over time; however, the decrease in exposed communities at this key time was much larger.)

The Seveso Congenital Malformations Registry enrolled all live births and stillbirths occurring January 1, 1977, through December 31, 1982, to women residents of zones A, B, R, and non-ABR (Mastroiacovo et al., 1988). A total of 15,291 births (live and stillbirths) and 742 birth defects were recorded: zone A, 26 births and no birth defects; zone B, 435 births and 25 birth defects (57.5/1,000 births); zone R, 2,439 births and 110 birth defects (45.1/1,000 births); zone non-ABR, 12,391 births and 605 birth defects (48.8/1,000 births). Birth defects were confirmed by medical records. Relative risk estimate for total defects comparing zones A+B with zone non-ABR is 1.2 (90% CI = 0.88-1.64) (Table 7-48). The rate of birth defects occurring early in the observation period (first quarter of 1977) did not differ from the rate of birth defects occurring later in the observation period (data not shown), and there were no discernible patterns of defects within or between the exposure groups.

To document an increase in the rate of an event, sound baseline information is required. No reliable information regarding rates of birth defects in this area was available until the establishment of the Seveso Congenital Malformations Registry 6 months after the incident. Thus the potential contribution of 2,3,7,8-TCDD to the congenital malformation rate cannot be separated from improved case ascertainment. Prior to this time, only certain birth defects were required to be reported to Italian health officers (Reggiani, 1980b). In addition to the limitations due to legal requirements, there were other reasons for the underreporting of malformations: "Traditionally, Italian physicians have under-reported congenital malformations because of their severe negative social implications." (Tuchmann-Duplessis, 1980a) Although physicians and midwives were encouraged to do more complete recording, Reggiani (1978) concluded that the malformation data are "missing" for 1976, and "incomplete" for the first trimester of 1977. The influence of spontaneous abortions on the birth defect rate is likewise unknown. As with congenital malformations, reliable background data for spontaneous abortion in the study area were not available. The small number of conceptions available for study limits the power of these studies to detect an association between 2,3,7,8-TCDD exposure and spontaneous abortion and birth defects.

Another adverse outcome that has not been described in most epidemiologic studies is the effect of 2,3,7,8-TCDD on the chromosome. Pocchiari and colleagues described one study in which 30 therapeutic and 4 spontaneous abortions from the Seveso area were examined (Pocchiari, 1979). There were no indications of mutagenic, teratogenic, or embryotoxic effects that could be attributed to 2,3,7,8-TCDD exposure. However, it was difficult to determine maternal exposure status for any of the cases. A later study examined the association between 2,3,7,8-TCDD and cytogenetic abnormalities in fetuses from abortions induced shortly after the Seveso accident (Tenchini et al., 1983). The frequency of aberrant cells and the mean number of

aberrations per damaged cell were significantly higher in exposed versus unexposed fetuses. However, the paper omits important data, such as the timing of conception relative to the accident, how long after exposure the abortion occurred, the zone in which the mother and father resided at the time of conception and pregnancy, and tissue 2,3,7,8-TCDD concentration in the fetuses. No other studies have examined fetal tissue to corroborate these data. This approach offers exciting possibilities for future research, as genetic techniques in the area of DNA-adduct analyses become more widely available.

7.13.12.3. *Studies of Exposure to Agent Orange by Military Veterans and Vietnamese Civilians*

The problem of exposure documentation has also been a highly controversial issue in studies of potential exposure to Agent Orange in Vietnam and adverse health effects among both the Vietnam veterans and residents of Vietnam, and their offspring. An early study among the Vietnamese population encompassed a 10-year period in Vietnam from 1960 to 1969 (Cutting et al., 1970). Exposure was dichotomized into pre- or light-spraying years from 1960 to 1965 and heavy-spraying years from 1966 to 1969. A total of 480,087 births, 16,166 stillbirths, 2,866 hydatidiform moles, and 2,355 congenital malformations of all types were examined in this study. Pregnancy outcome data were collected from 22 hospitals.

Increases in the rates of stillbirths, molar pregnancies, and congenital malformations were noted in the coastal plain and delta areas following heavy spraying, although the authors emphasized the slight downward trend observed for all outcomes in the countrywide rates. Several biases in this sampling approach severely limit the interpretation of the study's findings. The births examined were not representative of the births in the country during that period. In addition, the hospital records were incomplete, and transport of the mothers to the selected hospitals resulted in uncertainty regarding maternal residence during the pregnancy.

A second investigation conducted in Vietnam used the HERBS tape (military records detailing Agent Orange spraying missions) covering the period from 1965 to 1971 to determine maternal exposure status according to area of residence (Kunstadter, 1982). HERBS data were matched to hospital records with the date of birth to generate an “estimated date of conception” and to maternal residence at birth to assign “potential for maternal exposure.” Birth outcome data were collected from hospital records, which were subject to incomplete ascertainment, inaccuracies, and incompleteness.

No association between spraying of Agent Orange and any type of birth defect or perinatal mortality was noted. Although cleft lip defects increased in proportion to other malformations

during the heavy spraying period, the total number of birth defects declined and continued to decrease after spraying activities ceased.

Finally, Australian investigators examined the relationship between service in Vietnam during 1962-1972 and birth defects (Report to the Minister for Veterans' Affairs, 1983). Cases were infants born with any of a defined set of congenital malformations in any of 34 hospitals in New South Wales, Victoria, and the Australian Capital Territory from 1966 to 1979. Control infants were matched to cases on maternal age, hospital, and time of birth, yielding 8,500 matched pairs for analysis.

Fathers of case and control infants were matched against a list of members who had served in the Australian Army during the specified time period. No associations were detected for Vietnam service and total birth defects (OR = 1.02, 95% CI = 0.8-1.3) or for any of the approximately 100 birth defects examined. Length of service in Vietnam, time between deplanement and conception, and Vietnam service prior to and following conception were considered in the analysis.

A critical point that should be emphasized regarding the Australian study is the assessment of service in Vietnam as the exposure of interest. The author clearly stated that investigations had indicated that exposure to herbicides was "infrequent and probably very low in Australian troops in Vietnam; the study does not exclude possible effects of herbicides in situations of substantial exposure" (Report to the Ministry for Veterans' Affairs, 1983).

A series of unpublished studies conducted by Vietnamese investigators was reviewed by Hatch (1984a) and should be mentioned in this review. While these reports also have limitations, including incomplete background data for rates of reproductive events and sparsity of epidemiologic details provided in the studies, the assessment of Vietnamese populations offered the opportunity to evaluate pregnancies with various patterns of parental exposure.

Investigations conducted in northern Vietnam assessed pregnancies with no maternal exposure to spraying activities; paternal exposure was presumed to have occurred only when the father had performed military service in the south. Studies of couples in southern Vietnam compared reproductive outcomes observed in sprayed versus nonsprayed areas and represented potential associations between either maternal and/or paternal herbicide exposure and risk of adverse pregnancy outcome.

Three studies examined presumed paternal herbicide exposure and birth defects among pregnancies in northern Vietnam. Lang and van compared the frequency of birth defects during the period 1975-1978 as a function of the father having served in south Vietnam (Hatch, 1984a). Among 2,547 offspring whose fathers had never served in the south, the birth defect rate was 6 per 1,000 (N = 15). Among 511 offspring whose fathers had served in the south, the rate was 29

per 1,000 (N = 15). Similar results were obtained in a study by Lang and colleagues at unspecified agricultural and handicraft cooperatives in northern Vietnam (Hatch, 1984a). The congenital malformation rate among "exposed" pregnancies (paternal service in southern Vietnam) was 23-26 per 1,000 (71 or 82 of 3,147). In comparison, the rate among the unexposed pregnancies was 5 per 1,000 (10 of 2,172).

In what is perhaps the most stringent of the Vietnamese studies by Can et al. (reported in Hatch, 1984a), 40,064 women from three rice-growing districts in northern Vietnam were assessed (although few details are provided on the method of selection). All of the women were married and pregnant at least once during the war and had no history of tuberculosis, syphilis, or malaria, or of using antibiotics or hormones during pregnancy. "Detailed" interviews were conducted by physicians and midwives, and district health records were consulted in an attempt to validate reported pregnancies and outcomes. Only pregnancies conceived during the conflict were considered in this study. There were a total of 121,993 pregnancies among the 29,041 women whose spouses were "nonexposed" and 32,069 pregnancies among the 11,023 women whose spouses had served in the south. Service in south Vietnam was associated with an increased rate of spontaneous abortion ($p = 0.05$). The increased rate of congenital malformations among the exposed pregnancies (0.6%) compared with the unexposed (0.4%) did not achieve statistical significance ($p = 0.10$).

In attempt to further assess this difference, these investigators conducted a case-control study in which they examined a random sample of 61 families of children who had survived with a birth defect. A control group of 183 families of normal children (matched on maternal age, number of deliveries, living environment, and age) was selected. Forty-nine percent of children with a birth defect had a father who had served in south Vietnam, compared with 21% of the children without malformations, yielding an odds ratio of 3.6 (95% CI = 1.9-6.7).

Additional unpublished studies conducted in Vietnam by Vietnamese investigators were reviewed by Constable and Hatch (1985). The reader is referred to this source for details of the studies. It was concluded that studies of presumptive paternal "herbicide" exposure prior to or at conception were suggestive of a relationship with congenital malformations. The evidence for an association with spontaneous abortion was "less convincing," and for molar pregnancies no relationship appeared to exist. Those studies that examined both maternal and paternal "herbicide" exposure were also suggestive of a relation to birth defects as well as spontaneous abortion, stillbirths, and molar pregnancies. Follow-up studies by these Vietnamese investigators supported these earlier findings (Huong et al., 1989; Phuong et al., 1989b).

In the next section, the impact of assays to measure individual levels of 2,3,7,8-TCDD is discussed, and studies of 2,3,7,8-TCDD exposure and reproductive effects that have been published since 1984 are presented.

Review of the Literature From 1984 Through 1995

During the interval since 1984, assays that had been developed to measure TCDD in serum and adipose tissue were being tested and refined. Several investigators have since used these assays in (usually small) subsets of their study populations to estimate exposure to 2,3,7,8-TCDD in their total sample and also in attempts to validate their assumptions regarding magnitude of exposure for their study subjects. Subsets were generally selected to represent subjects designated as "high" versus "low" exposure by the study investigators, utilizing various information sources including self-reports, company or military records, etc. Table 7-49 presents the results of the exposure analyses (Mocarelli et al., 1991; Patterson et al., 1986b; Smith et al., 1992; Centers for Disease Control Veterans Health Studies, 1988; Fingerhut et al., 1991a; Schecter et al., 1989; Kahn et al., 1988; Kang et al., 1991; Roegner et al., 1991; Phuong et al., 1989b).

These data illustrate wide variability in groups presumed to have been exposed to 2,3,7,8-TCDD at levels above background ($\leq$20 pg/g). For example, the mean and median serum levels of Vietnam ground combat troops with service in areas heavily sprayed with Agent Orange did not exceed the levels found in the U.S. general population. There is evidence for higher exposure to 2,3,7,8-TCDD among certain subgroups of Vietnam veterans (et al., 1988; Roegner et al., 1991) as well as residents of Vietnam (Phuong et al., 1989b), Seveso (Mocarelli et al., 1991), and Missouri (Patterson et al., 1986b), and occupational groups (Fingerhut et al., 1991a; Beck et al., 1989).

With the exception of the Ranch Hand study (Roegner et al., 1991), these subsets were selected to describe 2,3,7,8-TCDD exposure in the total study sample and not for an examination of the relationship between 2,3,7,8-TCDD and reproductive events. In addition, the data from the Ranch Hand population indicated a serum 2,3,7,8-TCDD half-life of 7.1 years (Pirkle et al., 1989), but serum samples in this group were collected and analyzed at 11- and 15-year intervals following exposure. Questions regarding the impact of initial dose, age, gender, and pregnancy itself on half-life in humans remain unanswered at this time.

7.13.12.4. ***Environmental Studies***

7.13.12.4.1. ***The Times Beach, Missouri, 2,3,7,8-TCDD episode***. In 1971, a waste oil dealer in Missouri disposed of waste sludge containing approximately 29 kg 2,3,7,8-TCDD by mixing it with waste oils as a dust control spray, which was subsequently distributed throughout the State. General media announcements from health officials were made, urging persons potentially exposed to 2,3,7,8-TCDD to participate in a survey and health screening process. People were warned of their potential exposure by virtue of their residence, employment, or engagement in recreational activities in the contaminated sites. A pilot study was initiated in 1983, in which a subset of those persons who had responded to the media announcements was assessed (Stehr et al., 1986). Approximately 800 completed questionnaires were screened to select participants; it was not clear if this number represents all of the questionnaires that had been returned up to that time.

This phase of the study was intended to identify potential problems for future investigations. Persons determined to be at "high" versus "low" risk for dioxin exposure, based on their completed surveys, were selected. "High risk" was defined as either (1) reported residence or occupation in areas with TCDD levels between 20 and 100 ppb for at least 2 years or in areas with TCDD levels >100 ppb for at least 6 months, or (2) participation in activities requiring close contact with soil in areas with TCDD concentrations as described for similar periods of time. "Low-risk" persons were determined to have had no access to, or "regular high-soil-contact activities" in, any known contaminated area. Controls were frequency matched with the high-exposed group on type of exposure site, age, sex, race, and socioeconomic status. Sixty-eight "high-risk" persons (83% of those eligible) and 36 "low-risk" persons (90% response) were evaluated through physical, neurological, and dermatological examinations; laboratory tests; and interviews.

Information on reproductive outcomes was obtained during the interview administered to the subjects "or their nearest relative." None of the outcomes observed differed significantly by exposure status (Table 7-48), although high-risk women had a later mean age at menarche ($p = 0.06$). A total of 30 births were available for assessment in this sample.

The following year, a more intensive study was undertaken to test the results found in the pilot study (Hoffman et al., 1986). The exposed group consisted of residents of the Quail Run Mobile Home Park in Gray Summit, Missouri, where TCDD levels in the soil were measured at up to 2,200 ppb. Data on 95 of the approximately 207 households in the park were available; 154 persons (74%) who were "both eligible and interested" agreed to participate. The unexposed group consisted of 155 residents of a nonexposed trailer park, representing 77% of those "both eligible and interested" in participation.

The protocol was similar to that employed in the pilot study described above. The authors reported that "no differences were found between the exposed and unexposed groups in the frequency of reproductive disorders or adverse pregnancy outcomes, such as fetal deaths, spontaneous abortions, and children with congenital malformations." No sample sizes or statistical test results for any of the outcomes were reported. Clearly, these studies of Missouri residents were not designed to investigate the relationship between dioxin exposure and reproductive outcomes, and not very much can be learned about this association from these results.

In a retrospective cohort study by Stockbauer et al. (1988), the association between 2,3,7,8-TCDD and reproductive outcomes was examined among residents of contaminated areas in Missouri. All live births and stillbirths that occurred in the nine residential areas identified as contaminated with TCDD during the period 1972-1982 were identified through Missouri vital statistics records. A total of 402 births were examined from six residential areas. TCDD levels in the soil from these six areas ranged from 241 to 2,200 ppb. 2,3,7,8-TCDD levels were not reported for the three areas where no births occurred during this interval, which would have been of interest to note.

A reference group of 804 unexposed births, matched for maternal age and race, hospital and year of birth, and plurality, was selected from the vital statistics records. Medical records were abstracted to ascertain birth defects in the matched sets. In addition, the births were linked to a statewide birth defects register that had been recently initiated. Data on several potentially confounding variables were obtained from birth certificates.

The exposed mothers tended to be less educated, had more children, were more likely to be in the extremes of the prepregnant weight distribution, and were more likely to smoke cigarettes. Statistical testing for these differences was not reported. Moreover, statistical adjustment for these potential confounders was performed only in the birth weight analyses, although there was little change in the birth weight risk ratios after adjustment.

Increased risk ratios were reported in the exposed group for infant death (OR = 2.0), fetal death (OR = 1.6), perinatal death (OR = 1.3), low birth weight (AOR = 1.5), and several subcategories of malformations, although none of these findings achieved statistical significance (Table 7-48).

Two approaches were used to determine a dose-response relationship. In the first, the study data set was matched against the Missouri central listing of dioxin-exposed persons, which yielded 98 of the exposed mothers and none of the control mothers. These 98 women were then dichotomized into "high" (N = 20) or "low" (N = 78) exposure groups. High exposure was defined as residence for at least 6 months in areas with $\geq$100 ppb TCDD in the soil or $\geq$2 years in

areas with TCDD levels from 20 to 100 ppb. Low exposure was defined as residence in areas with similar TCDD levels as described above, but for less than the required time period or residence at sites with 1-19 ppb TCDD. No evidence for a dose-response relationship was observed with this analysis.

The second approach categorized the births into two different intervals relative to the spraying of the soil with the TCDD-contaminated sludge in 1971 to 1973. When births in the 1972-1974 period were compared with births from 1975 to 1982, the authors reported that "the only birth outcomes with higher risk ratios in the earlier time period were very low birth weight, birth defects, and major birth defects." None of these observations were statistically significant, but sample sizes and testing results were not provided in the paper.

The authors acknowledged the possibility of exposure misclassification and also the "modest" power of the study to detect associations due to the small sample size.

7.13.12.5. *Studies of Vietnam Experience in Ground Troops and Ranch Hands Published 1984-1995*

7.13.12.5.1. ***Evaluation of exposure.*** Evidence from earlier studies to determine if Agent Orange exposure increased the risk of adverse pregnancy outcomes among Vietnam veterans has been described as "sparse, sometimes off the point, sometimes conflicting..." (Hatch and Stein, 1986). The general dissatisfaction with these studies had a common factor: the lack of a valid measure of dioxin exposure. Once the assays to document individual 2,3,7,8-TCDD exposure became available and served as the gold standard for assessing the exposure assumptions made by study investigators, this concern regarding exposure misclassification was shown to be justified. Until 1992, when the first study to examine reproductive outcomes among Vietnam veterans based on individual exposure measurements of 2,3,7,8-TCDD was published, this remained the major criticism of the research. Even though 2,3,7,8-TCDD serum levels were available for reanalysis of the 1984 data of the Ranch Hand study, they were not used in that report. A later reanalysis (in 1995) used estimated 2,3,7,8-TCDD level at the time of conception. Exposure indices were developed for several studies to aid in analysis of exposure outcome relationships.

7.13.12.5.2. ***Exposure indices: The CDC case-control study's exposure opportunity index.*** In the early 1980s, the CDC conducted a large case-control study that examined the relationship between service in Vietnam and risk of congenital malformations (Erickson et al., 1984). Although service in Vietnam was the major exposure variable, two additional measures of exposure were assessed. Vietnam veterans were asked if they believed they had been exposed to Agent Orange. In addition, an exposure opportunity index (EOI), developed by the Army Agent

Orange Task Force, assigned a score estimating the likelihood of exposure based on places and times of Vietnam service. These scores ranged from minimal (1) to high (5) opportunity for Agent Orange exposure.

The CDC then reported on a study, using the serum assay as the standard, to evaluate the validity of both self-reported exposure to Agent Orange and use of military records to fomulate the EOI used in the case-control study of military service in Vietnam and birth defects. The results revealed a poor correlation (no correlation coefficient was provided) between both of these exposure estimates and serum TCDD levels (Centers for Disease Control Veterans Health Studies, 1988). In addition, the distributions of serum 2,3,7,8-TCDD levels were nearly identical (median = 3.8 ppt) among 646 ground combat troops who had served in heavily sprayed areas compared with 97 veterans who had never served in Vietnam.

In a separate study, Kahn et al. (1988) measured serum 2,3,7,8-TCDD levels in 10 Vietnam veterans who reported that they had handled Agent Orange "regularly" while in Vietnam, 10 Vietnam veterans with little or no exposure to Agent Orange, and 27 Vietnam-era veterans. The levels of serum 2,3,7,8-TCDD among those men who had handled Agent Orange were significantly elevated (median = 25.1 pg/g blood fat) compared with the Vietnam control veterans (median = 5.3 pg/g) and the Vietnam-era veterans (median = 3.9 pg/g) ($p<0.01$).

The Baseline Ranch Hand study's exposure index. In 1984, the U.S. Air Force released preliminary results of a 20-year study designed to examine the personnel responsible for conducting the aerial spraying of herbicides in Vietnam (Lathrop et al., 1984). The analyses in this baseline study were based on cohort status, i.e., Ranch Hands ("exposed") versus controls ("nonexposed"). In an attempt to determine a link between exposure and clinical endpoints, an exposure index was developed to estimate individual 2,3,7,8-TCDD exposure. The exposure index was later found to be uncorrelated with dioxin levels in Ranch Hand veterans (Michalek, 1989).

In 1988, a report describing a U.S. Air Force and CDC collaborative pilot study utilizing the serum 2,3,7,8-TCDD assay among 200 Air Force Ranch Hand personnel was published. It was noted that the Ranch Hand personnel had significantly higher serum 2,3,7,8-TCDD levels than did controls (Wolfe et al., 1988). These data also indicated that the Ranch Hands as a whole were not as highly exposed to 2,3,7,8-TCDD as was the NIOSH cohort (Piacitelli et al., 1992) and the Seveso population (Mocarelli et al., 1991).

In 1992, the report describing reproductive outcomes among Ranch Hand personnel became available (Wolfe et al., 1992b). In addition to outcome verification, serum 2,3,7,8-TCDD levels were measured in a sample of Ranch Hands (N = 791) and the comparison population

(N = 942). A comparison of the exposure index used in the baseline Ranch Hand study with individual 2,3,7,8-TCDD levels revealed "considerable misclassification" among the study subjects.

As a result of these investigations, it became clear that the likelihood of exposure misclassification in studies of the relationship between 2,3,7,8-TCDD and reproductive events, without direct measures of individual exposure, casts considerable doubt as to the validity of the early findings.

An equally important finding resulting from these investigations was the inability of the exposure indices to classify exposure status in individuals (Needham et al., 1991). 2,3,7,8-TCDD analyses in small subsets of the total study sample, selected on the basis of presumed exposure as defined by an "exposure index" (either military or government records, self-reports, or 2,3,7,8-TCDD levels in soil samples), have demonstrated that the exposure classification schemes employed in these studies were not valid. Therefore, studies that defined exposure as paternal military service in Vietnam should be evaluated without inference to 2,3,7,8-TCDD exposure.

7.13.12.5.3. ***Study results: Atlanta Congenital Defects Program study***. In 1984, the CDC released the findings from the large case-control study that examined the relationship between service in Vietnam and risk of congenital malformations (Erickson et al., 1984). Case-group babies were infants with serious structural malformations born between 1968 and 1980 and registered with the Metropolitan Atlanta Congenital Defects Program (MACDP). Of 7,133 eligible cases, maternal interviews were obtained for 4,929 (69%). Control babies were selected from Georgia vital statistics records and were frequency matched to cases on race and year and hospital of birth. Of 4,246 eligible controls, maternal interviews were obtained for 3,029 (71%). Paternal interview rates were 56% and 57%, respectively.

While response rates were similar by case status overall, among nonwhites significantly more cases were not interviewed. The major reason for nonparticipation was the inability to locate subjects rather than subjects refusing to enroll.

Among the children with congenital malformations, 428 (9%) were fathered by Vietnam veterans and 4,387 (91%) were fathered by non-Vietnam veterans; identical percentages were noted among the control infants. The odds ratio for service in Vietnam and birth defects of any type was 0.97 (95% CI = 0.83-1.14). Odds ratios were also calculated for 96 separate categories of birth defects, with no significant associations observed.

The EOI developed for this study (as described above) also was not associated with total birth defects. However, significant associations were observed for spina bifida, cleft lip with or

without cleft palate, neoplasms, and coloboma. With the exception of the last defect, all three also showed evidence of a dose-response relationship.

For the analysis that examined potential associations between self-reported Agent Orange exposure and birth defects, the frequency of exposure among fathers and each type of malformation was compared with the frequency among fathers and all other defects in an attempt to reduce recall bias. Twenty-five percent (N = 74) of the Vietnam veterans reported that they believed they were exposed to Agent Orange during their service in Vietnam. The analysis of self-reported exposure and birth defects was negative on all counts, in contrast to the EOI analysis, which found significant associations as described above. However, the small numbers of cases of many individual defects resulted in a virtual lack of power to detect any associations for these specific defects.

CDC Vietnam Experience study. As part of a separate, large, multifaceted study mandated by Congress, the CDC evaluated the risk of service in Vietnam and adverse reproductive outcomes (Centers for Disease Control Vietnam Experience Study, 1988d, 1989). The Vietnam Experience Study protocol involved two phases. In the first phase, a random sample of male veterans who met eligibility criteria related to military service was selected for a telephone interview.

Of the eligible "exposed" group, i.e., those veterans who had served in Vietnam, 84% (N = 7,924) agreed to participate, and 84% (N = 7,364) of the nonexposed (those who had not served in Vietnam) were enrolled. Of these 15,288 veterans who completed the telephone interview, a random sample was selected for the second phase, which consisted of a comprehensive medical examination. For this phase, the response rates were 75% (N = 2,490) for the Vietnam veterans and 63% (N = 1,972) for the non-Vietnam veterans group.

During the telephone interview, veterans were questioned about miscarriage, induced abortion, ectopic pregnancy, live births, stillbirths, birth defects, as well as leukemia and other childhood cancers, and major health problems or impairments during the first 5 years of life.

A preliminary analysis of the interview data revealed that the Vietnam veterans had reported 40%-50% more birth defects than the non-Vietnam veterans. In addition, a difference between the cohorts for certain subcategories of malformations, including spina bifida, cleft lip with or without cleft palate, and hydrocephalus, was noted. Therefore, a substudy was conducted to compare the rates of total birth defects in Vietnam and non-Vietnam veterans as these events were recorded on hospital records.

The eligible sample for this substudy consisted of 2,282 veterans who had not yet received their medical examinations, as it would be easier to collect the additional information required and permission to obtain hospital records for their offspring from this group. Hospital records were

obtained for 92% (N = 1,791) of the offspring of Vietnam veterans and 91% (N = 1,575) of the offspring of non-Vietnam veterans.

When birth defects were identified from hospital records, there was no association of Vietnam service with total, major, minor, or suspected birth defects. From the telephone interview data, the odds ratio for Vietnam service and total birth defects was 1.3 (95% CI = 1.2-1.4); in the hospital records substudy, the odds ratio was 1.1 (95% CI = 0.7-1.8). It was concluded that this finding supported the explanation of differential reporting in the telephone interviews.

The odds ratios for selected categories of birth defects calculated from both the telephone interview and hospital records study are presented in Table 7-50. The rate of birth defects increased for both cohorts when malformations were identified in the medical records.

The extent of differential reporting between the two cohorts has also been described (Centers for Disease Control Vietnam Experience Study, 1989). Overall, the authors concluded that agreement between veterans' reports and hospital records for the presence of a birth defect was “relatively poor” for both cohorts. Positive predictive value, sensitivity, and the kappa statistic were slightly lower among Vietnam veterans (Table 7-51). It was further stated that there was no evidence of selection bias or participation bias in this substudy because no differences were noted between cohorts in health histories and demographic or military covariates, and the participation of both groups of veterans was high. However, the subjects in this substudy were selected from the group of veterans who completed the examination. The response rate for this phase of the study was not high, as noted above, with 75% of Vietnam veterans and only 63% of the non-Vietnam veterans participating in the medical examination. Although characteristics of the subset who agreed to undergo physical examination did not differ from the telephone interview sample, no data on those who refused the exam and no reasons for refusing to participate were provided in this paper.

Adjusted odds ratios for two additional outcomes verified in the hospital records substudy, low birth weight (AOR = 1.1, 95% CI = 0.8-1.4) and perinatal mortality (AOR = 1.6, 95% CI = 0.8-3.1), did not differ by Vietnam service status. A race-specific analysis of total, major, and minor defects showed an increased risk for total and minor birth defects among black veterans. The adjusted odds ratio was 3.3 (95% CI = 1.5-7.5) for total defects and 2.9 (95% CI = 1.1-8.0) for minor malformations. This finding is based on very small numbers, however, and on multiple occurrences of two minor defects in two families.

From data obtained during the telephone interview, the adjusted odds ratio for Vietnam service and spontaneous abortion was 1.3 (95% CI = 1.2-1.4). Although an excess among Vietnam veterans was noted across all three trimesters, only the association in the first trimester was significant. There was no attempt to confirm this endpoint by using hospital records. No

significant differences were observed for the reproductive outcomes of induced abortion (AOR = 1.0, 95% CI = 0.9-1.2), stillbirths (AOR = 0.9, 95% CI = 0.7-1.1), ectopic pregnancies (AOR = 1.0, 95% CI = 0.7-1.2), or childhood cancers (OR = 1.5, 95% CI = 0.8-2.8).

In addition to the reported excess of total birth defects in the telephone interview, Vietnam veterans also reported more neural tube defects and hydrocephalus than the non-Vietnam veterans. A second substudy was undertaken to examine the increase in cerebrospinal malformations (CSMs). In this substudy, an attempt was made to obtain hospital records for all of the offspring identified in the telephone interview as meeting one of the following criteria: (1) offspring with a CSM as reported by a veteran, (2) those with a reported condition that suggested a CSM, or (3) all reported stillbirths.

Of the 403 offspring reported to have a CSM, 109 were ineligible, 14% (N = 58) because of conception prior to father's military service and 12.6% (N = 51) classified as miscarriages. Again, the issue of the impact of spontaneous abortion on rates of birth defects is introduced.

The CSM substudy was limited by a poor response rate among the non-Vietnam veterans. The sample thus consisted of 127 offspring of Vietnam veterans (82.5%) and 94 children of the non-Vietnam veterans (67%). Compared with fathers who participated in the CSM study, nonparticipants were more likely to be nonwhite, less educated, unmarried, younger at the time of their child's birth, and have lower general technical test scores. There were also differences in paternal covariates between the participating cohorts that could confound the findings. Compared with Vietnam veterans, non-Vietnam veterans were better educated, had higher general technical test scores, were more likely to be married, were older when their child was born, were less likely to consume alcohol, and were more likely to have had a nontactical primary military occupational specialty (MOS) in the Army and to have served in both the later and earlier time periods.

The number of CSMs reported by the veterans that were verified by hospital records was examined separately by stillbirth and live birth status. Among the reported stillbirths, five CSMs were documented among children of Vietnam veterans and six among the non-Vietnam veterans. Ten of these 11 CSMs had not been reported by the veterans. Positive predictive values derived from this analysis were 6.5% for Vietnam veterans and 8.1% for non-Vietnam veterans.

Among the live births, 21 of 49 reported CSM cases were noted on hospital records for the Vietnam veterans; 6 of the reported 20 cases were observed among the non-Vietnam veterans group, yielding positive predictive values of 42.9% and 30%, respectively.

Tables 7-35 and 7-36 in the unpublished technical report of the study list the fathers' descriptions of the birth defects in their offspring obtained through the telephone interview by cohort (Centers for Disease Control Vietnam Experience Study, 1989). It was intriguing to note that among Vietnam veterans, for 22 of the 55 reported cases of birth defects, the hospital record

finding was "none." In five additional cases, the hospital record finding was "none of the nervous system." Of these 27 nondocumented reports of birth defects, 3 cases were reported as having died within the first year of life. Death during the first year of life was also reported for one of the eight unverified CSMs in the non-Vietnam veterans cohort.

In summary, the CDC investigators concluded that for "most reproductive and child health outcomes studied, Vietnam veterans were more likely to report an adverse event than were non-Vietnam veterans." In the two substudies conducted to compare rates that were identified through hospital records, no significant differences in adverse outcomes between the two cohorts were determined. However, the ability of this study to address the issue of 2,3,7,8-TCDD exposure and reproductive outcome is severely limited. The question of bias still remains in the two substudies. In addition, exposure was defined as service in Vietnam, which does not provide much insight into the question of the reproductive toxicity of 2,3,7,8-TCDD.

American Legion study. The relation of self-reported exposure to Agent Orange and reproductive outcomes was part of a study conducted among 6,810 American Legionnaires who had served during the Vietnam War (Stellman et al., 1988). Information was obtained through a questionnaire mailed to 2,858 veterans (42%) who had served in Southeast Asia and 3,933 veterans (58%) who had served elsewhere. No association between Agent Orange exposure and difficulty with conception, time to conception of the first child, or infant birth weight was observed. However, the proportion of spontaneous abortion was significantly higher among the spouses of veterans who served in Vietnam (7.6%) compared with controls (5.5%) ($p<0.001$). These figures were below the background rate for recognized spontaneous abortion (10%-15%) in the general population.

The significance of these findings is limited by the lack of verification of self-reported exposure, the low response rate, the lack of outcome verification through medical records, and the selection of veterans from the American Legion organization, as they may not be representative of all veterans who served during the Vietnam conflict.

Boston Hospital study. A case-control study to investigate the relationship between paternal military service in Vietnam and risk of spontaneous abortion was conducted at Boston Hospital for Women (Aschengrau and Monson, 1989). Cases identified through hospital records were spontaneous abortions $\leq$27 weeks gestation that occurred between July 1976 and February 1978 (N = 201). Paternal identity information from the hospital birth records was linked with national and State military records to identify those fathers who had served in Vietnam. Frequency of service in Vietnam was compared for cases and all full-term live birth controls (N = 1,119) born at

the hospital during this time period. No association was detected (OR = 0.88, 95% CI = 0.42-1.86).

The same investigators conducted a subsequent study that expanded the outcomes examined to include adverse outcomes in late pregnancy (Aschengrau and Monson, 1990). Case infants identified through hospital records included 857 congenital malformations, 61 stillbirths, and 48 neonatal deaths that occurred at the hospital during August 1977 and March 1980. "Exposure" was defined by using the same method as in the previous study. Frequency of paternal service in Vietnam was compared for cases and 998 normal-term infant controls. Again, no associations with any of these later adverse outcomes were detected (Table 7-48).

The Ranch Hand study -- reproductive outcomes: Baseline study - 1984. This initial report of the health of Ranch Hand personnel used cohort status (Ranch Hand vs. comparisons) as the basis for evaluating effects and exposure. This group of exposed veterans included those who served in Vietnam during 1962-1965, when Herbicides Purple, Pink, and Green were sprayed. These herbicides had higher TCDD concentrations (33 ppm, 66 ppm, and 66 ppm, respectively) than Herbicide Orange with 2 ppm TCDD (Lathrop et al., 1984).

The protocol consisted of a comprehensive personal and family health questionnaire and a physical examination, including an in-depth laboratory analysis. The response rates for each phase of the protocol were quite different both within and between cohorts. Participation in the questionnaire phase was 97% (N = 1,174) for the Ranch Hands and 93% (N = 956) for controls. In the physical examination phase, participation dropped to 87% (N = 1,045) for the Ranch Hands and 76% (N = 773) for controls.

Nonresponders were "on the average" younger than participants. Ranch Hand enlisted personnel had higher participation rates than officers, and black Ranch Hand officers had lower participation rates than nonblack officers. The difference in the response rates for the physical examination phase of the protocol was ascribed partially to the active encouragement of the Ranch Hand Association for participation and the intense media coverage that the study received. The authors stated that the "majority" of reasons given for nonparticipation were "no time-no interest" and passive refusal.

The reproductive outcomes evaluated in this phase of the study were ascertained through questionnaires obtained from both the veterans and their spouses or partners. A total of 7,399 conceptions were analyzed in this report. There were 3,293 conceptions among 1,174 Ranch Hands and 4,106 among the 1,531 controls.

No significant differences were reported for four "measures of fertility": (1) the number of childless marriages, (2) the number of couples having achieved their desired family size, (3) the

number of childless marriages per total number of marriages, and (4) the number of conceptions per years spent together, which included nonmarital relationships. The fertility analysis was performed on the total number of conceptions reported and was not adjusted for any confounding variables. Moreover, exposure in this analysis was defined by a simple dichotomy of Ranch Hands versus controls.

To examine the relationship between Ranch Hand status and spontaneous and induced abortion, stillbirths, and live births, exposure was stratified by pre- and post-Southeast Asia (SEA) service. The unadjusted analysis indicated that Ranch Hands had increased spontaneous abortion rates in both pre-SEA duty ($p = 0.06$) and post-SEA duty ($p = 0.13$). The report qualified this by stating that these inferences were based on analyses that were not adjusted and that "key factors affecting pregnancy outcome are of questionable value," although no similar qualification was given for the fertility analysis. After adjustment for maternal age, smoking, and alcohol use and paternal age, no significant difference was observed for spontaneous abortion.

Among the live births with complete data obtained to allow for adjustment of cofactors, no difference in risk of prematurity was noted. However, the estimate of gestational age, and all other outcomes studied, were based on parental report, which may be subject to errors in recall, and it was not clear whether prematurity was analyzed as only a dichotomous variable (<37 weeks, ≥ 37 weeks) or as a continuous variable. No analyses for birth weight differences by exposure status were performed in this effort; more recent data on IUGR and other pregnancy outcomes (e.g., infant death) are presented in Section 7.13.12.8.

Unadjusted analyses were conducted to examine the relationship between exposure and neonatal death, infant death, physical handicaps, birth defects, and learning disabilities. These analyses were stratified by pre- and post-SEA service periods. The results indicated that Ranch Hands were borderline statistically significantly more likely to report physical handicaps ($p = 0.07$), birth defects ($p = 0.08$), and neonatal deaths ($p = 0.02$) in the post-SEA analysis. After adjustment for the maternal and paternal covariates described above, the relationship with birth defects achieved statistical significance ($p = 0.04$); the other relationships were not statistically significant.

Twelve of the 76 birth defects reported to have occurred among the Ranch Hands after post-SEA service were skin anomalies (ICD Code 757). When these anomalies are excluded, this relationship is no longer statistically significant ($p = 0.14$), although "still of interest."

Finally, semen samples from Ranch Hands (N = 560) and controls (N = 409) were analyzed for sperm count and morphology. The response rates for this parameter were 72.5% and 76.5%, respectively, although some of the samples submitted were ineligible for analysis because of prior vasectomies and orchiectomies. Linear regression techniques examined sperm count as a

continuous variable and percentage of sperm with abnormal morphology as a dependent variable. Independent variables were age and exposure to industrial chemicals. No differences in either parameter were identified.

This finding contrasts with the semen analysis results obtained among 324 Vietnam veterans and 247 non-Vietnam veterans in the Vietnam Experience Study (Centers for Disease Control Vietnam Experience Study, 1988a). That analysis indicated that Vietnam veterans had significantly lower sperm concentrations (OR = 2.3, 95% CI = 1.2-4.3), below the clinical reference value (20 million cells/mL), than the non-Vietnam veterans. In addition, Vietnam veterans had a significantly lower average proportion of "normal" sperm heads. These analyses were adjusted for six covariates, although industrial chemicals were not among them.

The Ranch Hand study - 1992. The significant association between Ranch Hand status and birth defects found in the previous study was of sufficient interest to launch a massive project to verify all reported conceptions and pregnancy outcomes through medical record abstraction. In addition, in 1987 serum 2,3,7,8-TCDD levels were obtained from a subset of Ranch Hands and controls. In 1992, the Air Force released the results of the first study that examined the relationship between direct measure of individual serum 2,3,7,8-TCDD levels and verified reproductive outcomes (Wolfe et al., 1992b). A total of 4,607 conceptions were examined in this study; 2,533 were contributed by 791 Ranch Hands, and 2,074 were contributed by 768 controls.

Ranch Hand personnel were shown to have significantly higher 2,3,7,8-TCDD levels compared with the controls. The median values were 12.8 pg/g and 4.2 pg/g, respectively. The 98th percentile for Ranch Hands was 166.4 pg/g; for controls, 10.4 pg/g. 2,3,7,8-TCDD levels were determined in 1987. These results were used to estimate initial doses received during the veterans' tour in Southeast Asia but not the 2,3,7,8-TCDD level at the time of conception.

The fertility analysis performed in the earlier study was not repeated according to level of serum 2,3,7,8-TCDD (an omission currently being addressed; personal communication, J. Michalek, 2000). There was a significant variation in the association between 2,3,7,8-TCDD and miscarriage with time since SEA tour ($\leq$18.6 years or >18.6 years) and time of conception (pre- or post-SEA tour) among Ranch Hands with current 2,3,7,8-TCDD levels >10 ppt ($p = 0.01$) (Table 7-52). This was attributed to the low miscarriage rate among the pre-SEA Ranch Hands with current 2,3,7,8-TCDD levels >33.3 pg/g lipids. In examining post-SEA conceptions only, a linear trend can be seen for spontaneous abortions and increasing 2,3,7,8-TCDD levels among Ranch Hands who had "late tours" in SEA, i.e., less than or equal to 18.6 years had elapsed between their tour of duty and current 2,3,7,8-TCDD levels. The opposite trend is noted in Ranch Hands with "early tours," i.e., more than 18.6 years had elapsed between the end of duty and the 1987 blood

draw. It was concluded that 2,3,7,8-TCDD did not affect the rates of miscarriage because it seemed "implausible that dioxin would act differently in the two groups."

An alternative explanation might be that there is a relationship, but it cannot be detected by this type of analysis. To evaluate the relationship between 2,3,7,8-TCDD level and spontaneous abortion, 2,3,7,8-TCDD level at the time of conception must be considered. Assuming a half-life of 7 years in humans (Pirkle et al., 1989), it would seem reasonable, for example, to assume that the two groups of Ranch Hands with 2,3,7,8-TCDD levels of 10-14.9 pg/g of lipids with post-SEA conceptions may have had very different 2,3,7,8-TCDD levels at the time their children were conceived. This is possible because the early-tour veterans had more time to decrease their body burden of 2,3,7,8-TCDD before their bloods were drawn in 1987 than did their late-tour counterparts. Paternal TCDD level at the time of conception was estimated in a subsequent analysis of these data (Wolfe et al, 1995).

Table 7-48 illustrates the risk estimates for reproductive outcomes in the Ranch Hand study. Interestingly, the only statistically significant associations between 2,3,7,8-TCDD and adverse events (total birth defects, genital anomalies, and urinary system anomalies) occurred among Ranch Hands with 2,3,7,8-TCDD levels of 15-33.3 pg/g of lipids and not among those in the >33.3 pg/g group.

The report stated that the "expected dose-pattern" for 2,3,7,8-TCDD and total adverse reproductive outcomes (miscarriage, tubal pregnancy, other noninduced abortive pregnancy, or stillbirth) is the "linear one in which the highest anomaly rate occurs at the highest levels of dioxin." This statement raises at least two questions. If a linear response is assumed, might this imply that very early pregnancy losses occur at the highest 2,3,7,8-TCDD levels, so that the conceptus would not survive long enough to be clinically recognized? Or are very early pregnancy losses and clinically recognized spontaneous abortions two separate entities with different thresholds? Such a scenario has been suggested to explain changes in spontaneous abortions observed after exposure to radiation in Hiroshima (Miller and Blot, 1972).

These questions are of interest because the rate of each of these endpoints may directly affect the rates of all subsequent reproductive outcomes that are available for examination. The miscarriages do not include the very early losses, as 99.6% of reported miscarriages were verified through medical records. Very early losses are unlikely to be identified by the woman or clinically.

An analysis in which the 1987 dioxin levels are used to estimate dioxin level at time of conception would be a worthwhile effort. If a relationship between paternal 2,3,7,8-TCDD level and adverse reproductive outcome does exist, this may help determine the dose-response pattern of the relationship.

No evidence was found to support an association between 2,3,7,8-TCDD and total adverse outcomes. These findings should be viewed with caution in view of the above comments concerning the unexplored area of events early in gestation.

Overall, there was little convincing evidence to support an association between birth weight, examined as both a continuous variable and dichotomized (<2,500 g or ≥2,500 g), and paternal 2,3,7,8-TCDD level. Analyses that adjusted for covariates included maternal and paternal age, maternal alcohol use and smoking, and race of the father. No assessment of 2,3,7,8-TCDD and prematurity was reported.

The potential association between cohort status and birth defects was examined for all defects combined and 12 additional categories of malformations. The only categories with sufficient numbers of verified post-SEA cases to detect a relative risk of 2 were total birth defects (229 cases among 1,045 Ranch Hands and 289 cases among 1,602 controls) and musculoskeletal deformities (132 cases among Ranch Hands and 180 among controls).

A significant variation was observed in the association between total birth defects ($p = 0.03$), defects of the respiratory system ($p = 0.03$), and urinary system abnormalities ($p = 0.04$) by Ranch Hand versus control status with time of conception (pre- or post-SEA). All of these findings were due to a lower rate among Ranch Hands in the pre-SEA conceptions and a higher rate among the post-SEA conceptions for the Ranch Hands.

Analyses of birth defects by 2,3,7,8-TCDD level did not find any "consistent patterns" to support an association. For example, among children of enlisted flying and enlisted ground personnel, children of Ranch Hands with 2,3,7,8-TCDD levels ≤10 pg/g lipids had higher rates (433 per 1,000 and 317 per 1,000) than children of controls with background 2,3,7,8-TCDD levels <10 pg/g lipids (229 per 1,000). However, rates of children of enlisted ground personnel with 2,3,7,8-TCDD levels ≥33.3 pg/g lipids were not significantly elevated. Again, these analyses were not based on 2,3,7,8-TCDD level at time of conception. Moreover, if the higher 2,3,7,8-TCDD levels were related to early pregnancy loss, these results would make more biological sense, as the abnormal conceptuses due to 2,3,7,8-TCDD exposure would have been lost before the pregnancy was recognized.

There was also a significant association between 2,3,7,8-TCDD levels and neonatal death (OR = 5.5, 95% CI = 1.5-20.7). Insufficient numbers (N = 13) precluded the calculation of an adjusted odds ratio for this finding.

Finally, no association was detected between 2,3,7,8-TCDD level and either sperm count or percentage of abnormal sperm. These analyses were based on semen samples that had been collected in 1982.

The Ranch Hand study - 1995. This study includes pregnancies to those men described above; but the group has been restricted to confirmed pregnancies occurring after the beginning of service in Vietnam in those men who participated in the 1987 physical, gave blood to evaluate serum dioxin levels, and had usable laboratory measurements (Wolfe et al., 1995). This group potentially included 872 Ranch Hand veterans and 1,036 comparison subjects. In fact, 454 Ranch Hand veterans (RH) yielded 1,006 recognized conceptions and 419 veterans yielded 792 live births, while 570 comparison subjects yielded 1,235 recognized conceptions and 531 controls yielded 981 live births. Paternal dioxin level at the time of conception was used to generate four exposure groupings: (1) comparison with current level ≤ 10 ppt, (2) RH with current level ≤ 10 ppt, (3) RH with current level > 10 ppt and estimated initial level≤ 110ppt, and (4) RH with current level > 10 ppt and estimated initial level > 110 ppt. Comparisons with > 10 ppt dioxin were eliminated from the group, as having higher than "background" levels without an understanding of the probable source of the exposure. The children in the second group (RH with < 10 ppt) were considered separately because the fathers' levels could not be used to estimate exposure levels at the time of pregnancy. Levels at conception were estimated using a fixed 7.1 year half-life with a first-order decay rate. As the time between measurement (1987) and conception varied from 15 to 26 years, the number of half lives ranges from about two to a little over three.

All analyses were adjusted for paternal race, age and military occupation and maternal age, and smoking and drinking during pregnancy. In addition to these, analyses of spontaneous abortion were adjusted for spontaneous abortions occurring prior to service. The proportion of men who fathered recognized pregnancies or live births were about the same in both groups, Ranch Hand or comparison.

Analyses show modest, borderline significant increases in spontaneous abortion (Table 7-48), defects of the circulatory system and heart (OR: 2.3; 95% CI = 1.0-5.1), all anomalies (OR: 1.3; 95% CI = 1.0-1.6), major birth defects (OR: 1.7; 95% CI = 1.1-2.7), and some developmental delays (OR: 1.5; 95% CI = 1.0-2.3), all of these for the low RH group only. Dose-response patterns were not observed, and more detailed analyses were not possible because of the small number of adverse outcomes in each grouping.

7.13.12.5.4. ***Comment.*** The data described above do not present strong evidence for an association of paternal dioxins with developmental effects, occurring pre-conceptionally, prenatally, or identified around the time of birth. These studies are limited by the ability to accurately define exposure at the critical windows for the events. The developmental studies are retrospective, typically using a surrogate measure of exposure (recall, records of work place or service in Vietnam, etc.). Overall, only a few of the developmental studies have collected

biological measurements of dioxin levels at the time of the study (e.g., the Ranch Hand studies, the CDC studies of Vietnam experience in ground troops). Several efforts have compared surrogate exposure measures with serum levels: (1) a comparison of serum levels with CDC's exposure opportunity index and with the subject's self-report of exposure (CDC, 1988) showed that the surrogates were not a good estimate of the measured levels; (2) a rather small comparison of Vietnam veterans (10 reported exposed, 10 reported little or no exposure) and 27 Vietnam-era veterans (Kahn et al., 1988) showed a significant elevation for the exposed men compared to the other two groups; and (3) in the Ranch Hand study, comparisons of serum levels from a sample of men to the exposure index revealed "considerable misclassification" (Wolfe, 1992b). Given that the second study was rather small, and confidence intervals included background exposure, those data are of limited use. In general, the results described above suggest that many of the studies reported have subjects misclassified by exposure. If so, effects of exposure could be masked.

Few of the results in the studies give an indication of an effect of dioxin on pregnancy outcomes; some did show increased birth defects, but many of these were based on small numbers. As mentioned above, the potential effects of fetal loss on the examination of malformations is difficult to address, but might affect these results, especially in the higher exposure groups.

7.13.12.6. ***New Issues - Developmental Outcomes (1996-1999)***

7.13.12.6.1. ***Dental effects.*** An investigation of dioxin exposure and tooth development was done in Finnish children as a result of studies of dental effects in dioxin-exposed rats, mice, and nonhuman primates (Chapter 5), and in PCB-exposed children (Rogan et al., 1988). The Finnish investigators examined enamel hypomineralization of permanent first molars in 6-7 year old children (Alaluusua et al., 1996; Alaluusua et al., 1999). These molars were mineralized during the postnatal period, when the children are exposed through breast feeding. The population was first identified in Helsinki and Kuopio as part of an international effort, coordinated by WHO/EURO, to evaluate possible health effects associated with levels of PCDDs and PCDFs in breast milk. Approximately 150 women were recruited from each area, with the commitment to provide a breast milk sample at 4 weeks postpartum, if still lactating. A total of 167 samples were obtained, with about a 50% response rate in Helsinki (77 women provided samples) and about 60% from Kuopio (90 women provided samples). Exposure to each child was estimated using the TEQ for PCDDs and PCDFs and their elimination constant, plus the length of time the child was breast fed. At age 6 or 7, 102 children's teeth were examined (61% of those with breast milk samples). Defects were scored as to severity and size, blind to exposure score. Duration of lactation ranged from 1 to 36 months (mean 10.5 +/-5.5 sd) and TEQs from 3.8 to 99.4 pg/g milk

fat (mean 19.8 +/-10.9 sd). The length of time breast feeding was not significantly associated with mineralization changes, nor was the TEQ alone. However, when the levels and length of breast feeding were combined in an overall score, a statistically significant association was observed (r = 0.3, p = 0.003, regression analysis). The beta from the analysis was not presented, so the slope of the relationship is unknown. The levels in breast milk might also be a surrogate for *in utero* exposure; these samples were collected after 4 weeks of breast feeding, and so might not be as good a surrogate as samples collected earlier in lactation.

7.13.12.6.2. ***Comments*****.** These data present interesting findings relating hypomineralization of permanent first molars and TEQ exposure through breast feeding. Unfortunately, the presentation of the results is incomplete: They present limited information on adjustment for other risk factors/ confounders, have a small number of subjects and consequently low power, and since the beta was not presented for the regression analyses, the potential biological significance cannot be examined. This would be an interesting outcome to examine in additional studies.

7.13.12.7. ***Sex Ratio at Birth***

Sex ratio has been reported to vary with a great number of factors, including race, timing of conception within the cycle, certain parental diseases, and gestational age (James, 1987; Kellokumpu-Lehtinen and Pelliniemi, 1984). The sex ratio is defined by demographers as (number of male births)/(number of female births)*100. However, many of the papers covered in this section present the proportion of male births of the total, rather than an actual ratio. In this discussion, while the endpoint will still be called "sex ratio," all data will be presented as the proportion for consistency with the original literature and ease of comparison among the studies.

In response to a report of hormonal variations in men occupationally exposed to dioxin (Egeland et al., 1994), James (1995, and repeated later [1997a,b]) proposed that with high gonadotropin and low testosterone levels, sex ratios could be lowered (fewer male births compared to female births). A 1996 letter (Mocarelli et al., 1996) reported an excess in female births conceived following the Seveso accident. This included births from April 1977 to December 1984, a time period approximating the half-life of dioxin. Seventy-four births occurred during this time within the A-zone; 26 (35.1%) were males and 48 females (65.9%), compared to the expected value (51.4% males [James, 1987]) used by the investigators. Since 1988, these investigators measured dioxin levels in archived serum samples. Of the 74 births, 17 occurred in families with both parents in the A-zone. "Elevated" dioxin level was defined in this report as > 100 ppt (lipid adjusted), and ranged from 104 to 2,340 pg/g lipid in fathers and 126-1,650 pg/g lipid in mothers; 100 ppt or less was considered within normal range. Of this group, 100% (N =

12) births were female. Eighty percent of those with "low" dioxin levels were male (N = 5). In an unadjusted analysis, the overall sex ratio (0.235) was significantly different from the "expected value" ($X^2 = 12.68$, $p<0.001$), in an analysis unadjusted for other factors related to variations in sex ratio. After this time period, from 1985 to 1994, the sex ratio increased to 0.484 (N = 124), a value not significantly different from the "expected value." The authors mentioned that the reduced sex ratio in this small series of births could have resulted from excess males in spontaneous abortions (a theory that cannot be assessed with existing data), or that changes in sex ratio could result from the changes in hormonal balance.

The investigators revisited the Seveso Cohort, identifying all births for those who lived in A, B, or R contaminated at the time of the 1976 explosion (Mocarelli et al., 2000). Parents with less than or equal to 15 ppt TCDD were compared to those above (all together, or split into categories: >15-80 ppt, >80 ppt). After comparing levels in mothers and fathers in 1976, for a total of 674 births in 452 families, a pattern of reduced birth ratios was noted for paternal exposure only, or where both parents were exposed, but not where only the mother was exposed. More detailed analyses focused on paternal exposure, with the observation that the reduction in sex ratio was greater for those fathers who were less 19 years old at exposure in 1976 (sex ratio: 0.382; 95% confidence intervals: 0.30-0.47) versus those who were older (sex ratio: 0.469; 95% confidence intervals: 0.41-0.53). In additional, the sex ratio in offspring to both groups of exposed fathers were significantly less than unexposed fathers of all ages (sex ratio: 0.557; 95% confidence interval: 0.50-0.62). The authors did not present data on age specific sex-ratio among the unexposed fathers, thus leaving the comparison incomplete. An additional analysis would have been more informative: the interaction of paternal age by paternal exposure level for sex ratio. Also, details of factors considered and controlled in the multivariable analyses were not presented, limiting the examination of this interesting study. This study presents intriguing data on the possible relationship of sex ratio and age at dioxin exposure.

Dimich-Ward (1996, 1998) and colleagues examined 23,829 production and maintenance workers employed in 11 sawmills in British Columbia between 1950 and 1985. These sawmills used dioxin-contaminated chlorophenate as a fungicide for lumber. These workers were linked with vital records on live and stillbirths for 1952-1988, obtaining data on the birth date and sex of the 19,675 children born to the workers after beginning employment. The sex ratio of the entire group was 51.6% male and 48.6% female, proportions consistent with those typically observed. Exposures in this study were estimated by 10 experienced workers, because no measurements were available. These estimated measures were then combined with cumulative hours worked during different time periods. The exposure breakdowns, however, were not used in examination of these data; the proportion of males and females were erroneously presented (reversed) in the

heading of a table. Then James (1997) tested these overall proportions, found them statistically significant, and stated that they supported his hypothesis. A correction of the headers (Dimich-Ward, 1998), stating that the numbers had been transposed, resulted in a retraction of James' letter (1998). This study does not contribute much to the discussion, given the lack of specific exposure data, either on dioxins or other potential exposures.

Michalek and co-workers (1998) examined the Operation Ranch Hand study group for differences in sex ratio. Men were grouped in one of four exposure categories (comparison [n=1254] and background [n=346] both less than 10 ppt, low [n=277], and high [n=280] with >79 ppt) based on serum blood levels in 1987 or 1992 extrapolated to the time of conception, and using a fixed 8.7 year half-life for dioxin. No maternal data on dioxin exposure were available, but the investigators suspected that mothers had "background" levels. The analyses looked at those children conceived within 1 month, 1 year, or 5 years, and any time post-service. Confidence intervals (95%) were calculated using the binomial distribution. No significant differences were observed in any analyses. The authors suggest that the findings in Seveso might be associated with maternal exposure.

Rogan et al. (1999) evaluated sex ratio in their population of Taiwanese children whose mothers were affected by exposure to dioxin-like compounds (PCBs and PCDFs) after consumption of contaminated cooking oil (Yu-Cheng). Health effects identified in this population included developmental delays and ectodermal effects in children born to affected mothers. Overall the proportion of males in live births (n=137) from 1978-1985 was 0.496. When the first year was eliminated, to examine only those births conceived at the time the oil was first sold (June 1998), the proportion of males was 0.508, not different from that number used as a comparison on other analyses.

Examination of 44 (of 59) primiparous mothers in a cotton-growing region in Kazakhstan (Hooper et al., 1999), showed that those living near a reservoir with agricultural runoff (zone A) had higher levels of dioxin in breast milk than those located >10 miles away (zone B). This information was then used to group all live births in the region occurring 2-8 weeks before the sampling period in 1997. Women in zone A (N = 17) had mean breast milk levels of 53 pg/g versus those in zone B (N = 24) with mean levels of 21 pg/g. When the data were examined by zone, or by TCDD level ($\geq$30 pg/g versus < 30 pg/g), statistically significant differences were not observed. The numbers were small, limiting the power, but in all the subgroups except zone B (45.8%), more males were born (proportions ranging from 54.5% to 70.6%).

More recently, NIOSH (Schnorr et al., in press 2001) has examined its occupational cohort study for altered sex ratio at birth. The study compared births of male workers' mates (292 births with <20 ppt TCDD; 104 with 20-254 ppt TCDD; 88 with 255-1119 ppt TCDD; and 60 with

1120+ ppt TCDD) to 647 births to never-exposed referents (<20 ppt TCDD). The exposed proportions range from 0.51 to 0.55; none were significantly different from the referent pregnancies (proportion=0.54), either in unadjusted or adjusted analyses (adjusted for maternal education and paternal race). The pregnancies in this occupational setting experienced higher paternal TCDD exposures than the environmental studies; even in the highest exposure group, while limited in size, did not experience a change from the referents (1120+ ppt TCDD: proportion=0.55; 95% CI: 0.49-0.61 versus <20 ppt TCDD: proportion=0.54; 95%CI: 0.52-0.56)

7.13.12.7.1. ***Comments.*** Many of these analyses provide limited data for one or more of the following reasons: limited exposure data, no or limited adjustment for other risk factors/confounders, assumption of a gold standard of 51.4% males (and not having comparison groups) or small numbers. The recent NIOSH analysis, of occupationally exposed (adult) men, with a broad range of exposure, an appropriate comparison group and adjustment of the analyses, did not observe any differences.

Sex ratio at birth was significantly depressed in a group of 17 children in zone A of Seveso in the years shortly following the industrial accident. This pattern disappeared a few years later. However, a recent expanded effort suggests that paternal age at the time of exposure may be a key factor. Sex ratio differences were not observed in other groups examined. If effects are restricted to offspring of fathers less than 19 years old, as suggested in the new Seveso study, the lack of effect elsewhere could be explained by the groups examined: maternal levels of dioxin in community studies or studies of men older than 19. The findings in the most recent Seveso study emphasize the need for more attention on male-mediated development effects, and the potential importance of exposures prior to and during puberty.

7.13.12.8. ***Growth, Malformations, and Infant Mortality***

In recent years, those investigating developmental outcomes have started looking at a variety of measures of prenatal and postnatal growth. Outcomes considered have included birth weight and size, intrauterine growth retardation (IUGR), and postnatal measures up to the age of 42 months. IUGR, also known as small-for-gestational-age, basically combines information on birth weight with the length of gestation. Children with low birth weight are not necessarily IUGR because of different expected birth weights at different gestational ages.

New analyses of growth of children in the smaller Dutch study (38 children, Pluim et al., 1997) have been made. Birth weight data were recorded at delivery by the obstetrician or midwife. Weight and length were recorded at 10 and 20 weeks during postnatal examination, and used to calculate the Quetelet index (weight/length^2). In addition to these measures, the

circumference of the head was measured (1, 11, and 26 weeks) and area of the liver determined by ultrasound (10 days and 11 weeks). No differences were found between low and high exposure for any of the growth measures (using Student's t-test).

The Rotterdam study also examined birth weight and growth (Patandin et al., 1998). Birth weight was only evaluated in relation to PCBs and so will not be discussed here. Postnatal growth was examined in relation to TEQs for dioxins, furans and PCBs in breast milk multiplied by weeks breast fed. Using multivariable regression, and controlling for other factors potentially related to growth, no significant differences were observed at 3 months. A statistically significant decrease in growth in length was observed (beta = -0.21, $p = 0.04$) with TEQ, but not with weight or head circumference between 3 and 7 months of age. No differences were observed between 7 to 18 months or 18 to 42 months.

Another study examined the effects of background levels of PCDD and PCDF levels and birth weight in all consecutive births from January-May 1987 in one maternity clinic in an urban area (Helsinki, Finland) and in a rural area (Kuopio province) (Vartiainen et al., 1998). Approximately 150 women were recruited from each area, with the commitment to provide a breast milk sample at 4 weeks postpartum, if still lactating. A total of 167 samples were obtained, with about a 50% response rate in Helsinki (77 women provided samples, representing 26% of births) and about 60% from Kuopio (90 women, representing 30% of births). TEQs of breast milk were significantly higher in the urban area (26.3 pg/g TEQ versus 20.1 pg/g TEQ in Kuopio province). Correlation analyses (Pearson's correlation) were significant for all births and all male births. Regression analyses of all children showed a decreasing relationship of birth weight with TEQ of milk (beta = -0.00228), which appeared to be primarily in male births (beta = -0.00302; versus in females, beta = -0.00107). Statistical significance of the regressions was not presented, nor were details on other characteristics included in the models. When restricted to examination of first-born children (N = 84), no significant relationships were observed.

One report examines placental AH receptor binding of TCDD in IUGR, preterm birth, and structural malformation (Okey et al., 1997). The study group, 86 births, included 21 preterm births, 20 with IUGR (8 of these were preterm), and 7 infants with structural malformations. The B_{max} (concentration of AH receptor sites for TCDD) and K_d (affinity for binding of TCDD) were not significantly different for the different pregnancy outcomes. Some modest increases were observed for B_{max} (and less so for K_d) with IUGR (N = 10) and structural malformations (N = 5) over normal deliveries (N = 23), but the power was limited by small numbers.

Michalek and colleagues (1998) examined IUGR in their study of the veterans of Operation Ranch Hand. The analyses included 2,082 liveborn, singleton births occurring during or after the father's service in Southeast Asia, for whom paternal serum measures of dioxin were

available. Of the 2,082, 859 were in the Ranch Hand group and 1,223 were comparisons. If serum dioxin levels in 1987 or 1992 were >10 pg/g lipid, the investigators modeled the father's level at the time of conception of the child. For those at or under 10 pg/g lipid, levels at conception were considered to be "background." Levels greater than 10 and less than 79 were "low," and above that were "high." Length of gestation and birth weight were obtained from labor and delivery records. Included births occurred between 1959 and 1992; the earliest births were from comparison subjects. No differences were observed in IUGR across the exposure groups. Small, nonsignificant increases were seen in preterm birth (<37 weeks gestation) for Ranch Hand background and high groups (RR = 1.4, 95% CI = 0.9-2.3 and RR = 1.3, 95% CI = 0.8-2.3, respectively). Significant increases were observed in these groups for neonatal death (within the first 28 days of life): RR = 3.2, 95% CI = 1.0-10.3 for background, and RR = 4.5, 95% CI = 1.5-14.0 for high (for the low group: RR = 1.5, 95% CI = 0.3-7.5). Most of the Ranch Hand deaths were due to short gestation and low birth weight, but only a third in the comparison group. While these numbers were relatively small, the proportions in the background and high groups were much higher: comparison: 3.7% of 54 preterm births; background: 25% of 20; low: 0% of 6; high: 31.3% of 16. An examination of these data using occupation, so as to include all births, not just those with serum measures, also showed elevated proportions of infant deaths in preterm births in the exposed versus the comparison group. However, the proportions did not follow the relative exposures observed among the categories.

7.13.12.9. *Comment*

At this time, the data relating growth measures and neonatal death are limited. For example, in one study, decrements in length (but not other measures of growth) were observed early, but disappeared with increasing age (Patandin et al., 1998). Some changes were observed in the Ranch Hand study for preterm birth and neonatal death, but these did not follow an exposure-response relationship (Michalek et al., 1998). The Finnish data are interesting because birth weight did decrease in males, with increasing TEQ, but the lack of detail on the statistical analyses makes interpretation difficult.

7.14. NONCANCER EFFECTS OF INGESTION OF RICE OIL CONTAMINATED WITH POLYCHLORINATED DIBENZOFURANS, QUATERPHENYLS, AND BIPHENYLS IN JAPAN (YUSHO) AND TAIWAN (YU-CHENG)

This section briefly reviews the noncancer effects observed in Yusho (Japan) and Yu-Cheng (Taiwan) victims, individuals exposed by ingestion to large concentrations of compounds structurally related to dioxins, namely polychlorinated dibenzofurans, quaterphenyls, and biphenyls. The history of each incident, the chemicals in question, and levels of exposure are described in this chapter. In addition, other reviews have summarized the numerous papers dedicated to Yusho and Yu-Cheng (Lü and Wong, 1984; Kuratsune, 1989; Rogan, 1989).

Reports describing effects among individuals who ingested the contaminated rice oil both in Taiwan and Japan are limited to acute rather than chronic effects. Studies have not comprehensively evaluated long-term effects even though over 30 years have passed since the Yusho incident and over 20 years since the Yu-Cheng incident and that serum levels of some contaminants are available for both populations. Recent epidemiologic studies have concentrated on the development of offspring of Yu-Cheng mothers. These children were exposed *in utero* at the time the contaminants were ingested, or were conceived after the poisoning and were exposed to residual contaminants transplacentally or through breast milk (Chen et al., 1992; Lai et al., 1993, 1994; Hsu et al., 1993; Guo et al., 1993,1994a,b, 1995a,b,1996; Chao et al., 1997; Yu 1994, 1998).

7.14.1. Acute Effects in Adults and Children Directly Exposed to Contaminated Rice Oil

In both groups, the most notable acute effects are dermatologic and neurologic signs and symptoms of fatigue, headaches, and gastrointestinal distress (nausea, vomiting, abdominal pain) (Kuratsune, 1989; Rogan, 1989).

7.14.1.1. *Yusho*

The initial recognition of Yusho occurred in 1968. As of 1983, a total of 2,060 individuals were identified as part of the Yusho population (Masuda et al., 1985). Five years after exposure ended, the mean concentrations of PCBs in the adipose tissue, liver, and blood of Yusho cases were 1.9 ppm, 0.08 ppm, and 6.7 ppb (Masuda et al., 1985), respectively, which were about twice the levels in the control group. Adipose tissue levels of PCDFs ranged from 6 to 13 ppb (Masuda et al., 1985). Sixteen years after exposure, mean PCQ level in adipose tissue of Yusho cases was 207 ppb, approximately 100 times the level in Japanese controls (Kashimoto et al., 1985).

In addition to the major health effects, other possible outcomes were examined. Effects observed shortly after exposure included elevated triglyceride levels and effects on female reproductive hormones, noted by changes in menstrual and basal body temperature patterns and lowered excretion of estrogens and pregnanediol in exposed women (Kuratsune, 1989). However,

fertility and other measures of reproductive function were not evaluated. Evidence of chronic bronchitis and respiratory infections still remained 14 years after exposure ended (Nakanishi et al., 1985). However, more than 10 years postexposure, PCB levels were not related to levels of serum triiodothyronine (T3), thyroxine (T4), and thyroxine-binding globulin (TBG) (Murai et al., 1987). Although the liver is the suspected target organ for halogenated hydrocarbons, and marked proliferation in the endoplasmic reticulum was observed, clinical evidence of liver damage, such as alterations in liver enzymes or liver disease, was not observed (Kuratsune, 1989).

Dermatologic effects were the most evident signs, characterized by hyperpigmentation of the nails, gingivae, and face, and by nail deformities, horny plugs, comedones, acneform eruptions, cysts, and other abnormal keratotic changes (Urabe and Asahi, 1985). Acneform eruptions were observed on the face, cheeks, auricles, retroauricular areas, inguinal regions, and external genitalia (Urabe and Asahi, 1985). More than 80% of Yusho cases experienced one or more dermatologic effects (Kuratsune, 1989), which diminished in severity over time (Urabe and Asahi, 1985).

Ophthalmologic effects were characterized by swelling and hypersecretion of the meibomian glands and pigmentary changes of the conjunctiva (Kuratsune et al., 1972). More than 80% of Yusho cases exhibited ocular changes, which, in some cases, appeared to persist 15 years after exposure ended (Kuratsune, 1989).

Thirty percent of the cases reported having at least one symptom consistent with neurologic involvement, such as limb parasthesia and spasms, weakness, headaches, and fatigue (Kuratsune, 1972). As summarized by Kuratsune (1989), Kuriowa et al. (1969) found mostly sensory deficits, identified through slowed nerve conduction velocities, in 23 cases. Follow-up of these cases indicated that the neurologic symptoms disappeared over time; however, conduction velocities were not repeated.

A number of studies examined the immune status of Yusho cases (Kuratsune, 1989). Significant decreases in mean IgA and IgM and increases in IgG were noted in 28 cases tested in 1970 ($p<0.05$) (Nakanishi et al., 1985). Within 2 years, mean levels of all three immunoglobulins returned to normal. Small increases in the percentage of CD4 cells, small decreases in the percentage of CD8 cells, and enhanced lymphocyte stimulation were also noted in Yusho cases (Nakanishi et al., 1985).

Studies of offspring of Yusho cases have been limited to descriptions of effects on newborns exposed *in utero*. An early description of 13 children born to exposed mothers noted two stillborn infants, one of whom was diffusely and deeply hyperpigmented (Rogan, 1982). Neonates described in other reports were darkly pigmented and had marked secretions of the conjunctival palpebra, gingival hyperplasia, hyperkeratosis, calcification of the skull, low birth weight, and natal teeth (Yamashita and Hayashi, 1985). The abnormal pigmentation disappeared

after 2 to 5 months. No other physical abnormalities (neurologic, cardiovascular, or malformations) were identified.

7.14.1.2. *Yu-Cheng*

The initial recognition of Yu-Cheng occurred in 1979. As of 1983, approximately 2,000 individuals were found to have been exposed to the contaminated rice oil. Within the first year of exposure, mean serum PCB, PCDF, and PCQ levels for 15 cases were 60 ppm (range 4-188 ppm), 0.14 ppb (range <0.005-0.27 ppb), and 19.3 ppb (range 0.9-63.8), respectively (Kashimoto et al., 1985). Analysis of PCB levels in 1980-1981 in 165 cases (mean 38 ppb, range 10-720) (Rogan, 1989) and in 1985 in 32 cases (mean 15.4 ppb, range 0.6-86.8) (Lundgren et al., 1988) suggested that some PCBs were being eliminated. It is not clear from the reports if the samples were drawn from distinctly different individuals or included some of the same individuals.

The ophthalmologic and dermatologic changes observed in Yu-Cheng cases were very similar in character and anatomical distribution to those noted in Yusho cases (Lü and Wu, 1985). In 89 cases followed for up to 17 months, dermatologic conditions of 38% of the cases improved, 54% remained the same, and 7% showed deterioration of their conditions (Lü and Wong, 1984).

Like Yusho cases, Yu-Cheng cases examined within 2 years of exposure for nerve function exhibited slowing of sensory nerve conduction. They also exhibited motor nerve slowing and mixed deficits (Chen et al., 1981, 1983, 1985; Chia and Chu, 1984). Twenty percent of a population of 27 individuals also had abnormal EEGs (Chia and Chu, 1984). However, the authors suggest that any correlation between PCB exposure and the abnormal EEGs may be spurious because of low PCB levels in the cerebrospinal fluid (0.5-2.3 ppb) (measured in four subjects), despite much higher blood PCB levels of 48-64 ppb. A sample of 28 individuals with peripheral neuropathy in 1980 was reexamined in 1982 and was found to have normal EEGs and some recovery of sensory and motor nerve conduction velocity (Chia and Chu, 1985).

In 1981, immunologic function was assessed on different subsets of Yu-Cheng cases and summarized by Lü and Wong (1984). In 30 cases compared with unexposed controls, both IgA and IgM were significantly decreased, while IgG did not differ from controls. In this same group, percentages of active T-cells and T-cells were significantly increased ($p<0.05$), while total lymphocyte count and percentage of B cells were unchanged. Significant increases in helper T-cells (T4) but not suppressor T-cells (T8) were also observed. In another group of cases, response to lymphocyte-stimulating mitogens was mixed and the findings unclear. In 143 cases, reaction to streptococci antigen appeared to be significantly ($p<0.05$) depressed relative to controls.

Alterations in porphyrin levels and liver enzymes have been identified as acute reactions to exposure to halogenated polycyclic hydrocarbons, including PCBs. Porphyrin levels were

measured in two exposed groups (Chang et al., 1980; Gladen et al., 1988). In 1980, statistically significant elevations in 24-hour urinary excretion of uroporphyrin (exposed = 41.23 μg ± 24.56; unexposed = 13.57 μg ± 11.76, $p<0.01$) and α-aminolevulinic acid (exposed = 1.002 mg ± 0.600; unexposed = 0.715 ± 0.337, $p<0.05$) were noted among 69 subjects (Chang et al., 1980). Coproporphyrin and porphobilinogen levels were increased in the exposed group but were not significantly elevated. The second study group was composed of 75 children born between June 1978 and March 1985 to mothers who ingested contaminated rice oil (Gladen et al., 1988). Spot urines were collected in 1985. Mean total porphyrin (exposed = 95.2 μg/L; unexposed = 80.7 μg/L) and coproporphyrin (exposed = 72.4 μ/L; unexposed = 59.8 μ/L) excretion was elevated in the exposed subjects, possibly because of extremely high levels (>200 μg/L) in eight exposed children and two controls (Rogan et al., 1988). However, no porphyria cutanea tarda, a severe form of porphyria, was observed in either group of children. Moderate, but statistically significant, increases were observed in AST and ALT levels in 23 cases tested 1 year after exposure (Lü and Wong, 1984). LDH and bilirubin levels were not significantly elevated. As in Yusho cases, triglyceride levels were significantly increased by approximately twice the level in unexposed controls.

Recently, a follow-up study interviewed 59% of 600 surviving women who were 30+ years of age and less than 60 years of age in 1993. Drawing from registration data, women who lived in the same areas in 1979 and were within 3 years of age of cases were selected for comparison. Of these, 312 of 594 (53%) participated. The low response rate meant that not all case respondents had matches in the controls, and the reverse. The authors chose not to maintain matching in the analyses (unpaired X2 and t-tests), which may affect the results reported. In comparisons of the Yu-Cheng women and their controls, Yu-Cheng women were more likely to have abnormal menstrual flow (16.6% vs 7.5%, p <0.068), to have had a stillborn infant since 1979 (4.2% vs 1.7%, p <0.05), to have had a child die before adolescence (10% vs 6.1%, p<0.05), and decided to limit childbearing for health reasons (6.9% vs 2.0%, p <0.05). On the last point, the Yu-Cheng women who did not decide to limit childbearing did not have a difference in family size from the controls.

7.14.1.3. *Effects Observed in Offspring of Yu-Cheng Cases*

A concerted effort has been made to evaluate the overall development of children exposed prenatally to contaminated rice oil ingested by their mothers. Two studies are currently being conducted: one to evaluate children and controls born between 1978 and 1985 (termed “early-born”), and the second to evaluate children born in 1985 and later. Controls were matched within 30 days of age (15 days if less than one year of age), neighborhood, sex, mother’s age within 3

years, and combined parental education (within 3 years). The purpose of the two studies was to determine if there are differences among children exposed *in utero* or shortly after birth by the mothers' ingestion of the contaminated rice oil and children born 7 to 12 years after direct exposure to either parent ended (July 1, 1985 to December 31, 1991). Only a small sample of these children (n=31) have had serum levels of PCB and PCDF determined, so all the analyses are based on broad groupings, reducing their ability to look at exposure levels and health endpoints. The studies comparing the Yu-Cheng children and controls typically analyzed data using paired t-tests, with out adjusting for other potential risk factors (except for the matching of controls).

In terms of musculoskeletal development, several studies have documented delays and abnormalities (Yu et al., 1991; Rogan, 1989; Chen et al., 1993; Guo et al., 1994a). In one of the first studies conducted in 1985, Rogan and colleagues (1988) examined 117 children born since the mothers' exposure in 1979 and 107 unexposed controls. In this study, babies of exposed mothers were consistently smaller and shorter at birth than controls and had similar characteristics: natal teeth, neonatal conjunctivitis, and pigmentation. Exposed mothers reported a mean birth weight 479 g lower than that reported by control mothers; no validation of these reports using medical records was undertaken. As older children, they exhibited a variety of signs and symptoms: fragile chipped teeth and gum hypertrophy, pigmented and deformed fingernails and toenails, and abnormal lung auscultation. In this same study, neurologic developmental assessments were also conducted to evaluate development (Yu et al., 1991). Forty-nine percent of Yu-Cheng children compared with 22% of controls were developmentally delayed in 32 of 33 developmental milestones, 12% had clinical evidence of developmental or psychomotor delays compared with 2% of controls, and 7% of Yu-Cheng children versus 3% of controls had speech problems. These delays were noted at all ages and persisted over 2 years of testing. Delay was greater in children of smaller size and in children who had exhibited neonatal symptoms of intoxication.

In 1991, the musculoskeletal development of 56 Yu-Cheng children (age range 6-10 years) and their matched controls was again assessed (Guo et al., 1994a). Only children born first after the mother's exposure were shorter in stature (-3.4 cm, $p = 0.02$) and had decreased lean muscle mass (-2.9 gm, $p = 0.04$) and soft tissue content (-5.3 gm, $p = 0.06$). Another examination of 110 Yu-Cheng children and 108 controls, ages 8 through 14 years, found Yu-Cheng girls to be significantly shorter than controls, matched to the exposed children by age, sex, maternal age, parents' combined educational level, occupation, and neighborhood (Guo et al., 1993). As measured by the Tanner scale, sexual maturation was not slower in Yu-Cheng boys or girls. However, Yu-Cheng boys aged 11-14 had significantly shorter penis length, but testicular and scrotal development did not differ from the controls. Penile length was not related to sexual development as measured by the Tanner scale.

With a validated and standard battery of tests, cognitive and behavioral development of Yu-Cheng offspring were studied yearly from 1985 through 1991. Throughout the testing period, Yu-Cheng children scored consistently lower in the Stanford Binet IQ (SB-IQ) and 4-5 points lower than controls (with the same matching criteria as the above study) in three subscales of the Wechsler Intelligence Scale for Children, Revised (WISC-R): verbal IQ (VIQ), with significant differences observed in 1990 and 1991; performance IQ (PIQ); with significant differences in 1987-1991; and full-scale IQ (FIQ), with significant differences in 1989-1991 (Chen et al., 1992; Lai et al., 1993; Lai et al., 1994). When the PIQ, VIQ, and FIQ were examined by the age of the child, significant deficits were observed for ages 6-8 (Lai et al., 1994). The Yu-Cheng children scored lower on the mental development index (MDI) and the psychomotor development scale (PDI) of the Bailey scale, with a significant difference at 2 years of age (Lai et al., 1994).

Yu-Cheng children are also reported to exhibit more health, habit, and behavior problems as reported by parents responding to the Rutter's scale, and to manifest higher activity based on teachers' responses to the Teacher's Activity Check List (Hsu et al., 1993). Rutter's Child Behavior Scale A was used to screen children for their likelihood for social, health and behavioral problems (Yu et al, 1994). The scale, validated in Britain of children ages 9-12, assesses these outcomes through a questionnaire-checklist on each of the three topic areas. This study compared the 113 of the 118 Yu-Cheng children born between July 1978 and June 1985 to exposed women who participated in the seven year follow-up to their matched controls. Only those three years old or older were included in this evaluation. The results showed that, at all ages, the exposed children scored 14-38% worse on mean Rutter scores than did the controls. All age groups, except the 10-12 year olds were significantly different. For the health subscores, all age groups, except 5 year olds and 10 year olds were significantly different; for habits, all were significantly different except for 8, 11, and 12 year olds; and for behavior subscores, ages 4, 6, 7, 8, and 9 were significantly different.

In addition to these developmental measures, Raven's Colored Progressive Matrices (CPM - used for those 6 to 8 years of age) and Standardized Progressive Matrices (SPM - used for 9 year olds) were used to assess cognitive development (Guo et al., 1995a). Analyses used Wilcoxin one-sample test for comparison of exposed children to their matched controls, and an examination of differences for offspring born longer after exposure, regression analysis was used on year of birth. Significant deficits were observed for children aged 6 through 8, with no pattern of differential effects with year of birth. When the results were examined by sex, the significant effects were found only in males.

In a follow-up of these children, a random sample of 27 case-comparison pairs were selected from those pairs whose case was between 7 and 12 years of age (Chen and Hsu, 1994). These children were assessed for neuropsychologic changes (including cognitive -- WISC-R and auditory event-related potentials -- P300), and neurophysiological changes (including pattern visual evoked potentials -- P-VEP, and short-latency somatosensory evoked potentials -- SSEP). The exposed children had significantly lower verbal and full-scale IQs (VIQ and FIQ) and P300 latencies at Cz and Pz. No differences were observed for P-VEP or for SSEP.

In October 1991, researchers began analysis of physical and cognitive development of 104 children whose mothers were exposed and 109 children whose fathers but not mothers were exposed, and of three matched controls born after 1985 (Guo et al., 1993). Like children born before 1985, the later-born children were shorter in stature and lower in weight than controls, although the authors indicate that the differences were no longer statistically significant. Yu-Cheng children are reported to have higher activity levels but do not have temperament, physical, habit, or behavioral problems. Overall, scores on all tests in paternally exposed children were similar to those of the controls. However, maternally exposed children scored lower on the SB-IQ and on all subscales of the WISC-R.

Another report (Guo et al., 1994b), probably of the same children (born between 1985 and 1991) gave more details: Local household registration were used to identify these children and two comparisons from the same neighborhood, age, sex, mother's age within three years, and combined parental education (within three years). Only one comparison was used in this report. Researchers began analysis of physical and cognitive development of 120 children of 79 exposed mothers, 75 children of 52 exposed fathers, and 4 children of exposed mothers and fathers. The children's development was assessed using the Chinese Child Developmental Inventory (CCDI). The CCDI is a modification of the Minnesota Child Developmental Inventory (MCDI), a tool used to evaluate children from six month to six years of age. The scales in the CCDI include gross and fine motor activity, language skill, comprehension, self-help activities and personal-social skills. Of these, children of Yu-Cheng mothers had significantly lower scores for self help and general development (a summary scale); no significant differences were observed in children of exposed fathers. When the children of exposed mothers were examined by gender in comparison to their controls, Yu-Cheng girls scored significantly lower on self help, general development and on conceptual comprehension. Other borderline differences were observed for fine motor activity and situational comprehension. No significant differences were observed for sons of exposed mothers. Rutter's Child Behavior Scale A was used to screen children for their likelihood for health and behavioral

problems. No significant differences were reported for this measure in these later born children (versus effects observed in those born before July 1985 - Yu et al., 1994).

A report examined middle ear abnormalities in 1993 in 110 Yu-Cheng children and 96 matched controls (Chao and Hsu, 1994), born before July 1985. Ages ranged from 8 to almost 16 years. Of the 220 tympanic membranes evaluated in the Yu-Cheng children, 49 were abnormal compared to 34 out of 192 tympanic membranes in the comparison group ($p<<0.01$). A second report, apparently resulting from these examinations (Chao et al., 1997), presented the same results with slightly different numbers: In this 44 of 103 children (206 tympanic membranes assessed) were abnormal in the Yu-Cheng children, versus 18 of 96 control children (192 tympanic membranes assessed) ($p<<0.01$). In this second report, 30 Yu-Cheng children with serum levels of PCBs and PCDFs measured in 1991 were compared: this group was divided into those with and without middle ear diseases. In analyses unadjusted for other factors, significantly higher serum levels of 1,2,3,4,7,8-hexachloro-dibenzofuran ($p=0.046$) and 2,3,4,7,8-pentachloro-dibenzofuran ($p=0.022$) were observed for Yu-Cheng children with disease compared to Yu-Cheng children without. Differences were not observed for serum PCB levels.

The authors attributed the association with middle ear disease with, at least in part, immunologic effects. Yu and colleagues (1998) recently published a report directly examining immunologic function in Yu-Cheng children. In this effort, 105 Yu-Cheng children of exposed mothers and 101 control children, born between July 1978 and June 1987, were assessed. The Yu-Cheng children had significantly elevated rates of influenza during the 6 months preceding the 1995 physical examination. Blood was drawn for immunologic analyses, and compared for the exposed and control children. Due to laboratory problems, 29 samples from exposure, and 22 from controls were examined. In this limited comparison, no significant differences were observed in leukocyte classification and immune markers.

7.14.1.4. *Mortality Among Yu-Cheng Population*

Cause-specific mortality through December 31, 1991, for the 2,000 Yu-Cheng poisoning cases was assessed (Yu et al., 1997). Eighty-three deaths were identified from among the 1,837 persons whose vital status was known. Compared to the age, gender, and calendar-time specific mortality rates of the Taiwan general population, the overall SMR was significantly lower among the Yu-Cheng population (SMR = 80 (95% CI = 70-100). However, mortality from chronic liver disease and cirrhosis was statistically significantly increased in the Yu-Cheng population (SMR = 2.7, 95%CI = 1.3, 4.9) (Yu et al., 1997).

7.14.1.5. *Comment*

Data from Yusho and Yu-Cheng strongly implicate direct ingestion of contaminated rice oil with numerous acute effects of the skin and peripheral and central nervous systems. The data on immunologic function suggest possible effects, but the numbers of subjects in the various studies were too small to determine an exposure-response relationship. Similarly, data on elevated triglyceride and liver enzyme levels are from a small number of cases and, therefore, the relationship between exposure and the effect is unclear. Furthermore, there are few data to evaluate the long-term effects of these very high exposures. Because many of the 4,000 individuals who were exposed in these two episodes were children, longitudinal studies would be invaluable in assessing the long-term health effects of these exposures.

One difficulty in evaluating the various reports relating to Yusho and Yu-Cheng is the inability to determine if the effects are generalizable to the entire exposed population. It may be that the cases reported in the literature were those who tended to have the severest signs and symptoms and probably had the highest body burden of contaminants. Some reports included small numbers of cases and controls, relative to the size of the exposed population, and others had no controls. Finally, while much work has gone into determining severe acute effect, it would be interesting to know what chronic, age, and gender-specific effects are now being exhibited in the approximately 4,000 individuals directly exposed to the contaminated rice oil.

Another difficulty is the presence of several chlorinated hydrocarbons in the contaminated oil, which results in uncertainty as to which contaminant or combination of contaminants is responsible for the noted effects. The data on the offspring of exposed Yu-Cheng mothers and fathers are fascinating and disturbing. It appears that parental exposure, specifically, maternal exposure, to PCBs, PCDFs, and PCQs is directly linked to *in utero* exposure of the fetus, affecting neurodevelopment, selective musculoskeletal, and possibly sexual development of the offspring. The ongoing assessment of development in the Yu-Cheng children will contribute to the understanding of long-term consequences of these exposures on the children's future quality of life and highlights the importance of parental exposures to their children’s well-being. Prospective studies of fertility and reproductive experience in these offspring would provide insight into possible intergenerational effects of exposure to these compounds.

7.15. SUMMARY

The data presented in this chapter describe nonmalignant effects in epidemiologic studies of populations with the potential for exposure to chemicals contaminated with 2,3,7,8-TCDD. The purpose of this review is to highlight the salient results of the studies and to assess whether the observed effect was related to exposure to 2,3,7,8-TCDD.

In summary, based on the results of two or more studies, recent evidence suggests that, in adults, chloracne, elevated GGT levels, and altered testosterone levels appear to be long-term consequences of exposure to 2,3,7,8-TCDD (Table 7-53). In contrast, multiple studies show possible acute effects but few chronic exposure-related effects for dermatologic endpoints other than chloracne, such as eyelid cyst, hypertrichosis, hyperpigmentation, actinic keratosis, and Peyronie's disease; for liver diseases such as cirrhosis, liver enlargement, and hepatic enzyme levels (LDH, AST, ALT, and D-glucaric acid) other than GGT; and for lipid concentrations, porphyrias, and thyroid function; as well as renal, neurologic, and pulmonary disorders. Although the available data are suggestive of an association between TCDD exposure and other adverse outcomes, circulatory and heart diseases, diabetes and glucose metabolism, reproductive and developmental outcomes, and immunologic disorders require further study before their respective relationships to 2,3,7,8-TCDD can be more definitively assessed.

In the best of circumstances when reviewing studies, it would be ideal if all studies examined the same endpoints in the same manner, had sufficient statistical power to detect truly positive findings, had good estimates of extent of exposure, and had consistent exposure-response relationships. In the absence of ideal situations, epidemiologists examine the evidence of studies using “six tenets of judgment” (Hatch and Stein, 1986; Hill, 1965) to assess the collective wisdom of the study results. These tenets are temporality (sequence of events); degree of exposure; strength, consistency, and specificity of association; and biological plausibility.

In evaluating many of the studies that examined the relationship between serum 2,3,7,8-TCDD and, in some cases, dioxins, furans, and PCBs, there are several common threads that bear noting. They will be discussed first to avoid repetition throughout the summary.

In terms of temporality, all studies reviewed in this chapter were conducted after the presumed exposure occurred. Some of the studies obtained exposure data at (approximately) relevant time for the outcomes (e.g., Dutch developmental studies of dioxins, furans, and PCBs) or shortly after the exposure, as in Seveso; others were conducted many years after the groups' last exposure to evaluate more chronic health outcomes. One dilemma in assessing the effect of past exposures is ascertaining whether an effect observed many years postexposure is due to the exposure itself or to an exposure or event that occurred during the intervening period. Another problem is determining what, in the analysis, the investigator considered the most important of the possible confounding exposures. Finally, restricting examination of events to those that occurred after the exposure does not in and of itself satisfy this time-order criterion. Several factors must be considered, such as the half-life of the contaminant in the body and the concentration at the time of the event. Consistency in the results of similarly designed studies of exposed populations should help strengthen the conclusion of an effect or no effect.

Determination of the extent of exposure throughout the studies was varied. When the risk of disease increases with the dose or gradient of exposure, the evidence for causation is strengthened. It should be emphasized that there are many possible dose-response patterns, which may result in different threshold levels for different endpoints. Because of the exposure misclassification bias present in most dioxin research, with the exception of a few studies, it is not valid to attempt to determine dose-response relationships. To summarize, six studies evaluated the relationship between nonmalignant effects and body levels of 2,3,7,8-TCDD (or a mixture of dioxins, furans, and PCBs): the Ranch Hand study of U.S. Air Force personnel (Roegner et al., 1991; Grubbs et al., 1995); the study of 50 Missouri residents (Stockbauer et al., 1988); the evaluation of the BASF accident cohort (Ott et al., 1994) and the cohort of Hamburg chemical workers (Flesch-Janys et al., 1995); the NIOSH study of 281 TCP production workers (Egeland et al., 1994); and the two Dutch developmental series of studies (Series 1: Huisman et al., 1995a,b; Koopman-Esseboom et al., 1994a-c, 1995a,b, 1996; Weisglas-Kuperus et al., 1995, 2000; Series 2: Pluim et al., 1992, 1993, 1994, 1996). In 1988, the workers in the NIOSH study had the highest serum 2,3,7,8-TCDD concentrations (mean = 220 pg/g) of these six study groups. Of these six sets of studies, only the Dutch developmental studies examined common environmental exposures. Because the Dutch series examined a variety of dioxins, furans and PCBs (see Table 7-21b), the data are not strictly comparable to the other five studies.

In U.S. Army veterans (Centers for Disease Control Veterans Health Studies, 1988), serum 2,3,7,8-TCDD levels were measured, but the levels were not used to examine dose-response relationships. In the Veterans Health Studies, more than 99% of the serum 2,3,7,8-TCDD levels of the sample of both Vietnam and non-Vietnam veterans were at the background level (4 pg/g). Therefore, comparisons were made between the two groups as a whole.

Serum levels of Seveso residents were obtained for a small proportion (N = 20) of the total number of residents of zone A within 1 year of the reactor release (Mocarelli et al., 1991). The data suggest that the levels may be related to a number of factors, including age (younger children were outside at the time of the release), whether the resident was inside or outside, ingestion of local produce, or number of days of residence in the area after the release, to name a few. The data suggest that the potential for substantial exposure was high for individuals residing in the area. The range of levels in the 20 zone A residents was 820 pg/g to 56,000 pg/g (median = 7,400 pg/g). Thirty years after the explosion, Landi et al. measured serum 2,3,7,8-TCDD in 62 individuals randomly selected from zones A, B and non-ABR (Landi et al., 1997). Geometric mean serum concentrations were 53.2 pg/g lipid in zone A; 11.0 pg/g lipid in zone B, and 4.9 pg/g lipid in zone non-ABR. These data suggest that elevated levels persist but are decreased from the original levels of 1976.

The majority of the remaining studies examined the differences between individuals identified as exposed or unexposed, or with or without chloracne. Most of these studies did not evaluate other parameters that might explain differences in effects between exposed and unexposed, for example, the length of exposure. However, one study assessed dose-response relationships based on a statistical algorithm of intensity and highest dose of TCDD exposure (Bond et al., 1989).

In terms of the magnitude (or strength) of the association, this criterion refers to the degree to which the measure of association (e.g., odds ratio or relative risk) exceeds the null value of 1. The stronger the association between exposure and effect, the more convincing is the argument for causation. There is no definitive cut point to numerically define a meaningful measure of association. Other factors, such as the prevalence of the exposure in the population, affect the significance of the measure.

A critical element that should always accompany the effect measure is a confidence interval. Placement of an interval around the measure enables quantitation of the result for a more meaningful interpretation. An odds ratio of 30 is quite impressive, but if the 95% confidence interval is 0.9-200, the magnitude of the association is less impressive.

If an association between a factor and a disease is demonstrated across a variety of studies employing different designs and different populations (consistency), then the argument for causation is strengthened. Replication of an association under different conditions decreases the likelihood that confounding is responsible for the observed association. Consistency is a powerful criterion for causation, but only when "the variables under test (exposure, outcomes) are similar enough" to justify the comparison of the various studies' findings (Hoffman et al., 1986).

It should also be determined a priori that each study included in the critical evaluation process is in adherence to basic epidemiologic principles governing study design and analysis. Deficient studies with suspect results should be excluded. While this is not to imply that such studies have no worth, as invaluable information has often been derived from those studies that improve on subsequent examinations of the issue, they have no place in the evaluation process. Unfortunately, in studies of 2,3,7,8-TCDD and effects in humans, the probability of exposure misclassification forces exclusion of much of the research to date.

Specificity refers to the uniqueness of the association between a factor and an outcome. If the relationship were absolute, then only factor X would be related to only effect Y. It is indeed rare to encounter this type of association, which renders this criterion generally less useful in the evaluation process.

Finally, according to the criterion of biological plausibility, the observed association between exposure and effect should be consistent with existing theory and information from other

scientific disciplines. Certainly one would feel more secure in the causation debate if the biological basis for an observed association could be explained. However, biological implausibility may simply reflect gaps in existing scientific knowledge that could explain the relationship.

7.15.1. Effects Having a Positive Relationship With Exposure to 2,3,7,8-TCDD

The following section describes those endpoints for which there is good evidence from two or more studies suggesting an effect of exposure to 2,3,7,8-TCDD.

7.15.1.1. *Chloracne*

7.15.1.1.1. *Temporality.* Chloracne is one of the best known of the medical consequences of exposure to 2,3,7,8-TCDD-contaminated substances. In general, it has been observed in most incidents where substantial exposure has occurred, particularly among TCP production workers (Goldman, 1972; May, 1973; Bleiberg et al., 1964; Bond et al., 1987; Suskind and Hertzberg, 1984; Moses et al., 1984; Zober et al., 1990) and Seveso residents (Reggiani, 1978; Caramaschi et al., 1981; Ideo et al., 1985; Mocarelli et al., 1986; Assennato et al., 1989). As previously stated, chloracne appears within several weeks to months from the time of exposure, often resolving after discontinuation of exposure (Moses et al., 1984; Suskind and Hertzberg, 1984), although for some it may remain for extended periods after exposure ended (Moses et al., 1984).

7.15.1.1.2. *Degree of exposure, consistency of the association.* The amount of exposure necessary for development of chloracne has not been resolved, but studies suggest that high exposure (both high acute and long-term exposure) to 2,3,7,8-TCDD increases the likelihood of chloracne, as evidenced by chloracne in TCP production workers and Seveso residents who have documented high serum 2,3,7,8-TCDD levels (Beck et al., 1989; Fingerhut et al., 1991a; Mocarelli et al., 1991; Neuberger et al., 1991) or in individuals who have a work history with long duration of exposure to 2,3,7,8-TCDD-contaminated chemicals (Bond et al., 1989). The absence of substantial chloracne in U.S. Army Vietnam veterans whose mean serum 2,3,7,8-TCDD levels were at background (4 pg/g) (Centers for Disease Control Vietnam Experience Study, 1988d) and U.S. Air Force Ranch Hands whose serum 2,3,7,8-TCDD levels fell intermediate to those of workers and Army Vietnam veterans (Roegner et al., 1991; Burton et al., 1997) suggests that there is a higher incidence of the disorder among those with higher serum 2,3,7,8-TCDD levels.

7.15.1.1.3. *Strength of the association.* In earlier studies, chloracne was considered to be a "hallmark of dioxin intoxication" (Suskind, 1985). However, only in two studies were risk

estimates calculated for chloracne. Both were studies of different cohorts of TCP production workers (Suskind and Hertzberg, 1984; Bond et al., 1989); one group was employed in a West Virginia plant, the other in a plant in Michigan. Of the 203 West Virginia workers, 52.7% ($p<0.001$) were found to have clinical evidence of chloracne, and 86.3% reported a history of chloracne ($p<0.001$) (Suskind and Hertzberg, 1984). None of the unexposed workers had clinical evidence or reported a history of chloracne. Among the Michigan workers, the relative risk for cases of chloracne was highest for individuals with the longest duration of exposure (≥60 months; RR = 3.5, 95% CI = 2.3-5.1), those with the highest cumulative dose of TCDD (based on duration of assignment across and within 2,3,7,8-TCDD-contaminated areas in the plant) (RR = 8.0, 95% CI = 4.2-15.3), and those with the highest intensity of 2,3,7,8-TCDD exposure (RR = 71.5, 95% CI=32.1-159.2) (Bond et al., 1989).

7.15.1.1.4. ***Specificity of the association.*** Chloracne is associated with exposure to other polyhalogenated chemicals, including dibenzofurans, PCBs, naphthalenes, and others (Taylor, 1979). The likelihood of exposure to other polyhalogenated chemicals in the populations studied is probably low, particularly among the Seveso children, whose exposure was to TCP reactant effluents that were primarily contaminated with 2,3,7,8-TCDD. The issue is more relevant in chemical workers, who by virtue of their occupation, have the potential for exposure to other chemicals. Yet, much of the documented chloracne appeared shortly after TCP reactor releases (Ashe and Suskind, 1950; Goldman, 1972; May, 1973) or during TCP or 2,4,5-T production (Bond et al., 1989), suggesting that 2,3,7,8-TCDD was the chloranegenic agent.

7.15.1.1.5. ***Biological plausibility.*** Animal studies have been effective in describing the relationship between 2,3,7,8-TCDD and chloracne, particularly in rhesus monkeys (McNulty, 1977; Allen et al., 1977; McConnell et al., 1978). Subsequent to exposure to 2,3,7,8-TCDD, monkeys developed chloracne and swelling of the meibomian gland, a modified sebaceous gland. The histologic changes in the meibomian gland are physiologically similar to those observed in human chloracne (Dunagin, 1984).

In summary, the evidence provided by the various studies convincingly states what is already presumed, that chloracne is a common sequela of high levels of exposure to 2,3,7,8-TCDD. More information is needed to determine the level and frequency of 2,3,7,8-TCDD exposure needed to cause chloracne and whether personal susceptibility plays a role in the etiology. Finally, it is important to recall that the absence of chloracne does not imply lack of exposure (Mocarelli et al., 1991).

7.15.1.2. ***Gamma Glutamyl Transferase (GGT) Levels***

7.15.1.2.1. ***Temporality, degree of exposure, and strength and consistency of association.*** There appears to be a consistent pattern of increased GGT levels among individuals exposed to 2,3,7,8-TCDD-contaminated chemicals. Elevated levels of serum GGT have been observed within a year after exposure in Seveso children (Caramaschi et al., 1981; Mocarelli et al., 1986) and 10 or more years after cessation of exposure among TCP and 2,4,5-T production workers (May, 1982; Martin, 1984; Moses et al., 1984; Calvert et al., 1992) and among Ranch Hands (Roegner et al., 1991; Grubbs et al., 1995). All of these groups had a high likelihood of substantial exposure to 2,3,7,8-TCDD. In addition, for those studies that evaluated dose-response relationships with 2,3,7,8-TCDD levels, the effect was observed only at the highest levels or categories of 2,3,7,8-TCDD.

In contrast, although background levels of serum 2,3,7,8-TCDD suggested minimal exposure to Army Vietnam veterans, GGT was increased, at borderline significance, among Vietnam veterans compared to non-Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988a). In addition, despite the increases observed in some occupational cohorts, other studies of TCP production workers from West Virginia or Missouri residents measured but did not report elevations in GGT levels (Suskind and Hertzberg, 1984; Webb et al., 1989).

7.15.1.2.2. ***Specificity.*** In clinical practice, GGT is often measured because it is elevated in almost all hepatobiliary diseases and is used as a marker for alcoholic intake (Guzelian, 1985). In individuals with hepatobiliary disease, elevations in GGT are usually accompanied by increases in other hepatic enzymes, e.g., AST and ALT, and metabolites, e.g., uro- and coproporphyrins. Significant increases in hepatic enzymes other than GGT and metabolic products were not observed in individuals whose GGT levels were elevated 10 or more years after exposure ended, suggesting that the effect may be GGT-specific. However, in the Seveso male children and those with chloracne (both sexes), ALT was significantly increased concomitantly with GGT within 1 year of the reactor release (Mocarelli et al., 1986; Caramaschi et al., 1981). In a longitudinal analysis, both enzymes returned to normal levels within 5 years after exposure (Mocarelli et al., 1986; Assennato et al., 1989). In the NIOSH cohort, elevated GGT levels occurred only among workers with both high 2,3,7,8-TCDD concentrations and lifetime alcohol consumption. Yet, no other enzymes were found to be outside of normal ranges. Likewise, GGT was the single enzyme found to be significantly elevated in Ranch Hands compared to nonexposed referents (Roegner et al., 1991; Grubbs et al., 1995).

These data suggest that in the absence of increases in other hepatic enzymes, elevations in GGT are associated with exposure to 2,3,7,8-TCDD, particularly among individuals who were

exposed to high 2,3,7,8-TCDD levels. The fact that investigators observed a decline in enzyme levels in Seveso children but a continued elevation in TCP workers may reflect (1) differences in how exposure occurred (i.e., acute but high doses in Seveso versus continuous or frequent long-term, medium to high doses in TCP workers), (2) differences in the metabolism of the maturing versus mature system, (3) the fact that children grow rapidly, thus "diluting" a peak exposure within that group, or (4) some combination of these.

7.15.1.2.3. ***Biological plausibility.*** The animal data with respect to 2,3,7,8-TCDD-related effects on GGT are sparse. Statistically significant changes in hepatic enzyme levels, particularly AST, ALT, and ALK, have been observed after exposure to 2,3,7,8-TCDD in rats and hamsters (Gasiewicz et al., 1980; Kociba et al., 1978; Olson et al., 1980). Only one study evaluated GGT levels (Kociba et al., 1978). Moderate but statistically nonsignificant increases were noted in rats fed 0.10 μg/kg 2,3,7,8-TCDD daily for 2 years, and no increases were observed in control animals.

Among humans, increased levels of GGT may suggest activity such as cholestases, liver regeneration, or drug or xenobiotic metabolism. In human adults, most of 2,3,7,8-TCDD is stored in the adipose tissue and has a half-life of approximately 7 years (Pirkle et al., 1989). Continued GGT activity in adults with serum 2,3,7,8-TCDD levels many times over background levels may reflect continuous, low-level metabolism of 2,3,7,8-TCDD.

In summary, GGT is the only hepatic enzyme examined that was found in a number of studies to be chronically elevated in adults exposed to high levels of 2,3,7,8-TCDD. The consistency of the findings in a number of studies suggests that the finding may reflect a true effect of exposure but for which the clinical significance is unclear. Long-term pathologic consequences of elevated GGT have not been illustrated by excess mortality from liver disorders or cancer, or in excess morbidity in the available cross-sectional studies.

It must be recognized that the absence of an effect in a cross-sectional study, for example, liver enzymes, does not obviate the possibility that the enzyme levels may have increased concurrent to the exposure but declined after cessation. The apparently transient elevations in ALT levels among the Seveso children suggest that hepatic enzyme levels other than GGT may react in this manner to 2,3,7,8-TCDD exposure.

7.15.1.3. ***Reproductive Hormones***

7.15.1.3.1. ***Strength and consistency of association.*** Levels of reproductive hormones have been measured with respect to exposure to 2,3,7,8-TCDD in three cross-sectional medical studies. Testosterone, LH, and FSH were measured in TCP and 2,4,5-T production workers (Egeland et al., 1994), in Army Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988d),

and in Ranch Hands (Thomas et al., 1990; Grubbs et al., 1995). The risk of abnormally low testosterone was two to four times higher in exposed workers with serum 2,3,7,8-TCDD levels above 20 pg/g than in unexposed referents (Egeland et al., 1994). In both the 1987 and 1992 examinations, mean testosterone concentrations were slightly, but not significantly higher in Ranch Hands (Roegner et al., 1991; Grubbs et al., 1995). FSH and LH concentrations were no different between the exposed and comparison groups. No significant associations were found between Vietnam experience and altered reproductive hormone levels (Centers for Disease Control Vietnam Experience Study, 1988d). Only the NIOSH study found an association between serum 2,3,7,8-TCDD level and increases in serum LH.

7.15.1.3.2. ***Specificity.*** The NIOSH study excluded from analysis participants who had conditions that might have influenced gonadotropin and/or testosterone levels: history of prostate cancer, thyroid or other hormone usage, or liver cirrhosis. Similarly, in the Ranch Hand study, individuals with orchiectomies or who were taking testosterone medication were excluded from the analysis of testosterone; no participants were excluded from the analyses of FSH. The CDC study of Vietnam veterans did not describe the exclusions.

7.15.1.3.3. ***Biological plausibility.*** In rats, 2,3,7,8-TCDD has been shown to decrease testosterone levels (Moore et al., 1985; Moore and Peterson, 1988; Mebus et al., 1987) through a decrease in testosterone synthesis (Kleeman et al., 1990) or by decreasing the production of pregnenolone from cholesterol (Ruangwies et al., 1991). In addition, 2,3,7,8-TCDD has been shown in rats to reduce the responsiveness of the pituitary to testosterone (Bookstaff et al., 1990a) and of the Leydig cells to LH stimulation (Moore et al., 1991).

The findings of the NIOSH and Ranch Hand studies are plausible given the pharmacological and toxicologicalal properties of 2,3,7,8-TCDD. A mechanism responsible for the effects may involve the ability of 2,3,7,8-TCDD to influence hormone receptors. The aryl hydrocarbon (Ah) receptor to which 2,3,7,8-TCDD binds can cross-talk with steroid hormone receptors in both structure and mode of action. Studies suggest that 2,3,7,8-TCDD modulates hormone receptors, including estrogens (Romkes and Safe, 1988; Romkes et al., 1987), prolactin, and its own Ah receptor (Poland and Glover, 1980; Morrow et al., 1986). However, the effect of 2,3,7,8-TCDD on testosterone receptors has not been evaluated.

In summary, the results from both the NIOSH and Ranch Hand studies are limited by the cross-sectional nature of the data and the type of clinical assessments conducted. However, the available data provide evidence that alterations in human male reproductive hormone levels are associated with serum 2,3,7,8-TCDD.

7.15.2. Possible Effects of Exposure to 2,3,7,8-TCDD or Mixtures of Dioxins, Furans, and PCBs

The following section describes outcomes that may be related to 2,3,7,8-TCDD exposure. Further research would assist in the final evaluation of the effects of dioxin for the following outcomes.

7.15.2.1. *Possible Adult Effects*

7.15.2.1.1. ***Lipid concentrations.*** Animal studies indicate that 2,3,7,8-TCDD is associated with generally increased serum cholesterol and serum triglyceride levels. The effect of exposure to 2,3,7,8-TCDD-contaminated chemicals on lipids is not consistent in the available epidemiology studies. Elevations in total cholesterol and triglyceride levels were reported after high 2,3,7,8-TCDD exposure in TCP workers (Pazderova-Vejlupkova et al., 1981; Martin, 1984) and laboratory workers (Oliver, 1975). Despite their very high exposure to 2,3,7,8-TCDD-contaminated chemicals, neither adults nor children from Seveso had lipid levels above the referent level. Risk factors such as dietary fat intake, familial hypercholesterolemia, alcohol consumption, and exercise, which also affect cholesterol and other lipid levels, may be factors that were not considered in these studies.

Ranch Hands and the NIOSH cohort continue to have marginally elevated lipid concentrations despite the extended length of time between exposure and testing (Grubbs et al., 1995; Calvert et al. 1995). These most recent data suggest that high exposure to 2,3,7,8-TCDD contaminated substances are not related to significantly increased lipid concentrations, specifically total cholesterol and triglycerides. Nevertheless, slight but chronic elevations in serum lipids may put an individual at increased risk for disorders such as atherosclerosis and other conditions affecting the vascular system.

7.15.2.1.2. ***Diabetes and fasting serum glucose levels.*** Diabetes mellitus is a heterogeneous disorder that is a consequence of alterations in the number or function of pancreatic beta cells responsible for insulin secretion and carbohydrate metabolism. Depending on its type, diabetes has been attributed to endogenous factors such as genetic predisposition, to autoimmune processes, and to exogenous factors such as viral infections (Yoon et al., 1987) and chemical exposures, notably a rat poison (Miller et al., 1978) and some medications (Wilson and LeDoux, 1989), environmental toxins (Diabetes Epidemiology Research International, 1987), age, obesity, reduced physical exercise, diet, socioeconomic status, increased insulin resistance by the beta cells, and possibly parity (Pareschi and Tomasi, 1987).

The long-term risk of developing diabetes or other alterations in glucose metabolism after exposure to 2,3,7,8-TCDD is not well addressed by the available toxicological data. The results of the animal studies suggest that glucose levels are altered, generally decreased, by short-term, high-dose exposure to 2,3,7,8-TCDD, and that the response may be species-specific. Studies of rats and rhesus monkeys showed consistent decreases in serum glucose levels after daily doses administered over 30 days (Zinkl et al., 1973) or after a single dose of 2,3,7,8-TCDD (McConnell et al., 1978a; Gasiewicz et al., 1980; Schiller et al., 1986; Ebner et al., 1988) (Table 7-54). In one study, glucose levels continued to drop up to 3 weeks postexposure (Gorski et al., 1990). Dose-related decreases were also noted in CD rats fed 0.1, 1.0, or 10.0 μg/kg daily for 30 days (Zinkl et al., 1973). In contrast, lower daily doses of approximately 0.004 μg/kg/day administered to guinea pigs over a 90-day period produced no significant changes in either glucose or insulin levels (DeCaprio et al., 1986). Wasting syndrome, observed in many species after high dose exposure to 2,3,7,8-TCDD, is hypothesized to be related to various changes in the glucose transport mechanism and is mediated through the Ah receptor. Differences among the results of human and most animal studies may, hypothetically, be due to a number of factors, such as the species studied, the length of the exposure and the short observation periods of the toxicology studies, the rate of insulin metabolism after 2,3,7,8-TCDD exposure, possible differential effects of 2,3,7,8-TCDD on the various types of islet cells, and the high, usually single, 2,3,7,8-TCDD dose administered to the animals. Additionally in humans, with some exceptions, onset of diabetes occurs later in life; unfortunately, these characteristics were not evaluated in the chronic toxicity studies. Long-term feeding studies to evaluate the relationship among glucose levels, the development of diabetes, and 2,3,7,8-TCDD dose would be helpful in assessing the effect of exposure on the physiologic integrity of the islet cells. In addition, such studies may identify other factors that affect either directly or indirectly the function of the islet cells and the effect of 2,3,7,8-TCDD on the glucose transport mechanism. More discussion of glucose transport system effects and their potential relationship to diabetes is found in Part II: Chapter 3. Acute Subchronic, and Chronic Toxicity, Section 3.5. Also, a study by Matsumura and his colleagues is underway to determine whether there is a biological basis for the association between type II diabetes mellitus and dioxin levels in Ranch Hand veterans (personal communication, J. Michalek, 2000).

The results of the Ranch Hand morbidity study are in direct contrast with the results of the NIOSH mortality study, which included workers who were more highly exposed, with greater frequency and severity of exposure. The prevalence of diabetes in the exposed, and referent groups was similar and there was no significant positive trend between prevalence of diabetes and serum glucose levels. What was notable is that 60% of the workers who had serum 2,3,7,8-TCDD concentrations >1,500 pg/g lipid at the time of the study met the case definition for diabetes, and

that the adjusted geometric mean glucose concentration measured at the time of the study was statistically significantly higher than referent levels only in the half-life adjusted TCDD category 1,860-30,000 pg/g lipid. However, the analysis of the mortality data by exposure score, found decreasing prevalence of mortality from diabetes with increasing exposure score. The exposure score incorporated duration and intensity of exposure, among other factors. This puzzling picture suggests that in the NIOSH cohort, diabetes may not be well correlated with serum 2,3,7,8-TCDD concentration or duration of exposure.

The studies of Seveso populations and the NIOSH and IARC occupational cohort found very modest and generally statistically nonsignificant increases in mortality from diabetes. The results of each of these studies should be evaluated within the context of the limitations of the studies. Although the Seveso study is limited by a short follow-up period (15 years), all of the studies have small numbers of deaths from diabetes. It is well known that diabetes has a complex etiology ranging from genetic susceptibility, viral infections, and chemical insult to physical states such as obesity or pregnancy. The various mortality studies that examined the relationship between rates of death from diabetes and 2,3,7,8-TCDD exposure evaluated no data on important confounders such as the body mass index of cases, family history of diabetes, or the relationship between year of onset of the diabetes and exposure to 2,3,7,8-TCDD or chlorophenols. In addition, although the studies have reasonably good estimates of exposure to 2,3,7,8-TCDD, misclassification of exposure for many subjects is possible.

The analyses by Longnecker and Michalek (2000) provide only weak evidence to support a causal relationship between very low levels of serum 2,3,7,8-TCDD and increased risk of diabetes or changes in serum glucose or insulin. The risk measures are generally not strong or statistically significant, nor do they increase monotonically with increasing dose.

The current epidemiologic and toxicological data to date do not support a strong relationship between exposure to 2,3,7,8-TCDD and diabetes or alterations in glucose metabolism. However, there is some evidence to suggest that, particularly at high doses, 2,3,7,8-TCDD may perturb glucose metabolism in some species, a fact which needs further exploration.

7.15.2.2. *Possible Postnatal Developmental Effects*

Given that postnatal developmental effects of dioxin have been studied only in one human population (with the exception of some of the thyroid measures), these studies are being place in the “potential” category. Additional studies in other groups are recommended, as well as followup of these findings over time to evaluate whether these changes are temporary, with no long-term health effects, or an early indication of chronic effects. All the effects in this section were part of one or both of the Dutch developmental studies. The exposures assessed here are different from

the more typical "dioxin" study: the first series of studies (in Amsterdam) examined dioxins and furans, while the second (in Rotterdam and Grongenin) examined dioxins, furans, and PCBs. Thus, any effects observed could be from one agent or some mixture. Even though the studies may have picked out certain exposures as statistically significant, this does not mean that other factors not selected are not associated. For example, in the Rotterdam/Grongenin studies, only PCBs were evaluated prenatally and at birth, but these values were significantly correlated with dioxins, furans, and PCBs collected about 2 weeks after delivery. Many of the findings in the Rotterdam/Grongenin studies were associated with *in utero* PCB exposures measured in maternal blood (IUPAC 118, 138, 153, 180). However, of these, only 118 is considered dioxin-like. As the technology improves to measure dioxin levels in smaller samples, direct measurements will help clarify the issues related to surrogate measures (e.g. PCBs).

7.15.2.2.1. ***Neurobehavioral effects.*** Of the various endpoints covered by the series of reports on the Dutch population, the most interesting findings related the neurobehavioral endpoints. Prechtl's Neurologic Optimality Scores (NOS) and the related postural tone cluster scores and reflex cluster scores were collected at 18 months of age (Huisman et al., 1995a) and, at 42 months of age, children were assessed for cognitive abilities using the Kaufman Assessment Battery for Children (K-ABC) and for verbal comprehension using the Reynell Language Developmental Scales (RDLS) (Patandin et al., 1999).

The NOS scores were somewhat arbitrarily divided at the median and compared to the individual dioxins, furans, and PCBs, as well as their summary measures (Huisman et al., 1995a). A number of the levels of the above agents in breast milk were associated with the NOS, while the prenatal PCBs were not (Table 7-46). Coplanar PCB TEQ was associated with hypotonia (measured through the posture tone cluster score). This observation of hypotonia and prenatal PCB exposure is consistent with Rogan et al. (1986). An evaluation of motor function was associated only with the prenatal PCB levels. Because of the small volume of materal and cord blood collected, dioxins and furans were not measured during the prenatal period. An interaction observed with paternal smoking suggests that this issue should be examined further by collecting postnatal materal smoking data.

Statistically significant deficits in K-ABC were associated with $\sum PCB_{\text{maternal blood}}$ for the entire group, and in RDLS only in the formula-fed children (Patandin et al., 1999). Importantly, the current body burdens in the 42-month-old children were not associated with any cognitive deficits. Statistically significant changes were not observed in the breast-fed children, possibly because of the higher SES status, parental education, and parental verbal IQs. Another possibility is the beneficial effect of breast feeding in general.

Even though studies of Yu-Cheng children are not directly comparable to the above studies, they also showed neurobehavioral delays: increased psychomotor delays (Yu et al., 1991) and lower scores on IQ tests (Chen et al., 1992; Lai et al., 1993; Guo et al., 1993; Chen and Hsu, 1994).

Many of the other outcomes in the Dutch population were "better" in those with exposure: fluency cluster score (Huisman et al., 1995b), mental development index -- MDI (Koopman-Esseboom et al., 1996), and visual recognition memory test at 7 months of age (Koopman-Esseboom et al., 1995b). This may be a result of the inherent benefit of breast feeding (and length of breast feeding) over formula for those measures, or may be due to the way women select to breast fed (e.g., higher SES women, parents with higher educational levels). As noted above, this later notion is supported in a recent report by Patandin et al. (1999).

Transplacental exposures of mice demonstate neurobehavioral effects of dioxin and dioxin-like compounds. These include effects on postural endpoints, motor function, visual abilities, and learning. Perinatally exposed monkeys showed a deficit in cognitive function. Exposures are presented by dietary levels or dose given, and thus are difficult to compare to the exposure measures used in human studies. More details on these studies are presented in Chapter 5 (Developmental and Reproductive Toxicity).

Endpoints varied in the above studies, as did the components and levels of the exposures, overall; in spite of this, the data suggest the relationship between dioxin and dioxin-like compounds and neurobehavioral outcomes. Examination of other human populations and long-term follow-up of these study groups will greatly benefit this database.

7.15.2.2.2. ***Thyroid function.*** Two series of studies, both in The Netherlands but conducted in different groups, have examined thyroid function (Pluim et al., 1993; Koopman-Esseboom et al., 1994c). The two reports did have a finding in common: both observed higher TSH at 3 months of age with higher TEQs. They both had significant findings for T4, but they were in opposite directions. All these findings, plus other changes found in the second report (an increase in T4/TBG and a decrease in free T4) strongly suggest that more work be done in this area. These findings suggest a possible shift in the distribution of thyroid hormones, and point out the need for collection of longitudinal data to assess the potential for long-term effects associated with these changes.

7.15.2.2.3. ***AST and ALT.*** One study looked at blood measures in 35 perinatally exposed children in The Netherlands (Pluim et al., 1994). AST, ALT, and platelets all varied with exposure (Table 7-26). Even though all but three children had values within "normal" ranges, the distributions of

has shifted (e.g., an increase in platelets), which could have some currently unknown/unrecognized short- or long-term effect on health.

7.15.3. Effects for Which Further Research Is Needed

The following section describes endpoints for which the animal data have demonstrated exposure-related effects, but the human data are inconclusive and require further study.

7.15.3.1. *Diseases of the Circulatory System*

In general, the results of the cohort mortality studies of TCP production workers were remarkably similar. For all of the early studies, the SMRs for diseases of the circulatory system (ICD-9: ICD 390-459) were approximately 100, meaning that the death rate in the exposed population was nearly the same as that in the general population, controlling for age, race, gender, and calendar year (Fingerhut et al., 1991b; Zober et al., 1990; Bueno de Mesquita et al., 1993; Bertazzi et al., 1989, 1992; Collins et al., 1993; Bond et al., 1989; Coggon et al., 1991). None of the SMRs above 100 were statistically significantly elevated.

In the only study of its kind, Flesch-Janys and colleagues (1995) estimated exposure to PCDDs, PCDFs, and total TEQs for all members of the Hamburg chemical worker cohort based on a sample of workers with either serum or adipose tissue exposure measurements. Mortality from all cardiovascular diseases, and specifically from ischemic heart disease, was related to increasing 2,3,7,8-TCDD concentrations. More striking was the positive relationship betweeen Total TEQs and cardiovascular disease as a whole.

Mortality from circulatory system diseases among Ranch Hands (SMR = 110, 95% CI = 60-150) (Michalek et al., 1990) and Australian Vietnam veterans (RR = 1.7, 95% CI = 0.9-3.0) (Fett, 1987b) was nonsignificantly elevated. In an update of the Ranch Hand data, the SMR for all circulatory diseases combined among all Ranch Hands was not elevated (SMR = 100, 95% CI = 70-130) (Michalek et al., 1998). However, a significant increase in cardiovascular mortality was noted in enlisted ground crew (SMR=150, 95% CI =1.0-2.2). There was a deficit of deaths from this cause among U.S. Army Vietnam veterans compared to non-Vietnam veterans (Centers for Disease Control Vietnam Experience Study, 1988c). Elevated mortality from circulatory diseases among Seveso residents is considered by the authors to be the result of environmental stresses and possibly other risk factors rather than exposure to 2,3,7,8-TCDD (Bertazzi et al., 1989; Pesatori et al., 1998). The mortality pattern from circulatory and cardiovascular disease among the three zones does not suggest a pattern of effect. Perhaps further followup will clarify the story.

Diseases of the circulatory system, particularly heart disease, are the leading causes of death among populations of most developed nations. Leading risk factors include age, cigarette

smoking, elevated lipid levels, obesity, hypertension, diabetes, and physical inactivity (Smith et al., 1992). Among the studies that examined mortality from circulatory system diseases, none directly adjusted SMRs for known risk factors or attempted to evaluate jointly the contribution of known risk factors and 2,3,7,8-TCDD to the mortality rates (Fingerhut et al., 1991b; Zober et al., 1990; Bueno de Mesquita et al., 1993; Bertazzi et al., 1989, 1992; Collins et al., 1993; Bond et al., 1989; Coggon et al., 1991). More recent mortality studies attempted to control for known confounders; when possible, most used internal control groups. Still, the picture is inconsistent among the various cohorts. Therefore, given the strong contribution of these risk factors, it is not possible to rule out physical and personal risk factors in the etiology of diseases of the circulatory system and heart in these populations. However, the absence of a "healthy worker effect" for these causes of death suggests that future research be directed specifically at the relationship between circulatory and heart disease and exposure to 2,3,7,8-TCDD.

Cross-sectional morbidity studies have not found increases in the prevalence of circulatory or heart disease among TCP workers, Ranch Hands, or U.S. Army Vietnam veterans (Suskind and Hertzberg, 1984; Bond et al., 1987; Moses et al., 1984; Centers for Disease Control Vietnam Experience Study, 1988a; Calvert et al., 1998). In some cross-sectional studies, risk estimates were adjusted for some risk factors, depending on the study (Suskind and Hertzberg, 1984; Poland et al., 1971; Moses et al., 1984; Bond et al., 1983; Centers for Disease Control Vietnam Experience Study 1988a; Roegner et al., 1991). Ranch Hands were the only group to experience marginal differences in diastolic blood pressure, arrhythmias, and peripheral pulse abnormalities after adjusting for selected risk factors (Roegner et al., 1991).

The animal data suggest that at high levels of 2,3,7,8-TCDD, the vascular system, cardiac muscle, and valves and function may be affected by exposure (Kociba et al., 1978; Buu-Hoï et al., 1972; Brewster et al., 1988; Hermansky et al., 1988; Kelling et al., 1987; Canga et al., 1988). However, with the exception of the long-term feeding study (Kociba et al., 1978), the exposures in animals were single high doses and the human exposures (except Seveso) were chronic, medium to high doses.

In summary, the animal studies suggest that 2,3,7,8-TCDD causes pathologic changes that may lead to later circulatory system disease. However, long-term studies of mature and aged animals have not been carried out to evaluate these hypotheses and to correlate the results of the animal with the human studies. Few epidemiologic studies were designed to control for many of the risk factors known to cause circulatory system and heart disease, but a consistent absence of the healthy worker effect for circulatory disorders and heart disease in numerous mortality studies, and the positive relationship observed in one study between total TEQs and circulatory diseases, suggest the need for additional research in this area. These studies should also include methods to

quantify subject exposure to 2,3,7,8-TCDD and control of confounders related to circulatory diseases.

7.15.3.2. *Immunologic Effects*

The available epidemiologic studies on immunologic function in humans relative to exposure to 2,3,7,8-TCDD do not describe a consistent pattern of effects among the examined populations. Two studies of German workers, one exposed to 2,3,7,8-TCDD and the other to 2,3,7,8-tetrabrominated dioxin and furan, observed dose-related increases of complements C3 or C4 (Zober et al., 1992; Ott et al., 1994), while the Ranch Hands continue to exhibit elevations in IgA (Roegner et al., 1991; Grubbs et al., 1995). Other studies of groups with documented exposure to 2,3,7,8-TCDD have not examined complement components to any great extent or observed significant changes in IgA. Suggestions of immunosuppression in a small group of exposed workers as a result of a single test should be confirmed in other cohorts of similarly exposed populations (Tonn et al., 1996).

Comprehensive evaluation of immunologic status and function of the NIOSH, Ranch Hand, and Hamburg chemical worker cohorts found no consistent differences between exposed and unexposed groups for lymphocyte subpopulations, response to mitogen stimulation, or rates of infection (Halperin et al., 1998; Michalek et al., 1999; Jung et al., 1998; Ernst et al., 1998). However, in a single study, T-cell response to Inferon-γ in TCDD-exposed workers was negative in isolated peripheral blood mononuclear lymphocytes and positive in diluted whole blood (Ernst et al., 1998).

More comprehensive evaluations of immunologic function with respect to exposure to 2,3,7,8-TCDD and related compounds are necessary to assess more definitively the relationships observed in nonhuman species. Longitudinal studies of the maturing human immunologic system may provide the greatest insight, particularly because animal studies have found significant results in immature animals, and human breast milk is a source of 2,3,7,8-TCDD and other related compounds. Data from a longitudinal study of children (Weisglas-Kuperus et al., 1995, 2000) suggest long term effects. Additional follow-up and investigations of other populations would be informative.

7.15.3.3. *Adult Reproductive Outcomes*

7.15.3.3.1. ***Semen changes.*** The Vietnam Experience Study found a significant relationship between service in Vietnam and sperm abnormalities, whereas the Ranch Hand study did not confirm these results when exposure was defined by both cohort status and 2,3,7,8-TCDD levels.

However, the data on alterations in male reproductive hormone levels associated with occupational exposure to 2,3,7,8-TCDD emphasize that further research in these areas is required.

7.15.3.3.2. ***Endometriosis.*** Two published reports of infertility patients (Mayani et al., 1997; Pauwels et al., 1999) have raised the potential for an association between endometriosis and TCDD/TEQ exposure. These studies are small and of limited power. Studies of women from Seveso and New York State are currently underway and will add to the database on this outcome.

7.15.3.4. ***Developmental Effects***

This section includes all developmental effects except those postnatal developmental effects which are covered by outcome (thyroid, neurobehavioral outcomes, and AST and ALT). Outcomes related to fertility are also reported (e.g., time to pregnancy, birth rates, semen changes).

7.15.3.4.1. ***Consistency.*** A variety of study designs, including case-control, ecologic, cross-sectional, and historical cohort designs, have addressed the issue of 2,3,7,8-TCDD and reproductive effects in humans. Unfortunately, the different criteria for case definitions across studies make it difficult to compare the results. In addition, the method of case ascertainment for certain endpoints influences the rate of events observed. The Vietnam Experience Study substudies of veteran-reported birth defects compared with those identified through hospital records demonstrated that rates of self-reported outcomes differed by exposure status. Moreover, predictive value of self-reported events was poor in both cohorts. In contrast, rates of birth defects in the Ranch Hand study were similarly reported by the Ranch Hands and controls. Both groups underreported 7% of birth defects in children conceived prior to their SEA tour and 14% after their tour of duty.

7.15.3.4.2. ***Strength.*** No developmental effect measure greater than 2 was noted in any of these investigations. This is not surprising, given the limitations of the studies, particularly with regard to exposure misclassification. Therefore, the trends across these studies carry more import than "statistically significant" results.

7.15.3.4.3. ***Temporality, dose-response.*** Although these studies have restricted inclusion of reproductive events to those that occurred after exposure to 2,3,7,8-TCDD was suspected, no study has evaluated 2,3,7,8-TCDD levels at the time of the outcome. Determination of a 2,3,7,8-TCDD dose-response relationship with adverse reproductive outcomes would not be valid unless individual 2,3,7,8-TCDD levels were available. The recent Ranch Hand study estimated the

2,3,7,8-TCDD levels at the time of the developmental outcome, which is an important contribution toward understanding this phenomenon. However, with regard to early losses, this analysis would not be able to address those occurring very early in gestation, before recognition of the pregnancy by the woman or her physician, or their subsequent effect on identification of adverse outcomes identified later in pregnancy or at birth.

7.15.3.4.4. ***Biological plausibility.*** A growing body of animal research described in Chapter 5 lends biological plausibility to the association between dioxin and most of the reproductive endpoints evaluated in these studies, with the notable exception of molar pregnancies. There is growing evidence that dioxin affects testis and accessory gland weight, testicular morphology, spermatogenesis, and fertility in males. A model for a paternally mediated dioxin effect on congenital malformations has not been reported; however, increased interest in this area (Olshan and Mattison, 1994) may yield more information on this topic. Among female animals, the primary reproductive endpoints that have been examined include decreased fertility and pregnancy loss.

The mechanism by which 2,3,7,8-TCDD causes adverse reproductive and developmental effects has not been well described, although considerable insight has been gained from research focusing on the Ah receptor. Although the Ah receptor has been linked with birth defects in several mouse strains, it appears that the mechanism of effect may be dependent on the outcome evaluated, as well as other dioxin congeners to which the population is exposed. Clearly, these relationships in humans have not been adequately investigated.

The discovery in the Times Beach, Missouri; CDC; and Ranch Hand studies that self-reported dioxin exposure and exposure indices developed from the analyses of 2,3,7,8-TCDD in soil and military records are poorly correlated with serum 2,3,7,8-TCDD levels aids in understanding the inconsistencies of the research to date regarding 2,3,7,8-TCDD and effects. Thus, because of the likelihood of exposure misclassification in those studies lacking direct measures of exposure, the findings have historically been severely limited.

7.15.3.4.5. ***Spontaneous abortions.*** Miscarriages were investigated in several studies with different designs and varied patterns of parental exposure. Events were generally ascertained by self- or spousal report. When case ascertainment was through medical records, such as in the Ranch Hand study or the Vietnamese investigations, the events are by definition restricted to those miscarriages that were clinically recognized.

Research in the area of pregnancy loss indicates that 30%-50% of all conceptions are lost prior to or during implantation (Hertig et al., 1959). The rate of loss between implantation and

expected first menstrual period ranges from 22% to 30% (Wilcox et al., 1988; Sweeney et al., 1988). Thus it is clear that restriction of the examination of pregnancy loss to those events that are ascertained through medical records, or even self-reports, results in excluding a large proportion of the outcome of interest. In studies of environmental factors and spontaneous abortion where information is lacking concerning conception, "the conflation of different doses with different effects can mislead" (Kline et al., 1989). Because of these discrepancies, it would not be meaningful to pool the results of the research on the association between dioxin exposure and miscarriage to judge the "consistency" of the association.

Overall, it must be acknowledged that the data compiled to date are inadequate to address this issue. To simply enumerate and compare the number of "positive" versus "negative" studies to ascertain consistency in the research would be inappropriate. The reasons for this have been described above in detail, with emphasis on the high (40%-50%) exposure misclassification that has been documented in the majority of these investigations, the small sample sizes evaluated, lack of data on dioxin levels at the time of conception, and the unknown impact of early pregnancy loss on identification of birth defects. The animal and human evidence for a 2,3,7,8-TCDD-pregnancy loss relationship is sufficiently suggestive to warrant further investigation. Several studies of various designs and populations have demonstrated weak but consistent associations (Reggiani, 1978; Hatch, 1984b; Constable and Hatch, 1985; Huong et al., 1989; Phuong et al., 1989a; Stellman et al., 1988), whereas others have not (Townsend et al., 1982; Smith et al., 1982; Cutting et al., 1970; Kunstadter, 1982; Report to the Minister for Veterans' Affairs, 1983; Stockbauer et al., 1988; Erickson et al., 1984; Centers for Disease Control Vietnam Experience Study, 1989). (These studies include those that should be restricted to the assessment of military service in Vietnam and reproductive events.) Only two studies, one an analysis of the Ranch Hand developmental data (Wolfe et al., 1995) and the other a recent analysis of the NIOSH cohort (Schnorr et al., in press 2001), have used biological measurements and estimated the 2,3,7,8-TCDD levels present around the time of conception. The first study did note a modest increase in recognized spontaneous abortions and stillbirths but only at the low, but not the high, level. The Ranch Hand study leaves several questions unanswered, including the determination of a dose-response level and the impact of very early pregnancy losses on rates of recognized fetal death and birth defects that survive long enough to be "counted." The NIOSH study did not observe increases at any level.

7.15.3.4.6. ***Congenital malformations/birth defects.*** The confusing evidence regarding the relationship between dioxin exposure and birth defects suffers not only from the limitations described above for the studies of miscarriage but also from the lack of power to evaluate specific types of malformations. To increase the power to detect a potential relationship, the studies have

combined all birth defects together and calculated an odds ratio for total birth defects. Given evidence for etiologic heterogeneity among subgroups of birth defects (Khoury, 1989), it is probable that this approach dilutes the effect measure.

These studies also should more carefully examine type of parental exposure, i.e., paternal, maternal, or both. Timing of exposures and potential biological mechanisms for birth defects are different for maternal and paternal exposures. The field of paternally mediated effects is rather new, but future research may assist in the interpretation of these results (Olshan and Mattison, 1994). If dioxin exposure is related to malformations among the offspring conceived after paternal service in Vietnam, then the effect must occur either premeiotically, or anew with continuing circulating levels of TCDD. Some animal studies have found that spermatogonia and spermatocytes (premeiotic spermatogenic cells) were able to repair DNA after exposure to toxic agents, whereas spermatids and spermatozoa did not have this capability (Lee and Dixon, 1978).

A few studies (Hatch, 1984a; Constable and Hatch, 1985; Huong et al., 1989; Phuong et al., 1989a), including those investigations of the Yusho and Yu Cheng incidents (Rogan, 1982; Yen et al., 1989; Rogan et al., 1988) have suggested an association. Many studies have failed to find a relationship between dioxin and birth defects (Townsend et al., 1982; Smith et al., 1982; Cutting et al., 1970; Kunstadter, 1982; Stockbauer et al., 1988; Erickson et al., 1984; Centers for Disease Control Vietnam Experience Study, 1989; Mastroiacovo et al., 1988). Again, however, in view of the serious limitations of these studies of 2,3,7,8-TCDD and developmental and reproductive events, it must be concluded that the relationship between paternal dioxin exposure and congenital malformations remains unknown. However, if military service in Vietnam is the exposure of interest, there is only modest evidence to support an association with birth defects. Most of the data on grouped birth defects have very small numbers.

7.15.3.4.7. ***Dental effects.*** Finnish investigators examined the association of enamel hypomineralization of permanent first molars in 6-7-year-old children and TEQ exposure through breast feeding (these teeth develop during the first 2 years of life) (Alaluusua et al., 1996; Alaluusua et al., 1999). These data present interesting findings. Unfortunately, the presentation of the results is incomplete, so the potential biological significance cannot be assessed. This would be an interesting outcome to examine in additional studies.

7.15.3.4.8. ***Sex ratio at birth.*** Sex ratio at birth was significantly depressed in a group of 17 children in zone A, Seveso, in the years shortly following the industrial accident. This pattern disappeared a few years later. However, a recent expanded effort suggests that paternal age at the time of exposure may be a key factor. Sex ratios differences were not observed in other groups

examined. If effects are restricted to offspring to fathers less than 19 years old, as suggested in the new Seveso study, the lack of effect elsewhere could be explained by the groups examined: maternal levels of dioxin in community studies or studies of men older than 19. The findings in the most recent Seveso study emphasize the need for more attention on male-mediated development effects, and the potential importance of exposures prior to and during puberty. Because this outcome can easily be collected in studies of developmental effects, more thorough examination of this outcome could be useful.

7.15.3.4.9. ***Growth measures.*** Growth measures include endpoints such as intrauterine growth retardation (IUGR), low birth weight, and postnatal growth. Available evidence does not support an association between paternal dioxin level and low birth weight (Centers for Disease Control Vietnam Experience Study, 1989; Wolfe et al., 1992b, 1995; Michalek et al., 1998). In the Rotterdam study, decrements in length (but not other measures of growth) were observed early (months 3-7 postnatally) and associated with PCB levels, but disappeared with increasing age (Patandin et al., 1998). The Finnish data (Vartiainen et al., 1998) are interesting because birth weight did decrease in males with increasing TEQ, but the lack of detail on the statistical analyses makes interpretation difficult.

7.15.3.4.10. ***"Miscellaneous" endpoints.*** Additional reproductive outcomes that were evaluated in a subset of the studies include molar pregnancies (in the Vietnamese studies), neonatal and infant death, and childhood cancer and mortality. Mainly because of small sample sizes, it is difficult to reach conclusions regarding neonatal, infant, and child mortality and childhood cancers. Recently, the increased risk for neonatal death observed in the Ranch Hand study, the only study with individual TCDD levels, was investigated. Some changes were observed in the Ranch Hand study for preterm birth and neonatal death, but these did not follow an exposure-response relationship (Michalek et al., 1998).

Conclusion

In conclusion, the research to date has been successful in resolving some confusion surrounding the evidence for an association of dioxin exposure and various developmental and reproductive endpoints in humans. High occurrence of exposure misclassification, differences in case definitions across studies, and small sample sizes have severely limited the power of these studies to address these questions. Additional research that includes a measure of dioxin level at the time of conception for both the father and mother is necessary if the effect of dioxins on the spectrum of reproductive outcomes is to be understood.

7.15.4. Acute Effects

The following section reviews endpoints that were described in groups shortly after exposure to 2,3,7,8-TCDD but were not observed as chronic effects in studies conducted many years after exposure ceased. Also reviewed are endpoints observed as long-term effects in single studies.

7.15.4.1. *Dermatologic Conditions Other Than Chloracne*

Dermatologic conditions other than chloracne, such as hyperpigmentation, hypertrichosis, and eyelid cysts, have been related to exposure to 2,3,7,8-TCDD in early case reports (Ashe and Suskind, 1950; Suskind et al., 1953; Bleiberg et al., 1964; Poland et al., 1971; Bauer et al., 1961; Goldman, 1972; Jirasek et al., 1974; Oliver, 1975). However, these conditions may have been acute effects of 2,3,7,8-TCDD exposure that resolved over time or may be residual effects of chloracne, because they appear to occur more frequently in individuals with persistent chloracne (Suskind and Hertzberg, 1984). These conditions were not observed in studies in which the cohorts were examined years after cessation of exposure, in individuals with the potential for high exposure, or in those with high adipose or serum 2,3,7,8-TCDD levels (Moses et al., 1984; Webb, 1989; Roegner et al., 1991; Burton et al. 1998).

Actinic keratosis, Peyronie's disease, and basal cell carcinoma may not be associated with 2,3,7,8-TCDD. All three conditions were observed in only one study (Suskind and Hertzberg, 1984; Lathrop et al., 1984) and were not observed in studies of individuals with similar potential for exposure (Ott et al., 1994).

7.15.4.2. *Liver Enzymes Other Than GGT and Hepatomegaly*

A number of studies reported elevated liver enzymes, particularly AST and ALT, among individuals who were being exposed at the time of the measurement (May, 1973) or whose exposure was within a few years of the measurement (Jirasek et al., 1974; Mocarelli et al., 1986; Caramaschi et al., 1981). Follow-up studies or longitudinal analyses of exposed cohorts suggest that the increase in enzyme level resolves over time (Mocarelli et al., 1986; Assennato et al., 1989; Pazderova-Vejlupkova et al., 1981; May, 1982). In studies of exposed populations tested many years after exposure ceased, levels of AST and ALT were within normal range (Calvert et al., 1992; Webb et al., 1989; Roegner et al., 1991; Suskind and Hertzberg, 1984; Moses et al., 1984).

D-glucaric acid was tested in a number of 2,3,7,8-TCDD-exposed populations as an indicator of enzyme induction (Ideo et al., 1985; Martin, 1984; Roegner et al., 1991; Calvert et al., 1992). Shortly after the TCP reactor release, D-glucaric acid levels in Seveso children were elevated (Ideo et al., 1985). No other studies of exposed groups tested 5 to 37 years after exposure ceased found elevations of this enzyme (Martin, 1984; Roegner et al., 1991; Calvert et al., 1992).

These data suggest that certain hepatic enzymes are increased as a response to high, exogenous exposure to 2,3,7,8-TCDD. Once the exposure ends, the enzyme levels seem to decrease over time, as observed in the Seveso populations (Mocarelli et al., 1986; Ideo et al., 1985). Additional evidence of the acute nature of AST, ALT, and D-glucaric acid elevations is demonstrated by the lack of such increases in studies of highly exposed groups conducted long after exposure ceased (Calvert et al., 1992; Roegner et al., 1991; Grubbs et al., 1995; Martin, 1984).

As in the case of ALT, AST, and D-glucaric acid, hepatomegaly appears to be a condition reported in case reports after high exposure to 2,3,7,8-TCDD-contaminated chemicals, particularly among TCP production workers examined after a TCP reactor explosion and among Seveso residents (Ashe and Suskind, 1950; Suskind et al., 1953; Jirasek et al., 1974; Reggiani, 1980a). Later studies conducted after exposure ceased failed to find excess dose-related hepatomegaly in the exposed populations (Bond et al., 1983; Suskind and Hertzberg, 1984; Moses et al., 1984; Calvert et al., 1992; Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991; Webb et al., 1989; Hoffman et al., 1986). However, the absence of an effect in cross-sectional studies does not confirm the lack of an effect in the past.

7.15.4.3. *Pulmonary Disorders*

Early case reports suggest that exposure to 2,3,7,8-TCDD chemicals may cause temporary respiratory irritation (Zack and Suskind, 1980) and tracheobronchitis (Goldman, 1972). The data from two cross-sectional medical studies provide weak evidence of slightly decreased lung function among exposed individuals (Suskind and Hertzberg, 1984; Roegner et al., 1991). In these studies, the effects may be due more to smoking (Roegner et al., 1991) or to a substantial age difference between the exposed and unexposed groups (Suskind and Hertzberg, 1984). One study of highly exposed TCP production workers found no relationship between serum 2,3,7,8-TCDD levels and chronic obstructive pulmonary disease, bronchitis, or decreased pulmonary function (Calvert et al., 1992).

In conclusion, case reports indicate that intense acute exposure to 2,3,7,8-TCDD can produce respiratory irritation. However, the findings from controlled epidemiologic studies conducted many years after exposure do not convincingly support an association between 2,3,7,8-TCDD exposure and chronic effects on the respiratory system.

7.15.4.4. *Neurologic Disorders*

The results of case reports and epidemiologic studies demonstrate that exposure to 2,3,7,8-TCDD-contaminated materials is associated with symptoms referable to the central and peripheral nervous systems shortly following exposure and, in some cases, lasting many years

(Filippini et al., 1981; Ashe and Suskind, 1950; Moses et al., 1984). Overall, however, the neurologic status of workers, community residents, and Vietnam veterans exposed to 2,3,7,8-TCDD and evaluated from 5 to 37 years after last exposure appears to be normal (Centers for Disease Control of Vietnam Experience Study, 1988a; Lathrop et al., 1984; Sweeney et al., 1993). The data suggest that, although exposure to 2,3,7,8-TCDD may have been extensive as in exposed workers, Ranch Hands, and Seveso residents, the effects described in case reports may have been transient (Filippini et al., 1981; Lathrop et al., 1984; Centers for Disease Control Vietnam Experience Study, 1988a,b; Assennato et al., 1989; Alderfer et al., 1992; Sweeney et al., 1993). The findings of recent studies suggest that in adults there are no long-term neurologic effects caused by even high exposure to 2,3,7,8-TCDD-contaminated materials, but there is very little information with which to examine the effects of exposure on the developing human neurologic system.

7.15.4.5. *Porphyrias*

In rats and mice, exposure to 2,3,7,8-TCDD has been clearly shown to alter porphyrin metabolism (Goldstein et al., 1973; Smith et al., 1981; Jones and Chelsky, 1986; DeVerneiul et al., 1983; Cantoni et al., 1981; Goldstein et al., 1982). Whether 2,3,7,8-TCDD is associated with porphyrin changes in humans, particularly PCT, is a subject of unresolved debate. It has been suggested that the PCT and elevated urinary porphyrins observed in the New Jersey and Czechoslovakian workers during the years of operation of the plants were the result of exposure to hexachlorobenzene, which was produced at the same time as TCP (Pazderova-Vejlupkova et al., 1981; Jones and Chelsky, 1986). These statements have not been corroborated with strong studies. In the follow-up studies, urinary porphyrin levels of these TCP production workers were not elevated (Pazderova-Vejlupkova et al., 1981; Poland et al., 1971) or did not differ from levels in the control group (Calvert et al., 1993). Doss et al. (1984) also described transient elevations in coproporphyrins among 22 Seveso residents exposed to 2,3,7,8-TCDD.

Because 2,3,7,8-TCDD is a porphyrigen in rats and mice, it has been of interest to determine whether exposures may have contributed to the observed changes in porphyrin levels in human populations. The NIOSH study could not address the question of etiology or transient porphyria, but it did not find porphyria in highly exposed workers many years after their occupational exposure.

However, although porphyria was not found after 2,3,7,8-TCDD exposure, it may be an outcome of exposure to PCBs when there is a co-exposure to chlorophenols, as suggested by the study of pentachlorophenol workers (Hryhorczuk et al., 1998). Further research is recommended to examine these findings.

7.15.4.6. *Thyroid Function*

Many effects of 2,3,7,8-TCDD exposure in animals resemble signs of thyroid dysfunction or significant alterations of thyroid-related hormones. In the few human studies that examined the relationship between 2,3,7,8-TCDD exposure and hormone concentrations in adults, the results are mostly equivocal (Centers for Disease Control Vietnam Experience Study, 1988a; Roegner et al., 1991; Grubbs et al., 1995; Suskind and Hertzberg, 1984). However, concentrations of thyroid binding globulin (TBG) appear to be positively correlated with current levels of 2,3,7,8-TCDD in the BASF accident cohort (Ott et al., 1994). Little additional information on thyroid hormone levels has been reported for production workers and none for Seveso residents, two groups with documented high serum 2,3,7,8-TCDD levels.

Table 7-21b. Overview of biologic measurements in Dutch studies of postnatal developmental effects

Compound	IUPAC[a]	TEF[b]	Rotterdam/ Groningen[c] Breast milk [plasma/ cord blood][d]	Amsterdam[e] Breast milk	Compound	IUPAC	TEF	Rotterdam/ Groningen Breast milk [plasma/ cord blood]	Amsterdam Breast milk
PCDDs					**PCDFs (cont.)**				
2,3,7,8-TCDD	48	1	4.0	3.8	1,2,3,4,7,8-HXCDF	118	0.1	6.6	7.0
1,2,3,7,8-PECDD	54	0.5	10.6	10.6	1,2,3,6,7,8-HXCDF	121	0.1	5.7	6.2
1,2,3,4,7,8-HXCDD	66	0.1	8.7	1.3	1,2,3,7,8,9-HXCDF	124	0.1	3.6	3.2
1,2,3,6,7,8-HXCDD	67	0.1	47.4	49.1	2,3,4,6,7,8-HXCDF	130	0.1	0.3	BDL
1,2,3,7,8,9-HXCDD	70	0.1	6.7	6.5	1,2,3,4,6,7,8-HPCDF	131	0.01	7.9	6.1
1,2,3,4,6,7,8-HPCDD	73	0.01	63.2	54.3	1,2,3,4,7,8,9-HPCDF	134	0.01	0.2	BDL
1,2,3,4,6,7,8,9-OCDD	75	0.001	799.6	297.5	1,2,3,4,6,7,8,9-OCDF	135	0.001	2.2	1.3
PCDFs					**Planar PCBs**				
2,3,7,8-TCDF	83	0.1	0.8	2.0	3,3',4,4'-PCB	77	0.0005	19.3	
1,2,3,7,8-PECDF	94	0.05	0.3	0.2	3,3',4,4',5-PCB	126	0.1	152.0	
2,3,4,7,8-PECDF	114	0.5	22.7	21.9	3,3',4,4',5,5'-PCB	169	0.01	84.3	

Table 7-21b. Overview of biologic measurements in Dutch studies of postnatal developmental effects (continued)

Compound	IUPAC[a]	TEF[b]	Rotterdam/ Groningen[c] Breast milk [plasma/ cord blood][d]	Amsterdam[e] Breast milk
Nonplanar PCBs				
2,4,4'	28		12.1	
2,2',5,5'	52		2.6	
2,3',4,4'	66		11.6	
2,3',4',5	70		18.5	
2,2',4,4',5	99		19.7	
2,2',4,5,5'	101		1.5	
2,3,3',4,4'	105[f]	0.0001	9.4	
2,3',4,4',5	118[f]	0.0001	35.5 [0.16/0.04]	
2,2',3,3',4,4'	128		4.0	
2,2',3,4,4',5	137		16.8	
2,2',3,4,4',5'	138		129.9 [0.60/0.13]	
2,3,4,5,2',5'	141		1.1	
2,2',3,5,5',6	151		0.9	
2,2',4,4',5,5'	153		186.3 [0.91/0.18]	
2,3,3',4,4',5	156[f]	0.0005	21.0	
2,2',3,3',4,4',5	170[g]	0.0001	37.1	
2,2',3,3',4',5,6	177		6.3	
2,2',3,4,4',5,5'	180[g]	0.00001	76.8 [0.54/0.10]	
2,2',3,4,4',5',6	183		12.2	
2,2',3,4',5,5',6	187		20.0	
2,2',3,3',4,4',5,5'	194		8.6	
2,2',3,3',4,4',5,6	195		2.9	
2,2',3,3',5,5',6,6'	202		0.9	

[a] IUPAC: International Union of Pure and Applied Chemistry.
[b] TEF:Toxic Equivalence Factor (WHO, 1993).
[c] Measurements for this series of studies from Koopman-Esseboom et al., 1994.
[d] Mean values: breast milk in pg/g fat, blood in ng/g plasma.
[e] Measurements for this series of studies from Pluim et al., 1994.
[f] Mono-ortho PCBs.
[g] Di-ortho PCBs.

Table 7-22. Serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) levels in Seveso residents with chloracne and adipose tissue levels of 2,3,7,8-TCDD and hexachlorinated (HxCDD) dioxins in German chemical workers

Author	Population	2,3,7,8-TCDD level (pg/g)[a]	HxCDD level (pg/g)[a]	Year of chloracne diagnosis	Half-life extrapolated 2,3,7,8-TCDD[b]	Half-life extrapolated HxCDD[b]
Beck et al., 1989	Chemical workers[c]	174	247	1955	750	10,000
		99	166	1955	4,010	6,720
		147	5,101	1963	2,350	81,620
		61	172	1957(?)	2,470	6,970
		50	517	1969	380	3,940
		16	58	1955	650	2,360
		1,280	1,019	1978	3,380	2,690
		49	3,442	1974(?)	210	14,760
		50	9,613	1972(?)	260	50,740
		2,252	3,087	1984	2,850	3,910
		158	1,191	1977(?)	460	3,490
		6	283	1970	40	1,970
Mocarelli et al., 1991	Seveso residents	56,000[d]	—	1976-1977		
		27,800	—	1976-1977		
		26,400	—	1976-1977		
		15,900	—	1976-1977		
		12,100	—	1976-1977		
		17,300	—	1976-1977		
		7,420	—	1976-1977		
		1,690	—	1976-1977		
		828	—	1976-1977		

[a]pg/g of lipid (parts per trillion).
[b]Half-life extrapolation calculated by authors (Beck et al., 1989) using the formula $C_o = C_{t_n} \times 2^n$ where C_o = original concentration of 2,3,7,8-TCDD or HxCDD, C_{t_n} = concentration at time t, n = number of half-life periods, and t = half-life period of 5.8 years. Exposures occurred between 1949 and 1986.
[c]Measured in 1984.
[d]Measured in 1976.

Table 7-23. Mean serum levels of gamma glutamyl transferase (GGT) among Seveso and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans

Author	Population	Exposed			Unexposed		
		N	Mean level[a]	(SD)	N	Mean level[a]	(SD)
	Seveso residents						
Mocarelli et al., 1986	(1977) (Boys)	52[b]	9.73	(4.72-20.04)	42[b]	7.28	(3.71-14.26[c])
	(Girls)	32[b]	9.10	(3.62-22.85)	43[b]	8.05	(2.99-21.68)
	(1982) (Boys)	106[b]	9.70	(4.29-21.93)	138[b]	8.99	(4.45-18.20)
	(Girls)	117[b]	9.04	(4.25-19.23)	140[b]	8.59	(3.85-19.14)
Assennato et al., 1989	1976	193[d]	11.94	(16.80)	—[e]	—	—
	1982	152[d]	11.67	(7.94)	123[f]	11.23	(7.41)
	1984	142[d]	10.53	(7.07)	196[f]	11.19	(7.05)
	1985	141[d]	10.57	(7.38)	167[f]	10.94	(4.68)
	Missouri residents						
Webb et al., 1989	<20[g]	16	24.0	(15.5)	—	—	—
	20-60	13	17.7	(7.23)	—	—	—
	>60	12	32.8	(23.90)	—	—	—
Hoffman et al., 1986	Missouri residents in Quail Run Mobile Home Park	140	30.0[h]	(88.3)	141	20.1	(23.4)
May, 1982	TCP production workers in Great Britain	41	39.0	—	31	27.7[c]	—
Martin, 1984	TCP production workers in Great Britain	41	40.0	(14-91)	120	32.0	(11-90)
Moses et al., 1984	TCP and 2,4,5-T production workers in West Virginia	22[d]	26.3[c]	(27.0)	9[f]	17.4	(11.0)
Calvert et al., 1992	TCP and 2,4,5-T production workers in Missouri and New Jersey	280	58.5[c,i]	(73.7)	259	47.4	(41.1)

Table 7-23. Mean serum levels of gamma glutamyl transferase (GGT) among Seveso and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans (continued)

Author	Population	Exposed			Unexposed		
		N	Mean level[a]	(SD)	N	Mean level[a]	(SD)
Ott et al., 1993b	BASF accident cohort	133	30.5	(58.4)	6,708	29.9	(43.5)
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army ground troops	2,490	43.2[j]		1,972	41.1[k]	—
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel						
	Unknown ≤10[l,m]	338	31.49[c,o]	—	777	34.64[o]	—
	Low 15-≤33.3[l,m]	191	38.28[c,o]	—			
	High >33.3[l,m]	182	40.82[c,o]	—			
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel						
	Background [l,m,n]	362	32.60[o]	—	1025	34.34[o]	—
	Low [l,m,n]	251	36.99[c,o]	—			
	High [l,m,n]	502	37.67[c,o]	—			

[a]Units = U/L.
[b]Number of samples.
[c]$p < 0.05$.
[d]Chloracne.
[e]No data for controls in 1976.
[f]No chloracne.
[g]Adipose tissue level of 2,3,7,8-TCDD in pg/g of lipid.
[h]% abnormal: exposed = 3.6; unexposed = 3.6.
[i]% abnormal: exposed = 10.7; unexposed = 5.0; OR=227 (95% CI=1.17, 4.39).
[j]Geometric mean.
[k]% Abnormal (Vietnam veterans, 5.5%; non-Vietnam veterans, 4.4; OR=1.3, 95% CI=1.0-1.8).
[l] Serum 2,3,7,8-TCDD level in pg/g of lipid.
[m]Contrasted to unexposed comparison population.
[n]Background: current dioxin ≤10 pg/g of lipid.
Low: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin ≤143 pg/g of lipid.
High: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin >143 pg/g of lipid.
[o]Adjusted mean.

Table 7-24. Logistic regression model for an out-of-range serum gamma-glutamyl transferase[a] (GGT) level using the categorical TCDD[b] exposure measure[c]

Variable	Beta	Standard error of the estimate	X^2	*p*
Intercept	-4.12	0.50	67.01	<0.001
Exposure (worker = 1, referent = 0)	0.37	0.43	0.74	0.195
Per alcohol-year	-2.4×10^{-6}	2.6×10^{-3}	0.00	0.999
Current alcohol drinker (yes = 1, no = 0)[d]	0.90	0.42	4.70	0.030
Alcohol-years/exposure interaction[e,f]	7.2×10^{-3}	3.5×10^{-3}	4.24	0.039
Triglyceride level	3.8×10^{-3}	1.1×10^{-3}	11.94	<0.001

[a]Reference value: 96 IU/L; a level was considered out of range if it exceeded the reference value. Reference values were defined as the 95th percentile for the referent cohort.
[b]TCDD = 2,3,7,8-tetrachlorodibenzo-*para*-dioxin.
[c]N=536 observations.
[d]The results from this logistic regression analysis change little when this term is dropped from the model.
[e]Interaction between alcohol-years and exposure.
[f]Exposure odds ratios (ORs) for an abnormal γ-glutamyltransferase level among workers by selected alcohol-year levels, adjusting for all variables in the model, are as follows: OR=2.96 (95% confidence interval [CI]=1.34-6.54) for 100 alcohol-years; OR=1.79 (95% CI=0.81-3.97) for 30 alcohol-years; OR=1.45 (95% CI=0.63-3.36) for 1 alcohol-year; and OR=1.44 (95% CI=0.62-3.34) for 0 alcohol-years.

Source: Calvert et al., 1992b. Used with permission from the author.

Table 7-25. Serum alanine aminotransferase (ALT) among Seveso children and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans

Author	Population	Exposed N	Exposed Mean level[a]	Exposed (SD)	Unexposed N	Unexposed Mean level[a]	Unexposed (SD)
Mocarelli et al., 1986	Seveso children						
	1977 Boys	46[b]	12.25[c]	(7.14-20.99)	45[b]	9.33[c]	(3.73-23.33)
	Girls	100	12.97	(6.68-25.18)	141	11.99	(5.51-26.12)
	1982 Boys	33	10.74	(5.09-22.65)	39	10.74	(5.09-22.65)
	Girls	119	12.27	(6.5 -23.17)	136	12.19	(6.46-23.01)
Caramaschi et al., 1981	Seveso children	141[d]	3.5[e,c]		0[f]	0[e]	
Moses et al., 1984	TCP production workers; 10-30 years postexposure	105[d]	15.9	(13.0)	101[f]	15.7	(13.0)
Calvert et al., 1992	TCP production workers; 15-37 years postexposure	280[g]	33.8	(22.6)	259	33.0	(21.2)
Ott et al., 1994	BASF accident cohort	133	14.8	(8.4)	6,721	15.1	(10.0)
Hoffman et al., 1986	Missouri residents in Quail Run Mobile Home Park	134	—[h]		135	—[h]	
Webb et al., 1989	Missouri residents						
	<20[i]	16	22.7	(2.76)			
	20-60	12	22.5	(2.39)			
	>60	12	23.3	(3.06)			
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army ground troops	2,490	26.4[j,k]		1,972	25.8	
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel						
	Unknown ≤10[l]	338[m]	19.16	—	777	20.34	
	Low 15-≤33.3[l]	19[m] 1	20.83	—	—	—	
	High >33.3[l]	182[c,m]	20.09	—	—	—	
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel						
	Background[l]	367[m]	26.25	—	1,025	27.56	
	Low[l]	254[m]	27.47	—			
	High[l]	254[m]	27.09	—			

[a]ALT; units U/L.
[b]Number of samples.
[c]$p<0.05$.
[d]Chloracne.
[e]% abnormal.
[f]No chloracne.
[g]% abnormal: workers 4.3; unexposed 5.0; OR=0.85 (95% CI=0.38, 1.89).
[h]% abnormal: exposed 6.0; unexposed 3.0.
[i]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[j]Geometric mean.
[k]% abnormal; Vietnam veterans, 5.3; non-Vietnam veterans, 4.4; OR=1.2, 95% CI=0.9-1.5.
[l]Serum 2,3,7,8-TCDD in pg/g of lipid.
Background: current dioxin≤ 10 pg/g of lipid.
Low: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin ≤143 pg/g of lipid.
High: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin >143 pg/g of lipid.
[m]Adjusted mean.

Table 7-26. Blood measures and cumulative dioxin-furan TEQs from 11 weeks of breast feeding (Pluim et al., 1994)

Blood measure	Correlation coefficient	*p*-value
ALT	0.40	0.02
AST	0.44	0.009
Platelets	-0.48	0.011

Table 7-27. Mean D-glucaric acid levels among Seveso residents, TCP production workers, and Vietnam veterans

Author	Population	Exposed			Unexposed		
		N	Mean	(SD)	N	Mean	(SD)
Ideo et al., 1985	Seveso adults Levels measured in 1978 (Zone B)	117	27.1[a,b,c]	—	127	19.8[a,b,d]	—
	Seveso children Zone A, 1976	14[e]	39[a,b,c]	—	17[f]	20.5[b]	—
	Zone B						
	1979	26.8	—[g]	—	—	—	—
	1980	17.0	—	—	—	—	—
May, 1982	TCP production workers in Great Britain	41	2.07[h]	—	31	1.52[h]	—
Martin, 1984	TCP production workers in Great Britain	39	2.09[c]	(0.7-7.9)	126	1.59	(0.8-8.3)
Calvert et al., 1992	TCP and 2,4,5-T production workers in Missouri and New Jersey	273	14.1[i]	(11.1)	256	13.2[i]	(7.9)
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel						
	Unknown ≤10[j]	317	13.99[k,l]	—	727	14.11[k]	—
	Low 15-≤33.3	180	14.43[l]	—	—	—	—
	High >33.3	173	15.22[l]	—	—	—	—

[a]Units: μmol/g of creatinine.
[b]Median level.
[c]$p < 0.05$.
[d]Residents of unexposed community.
[e]Skin lesions.
[f]No skin lesions.
[g]d-glucaric acid levels measured in 1979 were significantly higher than levels measured in 1980 ($p < 0.05$), no data presented.
[h]d-glucaric acid/creatinine ratio.
[i]Units = μg/g of creatinine.
[j]Serum 2,3,7,8-TCDD levels in pg/g of lipid.
[k]Units = μM.
[l]Contrasted to unexposed comparison population.
[m]Adjusted mean.

Table 7-28. Mean total cholesterol levels among Seveso and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans

Author	Population	Exposed			Unexposed		
		N	Mean[a] level	(SD)	N	Mean[a] level	(SD)
Mocarelli et al., 1986	Seveso children 1977 1982	 16[b] 182[b]	 4.62 4.48	 3.26-5.98 2.47-5.99	 28[b] 250[b]	 4.45 4.41	 (3.12-5.77) (2.99-5.83)
Caramaschi et al., 1981	Seveso children	138	15.2[c,d]	—	120	12.5[c,e]	—
Assennato et al., 1989	Seveso residents 1976 1982 1984 1985	 193[d] 152[d] 142[d] 141[d]	 4.78 4.06 4.09 4.14	 (0.99) (0.80) (0.88) (0.91)	 —[f] 123[e] 196[e] 167[e]	 — 4.14 4.12 4.13	 — (0.77) (0.86) (0.78)
May, 1982	TCP production workers in Great Britain	41	5.97	—	31	6.6	—
Martin, 1984	TCP production workers in Great Britain	39	6.02[g]	—	126	5.6	—
Poland et al., 1971	TCP production workers in New Jersey	71	6.12	(0.82)	—	—	—
Moses et al., 1984	TCP production workers in West Virginia	105[d]	5.38	(0.88)	101[e]	5.37	(0.85)
Suskind and Hertzberg, 1984	TCP production workers in West Virginia	200	5.46	(0.07)	163	5.28	(0.08)
	TCP production workers: chloracne vs. never chloracne	105[d]	5.44	(0.08)	28[e]	5.30	(0.18)
Ott et al., 1994	BASF accident cohort	135	6.14[m]	(1.01)	6,581	6.37[m]	(1.17)
Calvert et al., 1996	TCP and 2,4,5-T production workers in Missouri and New Jersey	278	5.7[n]	—	259	5.6[n]	—

Table 7-28. Mean total cholesterol levels among Seveso and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans (continued)

Author	Population	Exposed			Unexposed		
		N	Mean[a] level	(SD)	N	Mean[a] level	(SD)
Hoffman et al., 1986	Missouri residents in Quail Run Mobile Home Park	142	4.97[g]	(0.96)	148	5.2	(1.09)
Webb et al., 1989	Missouri residents						
	<20[h]	16	5.88	(1.10)	—	—	—
	20-60[h]	12	6.60	(0.93)	—	—	—
	>60[h]	12	6.76	(0.97)	—	—	—
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	5.43[i,j]	—	1,972	5.36	—
Roegner et al., 1991	Air Force Ranch Hand personnel						
	Unknown ≤10[k]	338[l]	5.53[p]	—	777	5.51	—
	Low 15-≤33.3[k]	191	5.55[p]	—	—	—	—
	High >33.3[k]	182	5.68[g,p]	—	—	—	—
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel						
	Background[o]	362	5.71[p]	—	1,025	5.69	—
	Low [o]	251	5.68[p]	—			
	High [o]	251	5.76[p]	—			

[a]Units = mmol/L.
[b]Number of samples.
[c]% abnormal.
[d]Chloracne.
[e]No chloracne.
[f]No data for controls in 1976.
[g]$p<0.05$.
[h]Adipose tissue levels of 2,3,7,8-TCDD in pg/g of lipid.
[i]Geometric mean.
[j]% abnormal: Vietnam veterans, 5.1; non-Vietnam veterans, 4.7; OR=1.1, 95% CI=0.8-1.5.
[k]Serum 2,3,7,8-TCDD levels in pg/g of lipid.
[l]Contrasted to unexposed comparisons.
[m]Adjusted for age, body mass index, smoking history.
[n]Adjusted for age, body mass index, smoking, gender.
[o]Serum 2,3,7,8-TCDD levels in pg/g of lipid.
Background: current dioxin ≤10 pg/g of lipid.
Low: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin ≤143 pg/g of lipid.
High: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin >143 pg/g of lipid
[p]Adjusted mean.

Table 7-29. Mean triglyceride levels among Seveso and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans

Author	Population	Exposed		Unexposed	
		N	Mean (SD)	N	Mean (SD)
Mocarelli et al., 1986	Seveso children 1977 1982	 38[b] 207[b]	 0.97 (0.60-1.50) 0.91 (0.52-.60)	 36[b] 257[b]	 0.95 (0.63-1.51) 0.86 (0.47-1.56)
Assennato et al., 1989	Seveso residents 1976 1982 1984 1985	 193 152 142 141	 0.99 (0.43) 0.87 (0.40) 0.94 (0.59) 0.84 (0.44)	 — 123 196 167	 — — 0.85 (0.37) 0.88 (0.46) 0.87 (0.55)
May, 1982	TCP production workers, Great Britain	41[d]	2.03 —	31[e]	1.83 —
Martin, 1984	TCP production workers, Great Britain	39[d]	1.97[f] (0.4-4.0)	126[e]	1.41 (0.3-3.2)
Moses et al., 1984	TCP production workers, West Virginia	93[d]	1.69[g] (1.26)	93[e]	1.46 (0.73)
Suskind and Hertzberg, 1984	TCP production workers, West Virginia	200	1.65 (0.08)	163	1.76 (0.08)
Ott et al., 1994	BASF accident cohort	135	1.91[h] (1.19)	4,471	1.97[h] (1.65)
Calvert et al., 1996	TCP and 2,4,5-T production workers, Missouri and New Jersey	273	1.20[i] —	259	1.15[i] —
Hoffman et al., 1986	Missouri residents in Quail Run Mobile Home Park	141	1.07 (0.73)	146	1.19 (1.07)
Webb et al,. 1989	Missouri residents <20[h] 20-60[h] >60[h]	 16 12	 2.17 (2.08) 1.81 (1.19)	 — —	 — — — —
		12	2.69 (1.06)	—	— —

Table 7-29. Mean triglyceride levels among Seveso and Missouri residents, TCP production workers, BASF accident cohort, and Vietnam veterans (continued)

Author	Population	Exposed		Unexposed	
		N	Mean (SD)	N	Mean (SD)
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	1.06[j,k] —	1,972	1.05
Roegner et al., 1991	Air Force Ranch Hand personnel Unknown ≤10[k] Low 15-≤33.3[k] High >33.3[k]	 338[l] 191 182	 1.02[f,m,o] — 1.37[f,m,o] — 1.35[f,m,o] —	777	1.16 —
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel Background Low [l] High [l]	 362 191 182	 1.43[m,n] — 1.49[m,n] — 1.35[m,n] —	1,025	1.47

[a]Units = mmol/L.
[b]Number of samples.
[c]Adipose tissue 2,3,7,8-TCDD levels in pg/g of lipid.
[d]Chloracne.
[e]No chloracne.
[f]$p<0.01$.
[g]$p=0.056$.
[h]Adjusted for age, body mass index, smoking history.
[i]Adjusted for age, body mass index, smoking, gender.
[j]% abnormal: Vietnam veterans, 4.7; non-Vietnam veterans, 5.3; OR=0.9, 95% CI=0.7-1.2.
[k]Geometric mean.
[l]Serum 2,3,7,8-TCDD levels in pg/g of lipid.
[m]Contrasted to unexposed comparison group.
[n]Serum 2,3,7,8-TCDD levels in pg/g of lipid.
Background: current dioxin ≤ 10 pg/g of lipid.
Low: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin ≤143 pg/g of lipid.
High: current dioxin > 10 pg/g of lipid, 10 pg/g< initial dioxin >143 pg/g of lipid.
[o]Adjusted mean.

Table 7-30. Levels of thyroxine-binding globulin (TBG), thyroxine (T4), free thyroxine (FT4), or T4/TBG

Outcome	Author	Population	Exposed[a]			Unexposed[b]		
			N	Mean level	Standard deviation	N	Mean level	Standard deviation
Nursing infants								
Total T4 (nmol/L)								
	Pluim et al., 1992 Pluim et al., 1993	Neonates; Amsterdam, The Netherlands						
		At birth/cord blood	15	134.3	4.8[d]	18	122.5	4.1[d]
		1 wk postnatal	19	178.7[c]	5.5	19	154.5	6.3
		11 wks postnatal	16	122.2[c]	3.0	18	111.1	4.0
	Koopman-Esseboom, 1994	Neonates; Rotterdam, The Netherlands						
		2nd wk postnatal	39	159.9[c]	31.6	39	177.5	39.2
Free T4 (nmol/L)								
	Koopman-Esseboom, 1994	Neonates; Rotterdam, The Netherlands						
		2nd wk postnatal	39	23.0[c]	3.3	39	24.6	3.5
TBG (nmol/L)								
	Pluim et al., 1992 Pluim et al., 1993	Neonates; Amsterdam, The Netherlands						
		At birth/cord blood	15	589.5	30.5[d]	18	520.1	27.2[d]
		1 wk postnatal	19	546.2	19.1	19	532.6	16.3
		11 wks postnatal	16	500.7	13.0	18	519.0	29.4

Table 7-30. Levels of thyroxine-binding globulin (TBG), thyroxine (T4), free thyroxine (FT4), or T4/TBG (continued)

Outcome	Author	Population	Exposed[a]			Unexposed[b]		
			N	Mean level	Standard deviation	N	Mean level	Standard deviation
Nursing infants (continued)								
T4/TBG								
	Pluim et al., 1992 Pluim et al., 1993	Neonates; Amsterdam, The Netherlands						
		At birth/cord blood	15	0.232	0.008[d]	18	0.240	0.007[d]
		1 wk postnatal	19	0.332[c]	0.011	19	0.291	0.009
		11 wks postnatal	16	0.247[c]	0.009	18	0.220	0.008
BASF accident cohort								
TBG (mg/L)	Ott et al., 1994	BASF cohort	131	12.7	3.2	141	12.7	2.9
T4 (µg/dL)	Ott et al., 1994	BASF cohort	131	7.8	1.9	141	8.3	1.5
T4/TBG (mU/L)	Ott et al., 1994	BASF cohort	131	6.3	1.3	141	6.7	1.6

[a]High-exposure group: 29.2-62.7 ng toxic equivalents/kg (dioxin-furan TEQ per kg milk fat) (Pluim et al, 1992 and 1993); >30.75-76.43 pg dioxin-furan-TEQ/g fat (Koopman-Esseboom et al., 1994).
[b]Low-exposure group: 8.7-28 ng TEQ/kg (Pluim et al, 1992 and 1993); 12.44-30.75 pg dioxin-furan TEQ/g fat (Koopman-Esseboom et al., 1994).
[c]$p<0.05$ compared to the unexposed group.
[d]Standard error of the mean.

Table 7-31. Levels of triiodothyronine percent (T3%) uptake or free thyroxine index in Vietnam veterans

Author	Population	Exposed		Adjusted RR (95% CI)	Unexposed	
		N	Mean level		N	Mean level
T3% uptake						
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel				772	30.7
	Unknown ≤10[a]	338	30.7	1.1 (0.6, 2.1)		
	Low 15-≤33.3[a]	194	30.4	0.9 (0.4, 2.2)		
	High >33.3[a]	181[b]	30.0	0.5 (0.1, 1.5)		
	All Ranch Hand vs. all comparisons	937	30.6	1.14 (0.7-1.8)	1,198	30.6
Free thyroxine index						
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	2.2[c]	Adjusted OR (95% CI) 1.2 (0.9,1.5)	1,972	2.2[c]

[a]Serum 2,3,7,8-TCDD in pg/g of lipid.
[b]$p<0.05$ comparison of veterans at background level with ≥33.3 pg/g TCDD.
[c]Geometric mean.

Table 7-32. Levels of thyroid-stimulating hormone (TSH) in Vietnam veterans

Author	Population	Exposed		Adjusted RR (95% CI)	Unexposed	
		N	Mean level[a]		N	Mean level[a]
Vietnam veterans						
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	1.6[b]	Adjusted OR (95% CI) 2.0 (0.9-4.3)	1,972	1.6[b]
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel, 1988					
	Unknown ≤10[c]	338	0.948	1.45 (0.62-3.40)	616	0.920
	Low 15-≤33.3[c]	194	0.978	0.88 (0.24-3.02)		
	High >33.3[c]	181	1.026[d]	2.15 (0.80-5.79)		
Grubb et al., 1995	U.S. Air Force Ranch Hand personnel, 1992					
	Comparison ≤10[e]				1,027	1.58
	Background RH ≤10[e]	365	1.64	0.88 (0.40-1.92)		
	Low 10-≤143[e]	254	1.60	0.50 (0.15-1.67)		
	High >143[e]	255	1.64	1.72 (0.78-3.80)		
	Low + High	509	1.62	1.06 (0.53,2.15)		

[a]Units: μU/mL.
[b]Geometric mean.
[c]Serum 2,3,7,8-TCDD level in pg/g (ppt) of lipid.
[d]$p < 0.05$ compared to the unexposed group.
[e]Comparisons: current dioxin ≤10 ppt.
Background (Ranch Hand): current dioxin ≤10 ppt.
Low (RH): current > 10 ppt, 10 ppt < initial dioxin ≤143 ppt.
High (RH): current > 10 ppt, initial dioxin > 143.

Table 7-33. Levels of thyroid-stimulating hormone (TSH) in nursing infants and BASF accident cohort

Author	Population	Exposed			Unexposed		
		N	Mean level[a]	SD	N	Mean level[a]	SD
Nursing infants							
Pluim et al., 1992 Pluim et al., 1993	Neonates; Amsterdam, The Netherlands						
	At birth/cord blood	11[b]	11.9	1.9[c]	14[d]	10.4	1.3[c]
	1 wk postnatal	11	2.56	0.41	15	2.93	0.41
	11 wks postnatal	12	2.50[e]	0.26	18	1.81	0.19
Koopman-Esseboom, 1994	Neonates; Rotterdam, The Netherlands						
	At birth/cord blood	[f]	11.6[e]	8.0		8.5	6.0
	2nd wk postnatal	39[b]	2.6[e]	1.5	39[d]	1.9	0.8
	3 months	39	2.3[e]	1.0	39	1.6	0.6
BASF accident cohort							
Ott et al., 1993b,1994	BASF chemical workers	130	1.19	0.9	—[g]	—	—

[a]Units: µU/mL.
[b]High-exposure group: 29.2-62.7 ng toxic equivalents/kg (TEQ per kg milk fat) (Pluim et al., 1992 and 1993); >30.75-76.43 pg dioxin-furan-TEQ/g fat (Koopman-Esseboom et al., 1994).
[c]Standard error of the mean.
[d]Low-exposure group: 8.7-28 ng TEQ/kg (Pluim et al., 1992 and 1993); 12.44-30.75 pg TEQ/g fat (Koopman-Esseboom et al., 1994).
[e]$p<0.05$ compared to low-exposure group.
[f]Total for both high and low = 75.
[g]No referent values.

Table 7-34. CD4/CD8 ratios in Missouri residents, Vietnam veterans, and BASF accident cohort

Author	Population	Exposed			Unexposed		
		N	Mean level (SD)	Ratio	N	Mean level (SD)	Ratio
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel						
	Unknown ≤10[a]	126	1.72	—	301	1.89	—
	Low 15-≤33.3[a]	72	1.91				
	High >33.3[a]	72	1.99				
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	1.8[b]	OR < reference range 0.9 OR > reference range 1.1	1,972	1.8[b]	—
Hoffman et al., 1986	Missouri residents	135	1.9 (0.8)	% abnormal 8.2	142	1.9 (0.6)	% abnormal 6.3
Webb et al., 1989	Missouri residents						
	<20[c]	16	2.0 (0.7)	—	—	—	—
	20-60[c]	12	2.1 (1.0)				
	>60[c]	12	1.4 (0.7)				
Ott et al., 1994	BASF accident cohort	132	1.6 (0.94)	—	42[d]	1.5 (0.6)	—
Zober et al., 1992	BASF personnel exposed to TBDD and TBDF[e]	21	1.6 (0.5)	—	42	1.5 (0.6)	—
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel						
	Background[f]	139	1.50	—	399	1.48	—
	Low	94	1.58				
	High	106	1.57				

[a]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[b]Geometric mean.
[c]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[d]From Zober et al., 1992.
[e]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxins and TBDF = 2,3,7,8-tetrabrominated dibenzofurans.
[f]Comparison: current dioxin ≤10 pg/g of lipid.
Background: current dioxin > 10 pg/g.
Low: current dioxin > 10 pg/g, 10 pg/g < initial dioxin ≤ 143 pg/g.
High: current dioxin > 10 pg/g, 10 pg/g < initial dioxin > 143 pg/g.

Table 7-35. Total lymphocytes in 2,4,5-T production workers, Missouri residents, Vietnam veterans, and BASF accident cohort

Author	Population	Exposed			Unexposed		
		N	Mean level[a] (SD)[b]	Ratio	N	Mean level (SD)	Ratio
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel						
	Unknown ≤10[c]	127	1,954 —[d]	—	301	1,972 —	
	Low 15-≤33.3[c]	73	2,011 —				
	High >33.3[c]	74	2,032 —				
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	1,973 —	OR<reference range 1.0 OR>reference range 1.2	1,972	1,936 —	
Hoffman et al., 1986	Missouri residents	135	2,465 (724)	—	142	2,311(634)	
Webb et al., 1989	Missouri residents			% Lymphocytes			
	<20[e]	16	2,200 (830)	32			
	20-60[e]	12	2,300 (600)	32	—	—	
	>60[e]	12	2,200 (720)	28			
Jennings et al., 1988	2,4,5-T production workers exposed 17 yrs prior to the study	18	1,980 (840)	—	15	2,020 (470)	
Ott et al., 1994	BASF accident cohort	133	1,978.3 (805)	% Lymphocytes 33.4 (9.4)	42	2,267.6 (837.5)	% Lymphocytes 36 (12.4)
Zober et al., 1992	BASF personnel exposed to TBDD[g] &TBDF[g]	21	2,179.5 (678)	% Lymphocytes 33.4 (8.4)	42	2,267.6 (837.5)	% Lymphocytes 36 (12.4)
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel						
	Background[h]	141	2,066.7[i]	—	400	2,022.4	—
	Low[h]	95	1,988.6				
	High[h]	108	2,034.4				

[a]Units: counts/mm^3.
[b]SD = standard deviation.
[c]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[d]— = data not presented.
[e]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[f]From Zober et al., 1992.
[g]TBDD = 2,3,7,8-Tetrabrominated dibenzo-*p*-dioxins; TBDF = 2,3,7,8-Tetrabrominated dibenzofurans.
[h] Comparison: current dioxin ≤10 pg/g of lipid.
Background: current dioxin > 10 pg/g.
Low: current dioxin > 10 pg/g, 10 pg/g<initial dioxin ≤143 pg/g.
High: current dioxin > 10 pg/g, 10 pg/g<initial dioxin > 143 pg/g.

[i]Adjusted mean.

Table 7-36. B1 levels in production workers, 2,4,5-T Missouri residents, Vietnam veterans, BASF accident cohort, and extruder personnel

Author	Population	Exposed			Unexposed		
		N	Mean level[a] (SD)	Ratio	N	Mean level[a] (SD)	Ratio
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel Unknown ≤10[b] Low 15-≤33.3[b] High >33.3[b]	 127 71 73	 176 — 183 — 191 —	—	301	172 —	—
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel Backgound[e] Low [e] High [e]	 140 95 106	 245[f] — 224 — 220 —	— — —	400	214 —	—
CDC Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	240[c]	OR<ref. range 1.1 OR>ref. range 1.2	1,972	230[c] —	—
Webb et al., 1989	Missouri residents <20[d] 20-60[d] >60[d]	 16 12 12	 190 (865) 189 (983) 171 (573)	% B1 cells 9.1 8.3 7.8	—	—	—
Jennings et al., 1988	2,4,5-T production workers exposed 17 yrs prior to the study	18	210 (110)	—	15	160 (80)	—
Ott et al., 1994	BASF accident cohort	133	10.4[e] (6.0)	—	42	12.3[e,f] (5.1)	—
Zober et al., 1992	BASF personnel exposed to TBDD[g] and TBDF[g]	21	276.3 (156)	% B cells 12.5 (4.4)	42	286.4 (199.3)	12.3 (5.1)

[a]Units: cells/mm^3.
[b]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[c]Geometric mean.
[d]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[e]% B1 cells.
[f]From Zober et al., 1992.
[g]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxin.
TBDF = 2,3,7,8-tetrabrominated dibenzofuran.

Table 7-37. CD4 levels in production workers, Missouri residents, Vietnam veterans, and BASF chemical workers

Author	Population	Exposed			Unexposed		
		N	Mean level[a] (SD)	Ratio	N	Mean level (SD)	Ratio
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel						
	Unknown ≤10[b]	127	867 —		301	907 —	—
	Low 15-≤33.3[b]	72	945 —				
	High >33.3[b]	72	929 —				
Grubbs et al., 1995	U.S.A.F. Ranch Hand personnel			—	403	923 —	—
	Background[g]	141	961[h] —				
	Low	95	917 —				
	High	108	962 —				
CDC Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	1,020[c] —	OR<ref. range 1.0 OR>ref. range 1.4	1,972	990[c] —	—
Hoffman et al., 1986	Missouri residents	135	1,021 (353)	% Abnormal 0.7	142	1,033 (346)	% Abnormal 0.0
Webb et al., 1989	Missouri residents			% T4 cells			
	<20[d]	16	1,084 (485)	48	—	—	—
	20-60[d]	12	1,198 (391)	51			
	>60[d]	12	963 (403)	42			
Jennings et al., 1988	2,4,5-T production workers exposed 17 yrs prior to the study	18	950 (340)	—	15	1,040 (290)	—
Tonn et al., 1996	2,4,5-TCP production & maintenance workers	11	—	% of total 47.6 (8.1)	10	—	% of total 48.5 (10.6)

Table 7-37. CD4 levels in production workers, Missouri residents, Vietnam veterans, and BASF chemical workers (continued)

Author	Population	Exposed			Unexposed		
		N	Mean level[a] (SD)	Ratio	N	Mean level (SD)	Ratio
Ott et al., 1994	BASF chemical workers	133	—	% T4 cells 42.5 (10.4)	42[e]	—	% T4 cells 45.1 (8.9)
Zober et al., 1992	BASF personnel exposed to TBDD[f] and TBDF[f]	21	973.3 (381.9)	% CD4 44.8 (6.1)	42	1,032 (444.6)	% CD4 45.1 (8.9)

[a]Units: counts/mm^3.
[b]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[c]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[d]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[e]From Zober et al., 1992.
[f]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxins;
TBDF = 2,3,7,8-tetrabrominated dibenzofurans.

Table 7-38. CD8 levels in 2,4,5-T production workers, Missouri residents, Vietnam veterans, and BASF accident cohort

Author	Population	Exposed			Unexposed		
		N	Mean level[a] (SD)	Ratio	N	Mean level[a] (SD)	Ratio
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel Unknown ≤10[b] Low 15-≤33.3[b] High >33.3[b]	 126 71 73	 485 — 465 — 475 —		301	473 —	—
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel Background[h] Low High	 140 95 106	 645 — 606 — 618 —	—	400	634 —	—
CDC Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	560[c] —	OR<ref. range 1.0 OR>ref. range 0.9	1,972	550 —	—
Hoffman et al., 1986	Missouri residents	135	592 (223)	% Abnormal 1.5	142	578 (198)	% Abnormal 0.0
Webb et al., 1989	Missouri residents <20[d] 20-60[d] >60[d]	 16 12 12	 562 (215)[e] 645 (225) 807 (381)	% T8 cells 26 28 35			
Jennings et al., 1988	2,4,5-T production workers exposed 17 yrs prior to the study	18	630 (280)	—	15	590 (230)	—
Ott et al., 1994	BASF accident cohort	132	—	% T8 cells 31.9 (10.4)	42[f]	—	% T8 cells 32.0 (7.1)
Zober et al., 1992	BASF personnel exposed to TBDD[g] and TBDF[g]	21	665 (282.6)	% CD8 30.8 (7.9)	42	717.2 (282.4)	% CD8 32.0 (7.1)

[a]Units: counts/mm^3.
[b]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[c]Geometric mean.
[d]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[e]$p < 0.05$.
[f]From Zober et al., 1992.
[g]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxins; TBDF = 2,3,7,8-tetrabrominated dibenzofurans.

Table 7-39. IgG levels in Missouri residents, Vietnam veterans, and BASF accident cohort

Author	Population	Exposed			Unexposed	
		N	Mean level[a] (SD)	Ratio	N	Mean level[a] (SD)
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel Unknown ≤10[b] Low 15-≤33.3[b] High >33.3[b]	 335 190 175	 1,087 — 1,122 — 1,122 —	—	757	1,120 —
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel Background[h] Low[h] High[h]	 364 243 251	 1,126[i] — 1,111 — 1,115 —	—	1,035	1,1139 —
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	1,078[c]	OR < reference range 1.0 OR > reference range 1.0	1,972	1,077[c]
Webb et al., 1989	Missouri residents <20[d] 20-60[d] >60[d]	 16 12 12	 1,064[e] (273) 1,146 (193) 1,151 (223)	—	—	—
Ott et al., 1994	BASF accident cohort	132	1,199[f] (226)	—	194	1,182.6 (310.0)
Zober et al., 1992	BASF personnel exposed to TBDD[g] and TBDF[g]	21	1,057.7 (199.0)	—	42	1,102.9 (207.1)

[a]Units: mg/dL.
[b]Serum 2,3,7,8-TCDD in pg/g of lipid.
[c]Geometric mean.
[d]Adipose 2,3,7,8-TCDD in pg/g of lipid.
[e]$p < 0.05$ trend.
[f]Significant positive relationship between IgG and current 2,3,7,8-TCDD level and back-extrapolated 2,3,7,8-TCDD ($p < 0.01$).
[g]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxins; TBDF = 2,3,7,8-tetrabrominated dibenzofurans.
[h] Comparison: current dioxin ≤10 pg/g lipid.
Background: current dioxin > 10 pg/g.
Low: current dioxin > 10 pg/g, 10 pg/g<initial dioxin ≤143 pg/g.
High: current dioxin > 10 pg/g, 10 pg/g<initial dioxin > 143 pg/g.
[i] Adjusted mean.

Table 7-40. IgM levels in Missouri residents, Vietnam veterans, BASF accident cohort, and extruder personnel

Author	Population	Exposed			Unexposed	
		N	Mean level[a] (SD)	Ratio	N	Mean level[a] (SD)
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel Unknown ≤10[b] Low 15-≤33.3[b] High >33.3[b]	 335 190 175	 107 — 96 — 106 —	—	757	103
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel Background[g] Low[g] High[g]	 365 253 251	Data not presented		1,035	Data not presented
Centers for Disease Control Vietnam Experience Study, 1988a	U.S. Army Vietnam veterans	2,490	121[c] —	OR< reference range 1.0 OR> reference range 1.0	1,972	121[c]
Webb et al., 1989	Missouri residents <20[d] 20-60[d] >60[d]	 16 12 12	 128(89) 157(57) 114(44)	—	—	—
Ott et al., 1994	BASF accident cohort	132	139.6 (65.1)	—	192	134.7 (70)
Zober et al., 1992	Personnel exposed to TBDD[e] and TBDF[e]	21	142[f](52.6)	—	42	114.7[f] (46.5)

[a]Units: mg/dL.
[b]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[c]Geometric mean.
[d]Adipose 2,3,7,8-TCDD level in pg/g of lipid.
[e]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxins; TBDF = 2,3,7,8-tetrabrominated dibenzofurans.
[f]p=0.04.
[g]Comparison: current dioxin ≤10 pg/g of lipid.
Background: current dioxin > 10 pg/g.
Low: current dioxin > 10 pg/g, 10 pg/g<initial dioxin ≤143 pg/g.
High: current dioxin > 10 pg/g, 10 pg/g<initial dioxin > 143 pg/g.

Table 7-41. Levels of natural killer cells in Missouri residents, Vietnam veterans, and extruder personnel

Author	Population	Exposed		Unexposed	
		N	Mean level (SD)	N	Mean level (SD)
Roegner et al., 1991	U.S. Air Force Ranch Hand personnel Unknown ≤10[a] Low 15-≤33.3[a] High >33.3[a]	 126 70 72	 455[b,c] 378 386	291	414[b]
Grubbs et al., 1995	U.S. Air Force Ranch Hand personnel Background[g] Low[g] High[g]	 139[h] 94 106	CD16+CD56 242 — 219 — 237 —	399	248
Tonn et al., 1996	2,4,5-TCP production and maintenance workers	11	%CD56 5.4 (1.9)	10	%CD56 5.6 (1.6)
Jennings et al., 1988	2,4,5-T production workers exposed 17 yrs prior to the study	18	400[e] (210)[d]	15	590[e](230)
Zober et al., 1992	BASF personnel exposed to TBDD[f] and TBDF[f]	21	280.5 (175.2)	42	250.8(149.9)

[a]Serum 2,3,7,8-TCDD level in pg/g of lipid.
[b]Units: cpm.
[c]Net response.
[d]$p<0.05$.
[e]Units: $10^3/mm^3$.
[f]TBDD = 2,3,7,8-tetrabrominated dibenzo-*p*-dioxins;
TBDF = 2,3,7,8-tetrabrominated dibenzofurans.
[g]Comparison: current dioxin ≤10 pg/g of lipid.
Background: current dioxin > 10 pg/g.
Low: current dioxin > 10 pg/g, 10 pg/g<initial dioxin ≤143 pg/g.
High: current dioxin > 10 pg/g, 10 pg/g<initial dioxin > 143 pg/g.
[h]Adjusted mean.

Table 7-42. Developmental immunologic outcomes in a study of Dutch Children

Outcome	Exposure(s)	Correlation coefficient	*p*-value
Weisglas-Kuperus et al., 1995			
Monocytes At 3 months:	Total TEQ Dioxin-furan TEQ Mono-ortho PCB TEQ Di-ortho PCB TEQ	-0.64 -0.55 -0.67 -0.51	≤ 0.01 ≤ 0.01 ≤ 0.01 ≤ 0.05
Granulocytes At 3 months:	Total TEQ	-0.47	≤ 0.05
TCR$\gamma\delta^+$ T-cells At birth:	Total TEQ Dioxin-furan TEQ	0.50 0.57	≤ 0.05 ≤ 0.01
TCR$\alpha\delta^+$ T-cells at 18 months:	Total TEQ Dioxin-furan TEQ Di-ortho PCB TEQ	0.57 0.71 0.61	≤ 0.05 ≤ 0.01 ≤ 0.05
$CD3^+$ $CD8^+$ cells at 18 months:	Total TEQ Dioxin-furan TEQ Planar PCB TEQ Di-ortho PCB TEQ	0.65 0.80 0.71 0.68	≤ 0.05 ≤ 0.01 ≤ 0.01 ≤ 0.05
Weisglas-Kuperus et al., 2000			
Lymphocytes at 42 months	Total Maternal PCB Total Cord PCB	0.25 0.22	0.02 0.05
CD3+ at 42 months	Total Maternal PCB Total Cord PCB	0.25 0.21	0.02 0.07
CD3+CD8+ at 42 months	Total Maternal PCB Total Cord PCB	0.27 0.24	0.01 0.04
CD4+CD45RO+ at 42 months	Total Maternal PCB Total Cord PCB	0.25 0.26	0.02 0.02
TCR$\alpha\beta^+$ T-cells at 42 months	Total Maternal PCB Total Cord PCB	0.25 0.20	0.02 0.08
CD3+HLA-DR+ at 42 months	Total Maternal PCB Total Cord PCB	0.26 0.31	0.02 0.005

Table 7-43. Case reports of psychological and neurologic effects among individuals exposed to 2,3,7,8-TCDD-contaminated materials

Author	Exposure	Population	Evaluation	Findings
Ashe and Suskind, 1950 West Virginia	Precursor and reaction products of TCP process TCP,[a] NaOH,[b] 2,4,5-T[c]	4 employees involved in cleanup after 1949 explosion or worked with equipment used prior to explosion; studied 6 mos and 1 yr after explosion	Clinical history and examination	Headaches Insomnia Social withdrawal Nervousness Fatigue Crying spells Numbness in feet Decreased libido, muscle strength, sensory ability, myelin sheath and fiber destruction of sural nerve
Suskind et al., 1953 West Virginia	TCP 2,4,5-T	36 workers with chloracne after TCP reactor explosion 25 persons exposed during production of TCP and 2,4,5-T 1948-1953	Clinical history and examination	Fatigue Nervousness Irritability Reduced libido Back and limb pain Vertigo Paresthesia
Baader and Bauer, 1951 Nordheim-Westfalen, West Germany	PCP[d] TCP	10 men in PCP production experimental TCP production	Record review case history	Self-reported: pain and weakness Paresthesia and pain in gluteal and femoral region

Table 7-43. Case reports of psychological and neurologic effects among individuals exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Population	Evaluation	Findings
Bauer et al., 1961 Hamburg, West Germany	TCP 2,4,5-T	31 men in TCP and 2,4,5-T production with residual chloracne, continual "neuromuscular weakness," vasovagal disturbances, psychopathological disturbances" 5 yrs after first exam	Clinical history and examination Hamburg-Wechsler Test Rorschach Psychogram	Reduced libido Headaches, dizziness Decreased libido Irritability Depression Sleep disturbances Anorexia Paresthesia Tremor Muscle weakness Hamburg-Wechsler indicative of acquired decrease in mental efficiency Rorschach Psychogram indicative of decreased emotional reactivity, slowed thinking process for concentration
Goldman, 1972 Ludwigshafen, West Germany	TCP 2,4,5-T	42 BASF workers with chloracne after TCP reactor explosion in 1953	Clinical history and examination	Neurasthenia

Table 7-43. Case reports of psychological and neurologic effects among individuals exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Population	Evaluation	Findings
Jirasek et al., 1974 Spolano, Czechoslovakia	TCP 2,4,5-T PCP, HCB[e]	55 workers in TCP and 2,4,5-T production Followed: 1969-1973	Clinical examination history and examination	35 patients with "neurasthenic or depressive syndrome"
Oliver, 1975 England	Pure 2,3,7,8-TCDD	3 scientists synthesis of 2,3,7,8-TCDD	Not described	Subject A: Fatigue and headache Subject B: Headaches Loss of vigor and fatigue Irritability and anger Poor concentration Subject C: Loss of concentration (apathy and fatigue) "Loss of energy and drive" Some difficulty sleeping

Table 7-43. Case reports of psychological and neurologic effects among individuals exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Population	Evaluation	Findings
Pazderova-Vejlupkova et al., 1981 Spolano, Czechoslovakia	TCP 2,4,5-T PCP, HCB	4-year followup of 44 production workers	Clinical psychiatric examination	Psychiatric changes at start of "intoxication" 83% with neurotic symptoms; neurasthenia syndromes with depressive component; depressive syndrome with endogenous component (N=55) 16% with pseudoneurasthenia syndrome and CNS arteriosclerosis 3% with no psychiatric signs or symptoms Psychiatric changes in exposed individuals at followup (1973-1979) 58% with neurotic symptoms and no depressive or anxiety symptoms 18% with severe pseudoneurasthenia and signs of dementia (usually in patients over 50 years old but dementia occurred in 30-year-old patient)

Table 7-43. Case reports of psychological and neurologic effects among individuals exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Population	Evaluation	Findings
Pazderova-Vejlupkova et al., 1981 (cont.)				24% with no psychiatric signs or symptoms.
Kimmig and Schultz, 1957b Hamburg, Germany	TCP 2,4,5-T	31 production workers with chloracne (1953-1954)	Clinical history and examination	Tiredness (N=3) Headaches (N=5)
Poland et al., 1971 New Jersey	TCP 2,4,5-T 2,4-D[f] HCB TCP reactor explosion in 1960 Daily exposure 1951-1969	73 male workers in production, maintenance, office areas	Noted histories of smoking, alcohol, medications MMPI[g] given to 52 production and 17 unexposed administrative staff	Headaches (N=8) Severity of acne significantly correlated with high score on the mania scale of MMPI.

[a]TCP = 2,4,5-trichlorophenol.
[b]NaOH = sodium hydroxide.
[c]2,4,5-T = 2,4,5-trichlorophenoxyacetic acid.
[d]PCP = pentachlorophenol.
[e]HCB = hexachlorobenzene.
[f]2,4-D = 2,4-dichlorophenoxyacetic acid.
[g]Minnesota Multiphasic Personality Inventory.

Table 7-44. Cross-sectional studies of psychological and neurologic effects among residents of Missouri and Seveso exposed to 2,3,7,8-TCDD-contaminated materials

Author	Exposure	Study population	Comparison population	Evaluation	Findings
Webb et al., 1989 Missouri	2,3,7,8-TCDD-contaminated waste oil 1971	68 volunteers in State Dioxin Registry; estimated exposure to 20-100 ppb TCDD for 2 yrs or 100 ppb for 6 months	36 volunteers in State Dioxin Registry with no history of exposure to 2,3,7,8-TCDD	Missouri Dioxin Health Studies. Progress Report (1983)	No differences in neurologic exam or in feeling of pins-needles; loss of sensation in extremities, tingling in fingers and toes, diminished VIB 256, diminished VIB 64, diminished pin sensation, diminished thermal sensation (PRR=2%)[a]
Pocchiari et al., 1979 Seveso, Italy	TCP TCP reactor accident	446 residents of Seveso and Meda, Italy	255 residents of nearby towns without contamination	Not detailed but included clinical exam and NCV[b]	1977: neurologic damage in 6.7% of Seveso residents and in 1.2% unexposed residents 1978: neurologic damage in 11.7% of Seveso residents
	July 1976	200 workers from Icmesa plant	None	Exam, EMG[c], NCV	Workers: 4% neuropathic clinical signs exam, EMG, NCV

Table 7-44. Cross-sectional studies of psychological and neurologic effects among residents of Missouri and Seveso exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Study population	Comparison population	Evaluation	Findings
Filippini et al., 1981 Seveso, Italy	See description above	308 residents of Seveso, Italy	305 residents of nearby towns without contamination	Symptoms: pain, tingling, numbness Sensory review Muscle tone and strength NCV of ulnar and peroneal nerves	Elevated PRR for peripheral neuropathy in Seveso residents with indicators of exposure (high GGT, ALT, AST, or chloracne) (PRR=2.8, 95% CI=1.2-6.5) Seveso residents with predisposing factors (alcohol or inflammatory disease) (PRR=2.6, 95% CI=1.2-5.6)

[a]Prevalence risk ratio.
[b]Nerve conduction velocity.
[c]Electromyography.

Table 7-45. Cross-sectional studies of psychological and neurologic effects among TCP production workers and Vietnam veterans exposed to 2,3,7,8-TCDD-contaminated materials

Author	Exposure	Study population	Comparison population	Evaluation	Findings
Moses et al., 1984 West Virginia	TCP[a] 2,4,5-T[b] 1949 TCP reactor explosion	226 workers invited based on union record of employment in production of TCP or 2,4,5-T Definition of exposure = "current or history of chloracne"	Workers without chloracne (N=109) Conduction velocities	Review of symptoms (ROS) obtained by examining physician	Significant diff. with and without chloracne for: insomnia; decreased libido, erection, or ejaculation; no change for fatigue, irritability, nervousness, depression, or personality changes. Decreased pinprick sensation in 18.3% with chloracne; no decreased pinprick sensation without chloracne
Suskind and Hertzberg, 1984 West Virginia	TCP 2,4,5-T	204 workers or maintenance workers in TCP or 2,4,5-T dept.	163 workers never in TCP or 2,4,5-T Mean age of exposed population was younger (56.7 vs. 46.2) ($p<0.0001$).	Interviews and clinical examination	Decreased libido was more frequent among exposed by Mantel-Haenszel Chi by age. Nervousness/depression/ anxiety not increased in exposed (sample size sufficient to detect a twofold increase)

Table 7-45. Cross-sectional studies of psychological and neurologic effects among TCP production workers and Vietnam veterans exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Study population	Comparison population	Evaluation	Findings
Sweeney et al., 1993 Alderfer et al., 1992 Missouri and New Jersey	TCP 2,4,5-T	280 production workers with daily exposure New Jersey 1951-1969 Missouri 1968-1972	261 unexposed community residents matched for age, race, gender	Symptom and medical history; neurologic examination; neurophysiologic tests of vibration and thermal sensitivity; Beck Depression Scale; SCL-90-R	No significant difference for symptoms or any examination variable No significant difference in mood disorders
Lathrop et al., 1984	Vietnam service 1962-1971	1,208 Ranch Hands assigned to aerial spraying herbicides and insecticides Republic of Vietnam	1,238 men who flew cargo missions in Southeast Asia Matched by month of birth, race, and occupational code	Self-report of psychological or emotional illness Diagnostic Interview Schedule (modified) Self-reported depression	No difference Significantly more fatigue, anger, erosion, anxiety, closest for high school-educated Ranch Hands; no difference for college-educated Greater for Ranch Hands

Table 7-45. Cross-sectional studies of psychological and neurologic effects among TCP production workers and Vietnam veterans exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Study population	Comparison population	Evaluation	Findings
Lathrop et al., 1984 (cont.)				Cornell Index (self-administered inventory of neuropsychiatric symptoms) (psychophysiologic)	After adjustment for education 4/10 parameters abnormal (nervousness, anxiety, startle, psychosomatic, gastrointestinal system); abnormal parameters inversely related to education level.
				MMPI	High school-educated Ranch Hands showed significant deficits on scales for hypochondria, masculinity/femininity; mania/hypomania but comparisons show more denial; MMPI scores influenced by education ($p<0.01$)
				Halstead-Reitan Battery	No impairment in Ranch Hands
				Wechsler Adult Intelligence Scale (WAIS)	Scores related to educational level

Table 7-45. Cross-sectional studies of psychological and neurologic effects among TCP production workers and Vietnam veterans exposed to 2,3,7,8-TCDD-contaminated materials (continued)

Author	Exposure	Study population	Comparison population	Evaluation	Findings
Roegner et al., 1991	Vietnam service	720 USAF Ranch Hands; serum 2,3,7,8-TCDD levels were measured (lipid adjusted)	779 who flew cargo missions in Southeast Asia; serum 2,3,7,8-TCDD levels were measured	Self-report	No significant mental, emotional, or sleep disorders
				SCL-90-R[c]	No significant differences with increasing serum levels
				Cornell Medical Index (CMI)	Significantly higher mean schizoid and schizotypal scores in Ranch Hands over 33.3 pg/g 2,3,7,8-TCDD, but they did not relate to similar scales in the SCL-90-R
				Neurologic exam	Overall, no consistent relationship between neurologic abnormalities and TCDD level.

[a]TCP = 2,4,5-trichlorophenol.
[b]2,4,5-T = 2,4,5-trichlorophenoxyacetic acid.
[c]SCL-90-R: Symptom Checklist Revised.

Table 7-46. Studies of neurologic and behavioral effects among Dutch infants

Author	Exposure	Study groups	Evaluation	Findings N	Mean(SD)	Formula-fed N	Mean (SD)
Koopman-Essebaum et al., 1996	Total PCB-dioxin-furan TEQ from breast milk	Exposed: 105 breast-fed infants and their mothers	From Bayley Scales of Infant Development: Psychomotor Dev. Index (PDI) of infant at				
		Not exposed: 102 bottle-fed infants and their mothers	3 months,	99	118 (12)	100	117 (12)
			7 months, and	105	115 (15)[a]	102	111 (13)
			18 months of age	105	110 (17)	101	108 (14)
		All in the Rotterdam area	Mental Development Index (MDI) of infant at				
			3 months,	101	128 (31)	100	126 (13)
			7 months, and	105	115 (11)[a]	102	112 (9)
			18 months of age	105	113 (18)[d]	102	107 (17)
	CATEGORIES for total TEQ[b]: "Low" 3 mos.= 168-617 7+18 mos. = 168-769 "Med." 3 mos. = 618-810 7+18 mos. = 770-1,289 "High" 3 mos = 811-1,860 7+18 mos = 1,290-4,340	N=182		Regression analysis Coefficient	Std. error		
			PDI at 7 months[c]				
			Medium exposure	-9.5[d]	3.9		
			High exposure	-7.7	4.9		
			Breast feeding -duration	6.9[d]	2.3		
	$\sum PCB_{maternal\ blood}$ -- ng/g[e]	N=198	PDI at 3 months				
			Ln($\sum PCB_{plasma}$)	-4.8[a]	2.0		
			Breast feeding -duration	0.91	0.91		
		N=206	MDI at 7 months				
			Ln($\sum PCB_{plasma}$)	2.0	1.7		
			Breast feeding -duration	2.0[a]	0.9		

Table 7-46. Studies of neurologic and behavioral effects among Dutch infants (continued)

Author	Exposure	Study groups	Evaluation	Findings			
				N	Mean(SD)	Formula-fed N	Mean (SD)
Koopman-Essebaum et al., 1995b	Total PCB-dioxin-furan TEQ from breast milk	Exposed: 105 breast-fed infants and their mothers Not exposed: 102 bottle-fed infants and their mothers All in Rotterdam	From Fagan Test of Infant Intelligence: Visual Recognition Memory Test 3 months of age 7 months of age	105 105	61.5 (9.0) 59.9 (5.9)[c]	101 102	62.2 (10.7) 57.3 (5.9)
	CATEGORIES for total TEQ[b]: Low: 3 mos.= 168-617 7 mos. = 168-769 Med.: 3 mos. = 618-810 7 mos. = 770-1,289 High: 3 mos. = 811-1860 7 mos. = 1,290-4,340 $\sum PCB_{plasma}$ -- ng/g[e]	N=182 N = 181	Visual Recognition Memory Test at 7 months[c] Medium exposure High exposure Breast feeding -duration or Ln($\sum PCB_{plasma}$) Breast feeding -duration	Regression analysis Coefficient		Std. error	
					4.4[d] 4.6[a] -0.46 -0.50 1.63[d]		1.7 2.2 1.0 1.07 0.56
Koopman-Essebaum et al., 1995a submitted for publication	PCB-dioxin-furan TEQ from breast milk and thyroid status	Exposed: Breast-fed infants 104 in Groningen 105 in Rotterdam Comparison: Bottle-fed infants 107 in Groningen 102 in Rotterdam	Prechtl neurologic exam (2 wk):23 neuro. abnorm. 394 neurologically normal $\sum PCB_{cord\ blood}$[e] $\sum PCB_{maternal\ blood}$ Dioxin-furan TEQ Planar PCB TEQ Mono-ortho PCB TEQ Di-ortho PCB TEQ Total PCB-dioxin-furan TEQ	Neuro. Normal N	Mean (SD)	Neuro. Abnormal N	Mean (SD)
				352	0.5 (0.3)	20	0.4 (0.1)
				393	2.2 (0.9)	21	2.0 (0.6)
				189	30.0 (10.2)	12	25.4 (7.9)
				194	16.3 (7.4)[a]	12	11.7 (3.8)
				189	14.8 (5.3)	12	12.6 (4.6)
				189	4.4 (2.2)	12	3.7 (1.5)
				182	65.3 (21.6)[a]	12	52.5 (15.6)

Table 7-46. Studies of neurologic and behavioral effects among Dutch infants (continued)

Author	Exposure	Study groups	Evaluation	Findings	
				Odds ratio	95% confidence interval
Huisman et al., 1995a	Dioxins, dibenzo-furans, and PCBs in breast milk (No effects observed in maternal or cord blood)	Exposed: Breast-fed infants 104 in Groningen 105 in Rotterdam Comparison: Bottle-fed infants 107 in Groningen 102 in Rotterdam	Prechtl's exam at 10-21 days: Neurologic Optimality Score (NOS) ORs from logistic regression Total PCB-dioxin-furan TEQ[a] Dioxin-furan TEQ D54 (TEF=0.5) D66 (TEF=0.1) D67 (TEF=0.1) D70 (TEF=0.1) D73 (TEF=0.01) F83 (TEF=0.1) F114 (TEF=0.5) Planar PCB TEQ PCB169 (TEF=0.01) Non-planar PCB PCB70 PCB 99 PCB118 (TEF=0.0001) PCB138 PCB153 PCB156 (TEF=0.0005) PCB170 (TEF=0.0001) PCB177 PCB183 PCB187 $\sum PCB_{milk}$ Mono-ortho PCB TEQ Di-ortho PCB TEQ	3.21 3.12 2.23 1.64 3.03 1.23 1.61 1.31 2.48 1.67 2.33 1.88 2.01 2.21 2.73 2.76 2.55 2.33 1.96 2.32 1.87 2.93 2.78 2.38	1.37-7.48 1.36-7.18 1.10-4.52 1.08-2.50 1.34-6.81 1.03-1.48 1.01-2.56 1.04-1.66 1.16-5.32 0.97-2.87 1.13-4.80 1.29-2.72 1.19-3.40 1.24-3.95 1.40-5.35 1.39-5.48 1.31-4.95 1.19-4.56 1.14-3.39 1.21-4.46 1.07-3.28 1.45-5.90 1.40-5.59 1.21-4.71

Table 7-46. Studies of neurologic and behavioral effects among Dutch infants (continued)

Author	Exposure	Study groups	Evaluation	Findings: Coefficient (std error)	Findings: *p*-value
Huisman et al., 1995b	$\sum PCB_{cord\ blood}$ No effects observed with breast milk	Exposed: Breast-fed infants 104 in Groningen 105 in Rotterdam Comparison: Bottle-fed infants 107 in Groningen 102 in Rotterdam	Neurologic development in 18-month-old children: Neurologic optimality score Log($\sum PCB_{cord}$/0.8) Paternal smoking Log($\sum PCB_{cord}$/0.8) × paternal smoking Above analysis presented by paternal smoking status: Children w/nonsmoking fathers Children w/smoking fathers Fluency cluster score Log($\sum PCB_{cord}$) Breast (0) vs bottle (1) fed	 -0.149 (0.049) -0.402 (0.130) 0.200 (0.078) -0.149 -0.051 -0.295 (0.175) -0.450 (0.177)	 0.003 0.002 0.011 0.003 0.402 0.093 0.012

[a] $p<0.05$.
[b] pg PCB-dioxin-furan TEQ/g fat times weeks breast feeding.
[c] overall p for high + medium = 0.05.
[d] $p<0.01$.
[e] $\sum PCB_{maternal\ blood}$ (ng/g) -- maternal blood level sometime during 36-40 weeks of gestation. This and cord blood are measured in ng/g plasma.
[f] All summary logistic results presented; for individual chemicals, only those with ORs significantly greater than 1 are presented.

Table 7-47. Mortality from disease of the circulatory systems in populations exposed to 2,3,7,8-TCDD

Author	Population	Outcomes	No. of deaths	SMR	95% CI	Cohort size	Years of followup
Steenland et al., 1999	2,4,5-TCP and 2,4,5-T production workers, USA	Ischemic heart disease (ICD 410-414) Cerebrovascular disease (ICD 430-438)	456 92[2] 69	109 RR=1.75[a] 117[b] 96	100-120 1.07-2.87[a] 94-144[b] 74-121	5,132 608[b] 5,132	1942-1993
Hooiveld et al. 1998	2,4,5-TCP, 2,4,5-T, MCPA production workers, The Netherlands	Circulatory system (ICD390-459) Ischemic heart disease (ICD 410-414) Cerebrovascular disease (ICD 430-438)	45 16/(45) 33 10/(33) 9 3/9	100 RR=1.4[c] RR=1.5[d Medium] RR=1.5[d High] 120 RR=1.8[c] RR=1.5[d Medium] RR=2.3[d High] 140 RR=0.6[c] RR=2.0[d Medium] RR=0.8[d High]	80-140 0.8-2.5[c] 0.8-2.8[d] 0.8-2.9[d] 80-160 0.9-3.6[c] 0.7-3.6[d] 0.5-8.2[d] 60-260 0.4-5.1[c] 0.5-8.2[d] 0.2-4.1[d]	562 549 (males) 562 549 (males) 562 549 (males)	1955-1991
Vena et al., 1998	IARC expanded international cohort; 36 cohorts from 12 countries; workers employed in the production of phenoxyacid herbicide and chlorophenol & sprayers	Circulatory system (ICD 390-459) Ischemic heart disease (ICD 410-414) Cerebrovascular disease (ICD 430-438)	1,738 1,170[e] 1,151[f] 1,179 789[e] 1,151[f] 254 162[e] 1,151[f]	91 94[e] RR=1.51[f] 92 97[e] RR=1.67[f] 254 84[e] RR=1.54[f]	87-95 88-99[e] 1.17-1.96[f] 87-98 90-104[e] 1.23-2.26[f] 76-97 71-98[e] 0.83-2.88[f]	21,863 13,831	Varies by cohort 1939-1992

Table 7-47. Mortality from disease of the circulatory systems in populations exposed to 2,3,7,8-TCDD (continued)

Author	Population	Outcomes	No. of deaths	SMR	95% CI	Cohort size	Years of followup
Ott and Zober, 1996a	2,4,5,-T production workers or involved in cleanup after a TCP reactor release (Germany)	Diseases of the circulatory system (ICD not reported) TCDD[h] <0.1 µg/kg bw TCDD 0.1-0.99 µg/kg bw TCDD >1 µg/kg bw Ischemic heart disease TCDD <0.1 µg/kg bw TCDD 0.1-0.99 µg/kg bw TCDD >1 µg/kg bw Noncancer deaths: all causes Diseases of the circulatory system	37[g] 13 11 12 16 7 4 5 92 37	80 80 100 80 70 90 70 60 RR=1.03[i] RR=0.93[i]	60-120 40-140 50-170 40-120 40-110 30-180 20-170 20-130 0.88-1.22 0.70-1.24	243 males 4 females	1953-1992
Michalek et al., 1998	US Air Force Ranch Hands	Circulatory diseases (ICD 380-459) Pilots & navigators Enlisted flight engineers Administrative officers Enlisted ground personnel	39 12 8 0 24	100 90 30 — 150	70-130 50-160 — — 100-220	1,261 veterans 19,080 comparisons	1962-1993

Table 7-47. Mortality from disease of the circulatory systems in populations exposed to 2,3,7,8-TCDD (continued)

Author	Population	Outcomes	No. of deaths	SMR	95% CI	Cohort size	Years of followup
Pesatori et al., 1998	Residents of Seveso, Italy	Circulatory sys (ICD 390-459)		Rel. risk		PYAR[j]	1976-1991
		Zone A: males	5	1.6	1.1-2.5	5,541	
		Zone B	18	0.9	0.7-1.1	42,219	
		Zone R	126	1.1	1.0-1.2	271,483	
		Zone A: females	0	1.0	0.6-1.7	5,975	
		Zone B	15	1.0	0.8-1.2	41,391	
		Zone R	133	1.1	1.0-1.2	271,483	
		Ischemic heart disease (ICD 410-414)					
		Zone A: males	9	1.5	0.8-2.9		
		Zone B	36	0.8	0.6-1.2		
		Zone R	316	1.1	0.9-1.2		
		Zone A: females	1	0.3	0.0-2.0		
		Zone B	24	1.1	0.7-1.6		
		Zone R	210	1.0	0.9-1.2		
		Chronic ischemic heart disease (ICD 412, 414)					
		Zone A: males	5	3.0	1.2-7.3		
		Zone B	18	1.3	0.8-2.1		
		Zone R	126	1.4	1.1-1.7		
		Zone A: females	0	—	—		
		Zone B	15	1.3	0.8-2.2		
		Zone R	133	1.3	1.0-1.5		
		Chronic rheumatic heart disease (ICD 390-398)					
		Zone A: females	3	15.8	4.9-50.4		
		Zone B	0	—	—		
		Zone R	11	1.2	0.6-2.3		
		Cerebrovascular disease (ICD 430-438)					
		Zone A: males	5	1.5	0.6-3.7		
		Zone B	30	1.2	0.8-1.7		
		Zone R	190	1.1	0.9-1.3		
		Zone A: females	2	0.5	0.1-2.0		
		Zone B	26	1.0	0.7-1.5		
		Zone R	258	1.2	1.0-1.3		

Table 7-47. Mortality from disease of the circulatory systems in populations exposed to 2,3,7,8-TCDD (continued)

[a]Rate ratio calculated using Cox regression for cumulative exposure categories compared to an internal control group. Rate ratio for 7th septile exposure category.
[b]Chloracne cohort.
[c]Relative risks for 549 males, calculated using Poisson regression and using an internal control group.
[d]Relative risks calculated using Poisson regression adjusted for age, calendar period at end of followup, and time since first exposure/employment, comparing workers with estimated low $TCDD_{max}$=7.1 ppt (lipid adjusted) to workers with estimated medium $TCDD_{max}$=7.7 ppt to124.1 ppt (lipid adjusted) and estimated high $TCDD_{max}$=124.2 to 7,307.5 ppt (lipid adjusted).
[e]Workers exposed to TCDD or higher chlorinated dioxins.
[f]RR=relative risk calculated using Poisson regression, adjusted for age, gender, calendar period, employment status and years since first exposure and duration of exposure to phenoxy herbicides or chlorophenols. Comparison of workers exposed to TCDD or higher chlorinated dioxins to nonexposed workers.
[g]Expected deaths based on age, sex, calendar-period-specific death rates of the former West Germany, 1952-1992.
[h]Estimated 2,3,7,8-TCDD concentration based on 138 employees.
[i]Rate ratio calculated using Cox regression; TCDD μg/kg bw forced into model.
[j]PYAR: Person years at risk.

Table 7-48. Results of studies examining the effect of dioxin on reproductive and developmental outcomes in humans, 1984-1992

Author	Exposed group	Control group	Type of exposure	Data source: exposure/ outcome	Outcome	Outcome in exp. (N)	Outcome in unexp. (N)	OR	95% CI
Smith et al., 1982	548 male pesticide applicators who sprayed 2,4,5-T and other pesticides	441 agricultural contractors	Spraying of 2,4,5-T	Mailed survey/mailed survey	Total births	1,172	1,122		
					Congenital defect	13	9	1.19[a]	0.58-2.45
					Miscarriage[b]	43	40	0.89	0.61-1.30
					Stillbirth	3	0	—	—
Townsend et al., 1982	370 male chemical workers exposed to 2,4,5-T only and their spouses	345 employees not exposed to 2,4,5-T and their spouses	Working with chlorophenol processes	Interviewer-administered questionnaire/ interviewer-administered questionnaire	# Conceptions	418	2,031	—[c]	
					All fetal deaths	50	246	1.02	0.71-1.47
					Stillbirth	7	33	0.97	0.38-2.36
					Spontaneous abortions	43	213	0.96	0.65-1.42
					Infant deaths	6	39	0.82	0.30-2.09
					Health defects	32	155	0.93	0.60-1.43
					Congenital malformation	21	87	1.08	0.63-1.8
	Male chemical workers exposed to any dioxins				Total conceptuses	737	2,031		
					All fetal deaths	100	246	1.03[a]	0.78-1.37
					Stillbirth	15	33	1.06	0.54-2.09
					Spontaneous abortions	85	213	1.03	0.77-1.39
					Infant deaths	9	39	0.63	0.27-1.39
					Health defects	52	155	0.85	0.60-1.21
					Congenital malformation	30	87	0.85	0.53-1.35

Table 7-48. Results of studies examining the effect of dioxin on reproductive and developmental outcomes in humans, 1984-1992 (continued)

Author	Exposed group	Control group	Type of exposure	Data source: exposure/ outcome	Outcome	Outcome in exp. (N)	Outcome in unexp. (N)	OR	95% CI
Mastroia-covo et al., 1988	2,900 births in zones A, B, and R, Seveso, Italy, 1977-1981	12,391 births in study area outside zones A, B, and R	TCDD cloud released from chemical plant accident	TCDD soil analysis/ Seveso Congenital Malformations Registry	Total birth def. Multiple birth defects Syndromes Major birth defects Minor birth defects	137 10 5 67 70	605 38 29 343 262	0.97 1.12 0.74 0.83 1.14	0.83-1.13 0.63-2.02 0.33-1.63 0.67-1.04 0.92-1.42
Stehr et al., 1986	68 persons residing in areas of high TCDD conc.	36 persons with no known contact with contam. soil	Contact with TCDD-contam. soil	EPA soil analyses for TCDD/ interview	Infert. (males) Impotence Infert.(females)	— — —	— — —	— — —	NS NS NS
Hoffman and Stehr-Green, 1989	154 residents of Quail Run Mobile Home Park	155 residents nonexposed mobile home park	Contact with soil sprayed with TCDD for dust control	EPA soil analyses for TCDD/ interview	Fetal deaths Spontaneous abortions Congenital malformations	— — —	— — —	— — —	NS NS NS
Stockbauer et al., 1988	402 pregnancies to exposed mothers	804 pregnancies to unexposed mothers (matched on maternal age and race, hospital and year of birth, plurality)	Contact with soil sprayed with TCDD for dust control	EPA soil analyses for TCDD/vital statistics and hospital records	Birth defects-all Major birth defects Multiple birth defects Fetal deaths Infant deaths Perinatal deaths Low birth wt. Very low birth weight IUGR	17 15 2 4 5 6 27 1 14	42 35 11 5 5 9 36 4 26	0.78 0.84 0.34 1.60 2.00 1.33 1.59 0.50 1.09	0.40-1.47 0.40-1.66 0.03-1.65 0.32-7.43 0.46-8.69 0.39-4.20 0.89-2.81 0.01-5.05 0.50-2.28
Erickson et al., 1984	4,929 infants from the Met. Atlanta Congenital Defects Program	3,029 infants from Georgia vital statistics records	Vietnam military service	Self-reported, and Exposure Opportunity Index/birth defects registry and vital statistics	Total birth defects (96 subcategories also examined)	428	4,387	0.97	0.83-1.14

Table 7-48. Results of studies examining the effect of dioxin on reproductive and developmental outcomes in humans, 1984-1992 (continued)

Author	Exposed group	Control group	Type of exposure	Data source: exposure/ outcome	Outcome	Outcome in exp. (N)	Outcome in unexp. (N)	OR	95% CI
CDC, 1988d, 1989	7,924 Vietnam veterans	7,364 non-Vietnam veterans	Vietnam military service	Military records/self-reports	Total birth def. Spontaneous abortion Stillbirth Low birth wt. Childhood ca Sperm abnormalities: concentration motility morphology	826 1,566 126 100 25 51 91 51	590 1,190 131 87 17 20 58 29	1.3 1.3 0.9 1.1 1.5 2.3 1.2 1.6	1.2-1.4 1.2-1.4 0.7-1.1 0.8-1.4 0.8-2.8 1.2-4.3 0.8-1.8 0.9-2.8
Substudy #1, CDC 1988d, 1989	1,791 offspring of Vietnam veterans	1,575 offspring of non-Vietnam veterans	Vietnam military service	Military records/self-report and hospital records verification	Total birth def Low birth wt Perinatal mort. Suspected birth defects	130 51 58 21	112 37 54 21	1.0 1.1 1.0 0.9	0.8-1.4 0.7-1.8 0.7-1.5 0.5-1.7
Substudy #2, CDC 1988d, 1989	127 offspring of Vietnam veterans	94 offspring of non-Vietnam veterans	Vietnam military service	Military records/self-report and hospital record verification	Cerebrospinal malformations	26	12	1.8	0.8-4.0
Stellman et al., 1988	2,858 Vietnam veterans	3,933 non-Vietnam veterans	Vietnam military service	Survey/ survey	Difficulty conceiving 349 Time to conception Birth weight — Spontaneous abortion 231	363 4.4 yrs — 195	4.4 yrs	1.2 — — 1.3	NS NS NS 1.4-2.0
Aschengrau and Monson, 1989	201 spontaneous abortion cases at Boston Hospital for Women	1,119 full-term births at Boston Hospital for Women	Vietnam military service	Military records/ hospital records	Spontaneous abortion	8	44	0.9	0.42-1.9
Aschengrau and Monson, 1990	966 infants with late adv. preg. outcomes at Boston Hospital for Women	998 normal term infants at Boston Hospital for Women	Vietnam military service	Military records Hosp. records	Total birth def. ≥1 Major malf. Minor malf Stillbirths Neonatal deaths	55 18 11 5 3	656 151 189 51 36	1.3 1.8 0.9 1.5 1.2	0.9-1.9 1.0-3.1 0.5-1.7 0.4-3.9 0.2-4.2

Table 7-48. Results of studies examining the effect of dioxin on reproductive and developmental outcomes in humans, 1984-1992 (continued)

Author	Exposed group	Control group	Type of exposure	Data source: exposure/ outcome	Outcome	Outcome in exp. (N)	Outcome in unexp. (N)	OR	95% CI
Wolfe et al., 1992b	2,533 conceptions among 791 Ranch Hand personnel	2,074 conceptions among 768 non-Ranch Hand personnel	Spraying/ handling of Agent Orange	Serum TCDD levels/ hospital and medical records	Total birth def. ≤10[k] 15-≤33.3 >33.3	 202.1[l] 293.1 193.8	208.0	 0.96[m,n] 1.58 0.92	 0.69-1.34 1.10-2.27 0.64-1.32
					Nervous system anomalies ≤10[k] 15-≤33.3 >33.3	 0.0[l] 5.7 13.2	3.1	 — 1.88[m,o] 4.37[m,o]	 0.20-18.3 0.87, 21.8
					Respiratory sys. anomalies ≤10[k] 15-≤33.3 >33.3	 7.1[l] 5.7 4.4	2.0	 3.5[m,o] 2.83 2.17	 0.49-25.0 0.26-31.4 0.20-24.0
					Digestive system anomalies ≤10[k] 15-≤33.3 >33.3	 21.3[l] 34.5 17.6	24.5[l]	 0.83 1.30 0.64	 0.31-2.23 0.48-3.51 0.21-1.91
					Genital anomalies ≤10[k] 15-≤33.3 >33.3	 3.5[l] 51.7 13.2	18.3[l]	 0.19 2.92 0.72	 0.03-1.43 1.29-6.61 0.21-2.46
					Urinary system anomalies ≤10[k] 15-≤33.3 >33.3	 14.2[l] 34.5 22.0	12.2[l]	 1.16 2.88 1.82	 0.37-3.63 1.07-7.79 0.63-5.22
					Musculoskeletal deformities ≤10[k] 15-≤33.3 >33.3	 120.6[l] 143.7 105.7	134.6[l]	 0.88[m,n] 1.08 0.76	 0.59, 132 0.68-1.71 0.48-1.21

Table 7-48. Results of studies examining the effect of dioxin on reproductive and developmental outcomes in humans, 1984-1992 (continued)

Author	Exposed group	Control group	Type of exposure	Data source: exposure/ outcome	Outcome	Outcome in exp. (N)	Outcome in unexp. (N)	OR	95% CI
					Anomalies of the skin				
					≤10[k]	17.7[l]	21.4[l]	0.76	0.25-2.26
					15-≤33.3	34.5		1.83	0.72-4.70
					>33.3	8.8		0.46	0.11-1.95
					Circulatory system and heart anomalies				
					≤10[k]				
					15-≤33.3	14.2[l]	16.3	0.85	0.27-2.69
					>33.3	46.0		2.16	0.81-5.74
						8.8		0.32	0.04-2.52
Wolfe et al., 1995	1,006 conceptions among 454 Ranch Hand personnel	1,235 conceptions among 570 non-Ranch Hand personnel	Spraying/ handling of Agent Orange	Serum TCDD levels/hospital and medical records	Spontaneous abortion:				
					Comparisons		172	1	
					Background	57		1.1	0.8-1.5
					RH Low	56		1.3	1.0-1.7
					RH High	44		1.0	0.7-1.3
					Stillbirth:				
					Comparisons		13	1	
					Background	7		1.8	0.7-4.5
					RH Low	6		1.8	0.7-4.7
					RH High	1		0.3	0.0-2.3
					Developm'tal delays:				
					Comparisons			1	
					Background	24	71	1.2	0.8-1.8
					RH Low	26		1.5	1.0-2.3
					RH High	21		1.1	0.7-1.7
					Major birth defects:				
					Comparisons			1	
					Background	17	56	1.1	0.6-1.8
					RH Low	23		1.7	1.1-2.7
					RH High	19		1.2	0.8-2.1

[a]Relative risk.
[b]Rate: 86/1,000 births in applicators; 93/1,000 births in agricultural contractors (controls).
[c]Adjusted for mother's age at time of birth, birth control methods, labor and delivery complications, medical conditions and medications during pregnancy, smoking and alcohol use during pregnancy, high job risk, and gravidity.
[d]Rate: zone A: 0; zone B: 57.5/1,000 births; zone R: 45.1/1,000 births; zone non-ABR: 48.8/1,000 births.
[e]90% CI.
[f]Zones A and B.
[g]Zones A and B vs. non-ABR.
[h]Controls matched on maternal age, race, hospital of birth, plurality, and year of birth.
[i]Odds ratio adjusted for veteran's age at birth, year of entry in army, enlistment status, general technical test score, military occupational specialty, years between entry and birth, maternal age, and gravidity.[j]Children born after the father was stationed in Southeast Asia (SEA).
[k]Logit (p) = $\beta_0 + \beta_1 d_1 + \beta_2 d_2 + \beta_3 d_3$, where p = probability of an adverse reproductive outcome; d_1, d_2, d_3 are indicators for the dioxin categories: Unknown (Ranch Hands with up to 10 pg/g current dioxin), Low (Ranch

Hands with more than 15 pg/g of lipid and up to 33.3 pg/g of lipid current dioxin), and High (Ranch Hands with more than 33.3 pg/g of lipid current dioxin).

[l]Rate/1000 of abnormals.

[m]Unadjusted.

[n]Adjusted analysis not statistically significant.

[o]No adjusted analysis: total defects <10.

[p]Comparions: ≤10 ppt; Ranch Hand (RH) Background ≤ 10; RH LOW with current level> 10 ppt and estimated initial level≤≤110ppt; and RH HIGH with current level> 10 ppt and estimated initial level > 110 ppt.

Table 7-49. 2,3,7,8-TCDD levels (pg/g of lipid) for selected populations

Author	Study population	Specimen	Range	Mean	Median
Mocarelli et al., 1991	Seveso, Italy residents: 10 Zone A 10 former Zone A 10 non-ABR Zone	Serum	 828 - 56,000 1770 - 10,400 nd-137	 19,144 5,240 —	 14,000 4,540 —
Patterson et al., 1986b	39 Missouri residents with history of TCDD exposure 57 Missouri residents with no known TCDD exposure	Adipose tissue	2.8 - 750 1.4 - 20.2	79.7 7.4	17.0 6.4
Smith et al., 1992	9 New Zealand pesticide applicators 9 controls	Serum	3.0 - 131.0 2.4 - 11.3	53.3 5.6	37.6 9.3
CDC, 1988	646 Vietnam ground combat troops with service in heavily sprayed areas 97 non-Vietnam veterans	Serum	nd - 45 nd - 15	4.2 4.1	3.8 3.8
Kahn, 1988	10 "heavily exposed" Vietnam veterans 10 Vietnam veterans with "little or no" exposure 7 non-Vietnam veterans	Blood (per lipids) Adipose tissue Blood (per lipids) Adipose tissue Blood (per lipids) Adipose tissue	— — — — — —	46.3 41.7 6.6 5.1 4.3 3.2	25.1 15.4 5.3 5.4 3.9 3.5
Schecter et al., 1989	26 Vietnam veterans	Adipose tissue	nd - 11	5.8	—

Table 7-49. 2,3,7,8-TCDD levels (pg/g of lipid) for selected populations (continued)

Author	Study population	Specimen	Range	Mean	Median
Kang, 1991	36 Vietnam veterans 79 non-Vietnam veterans 80 civilians	Adipose tissue	— — —	13.4 12.5 15.8	10.0 11.4 11.8
Roegner et al., 1991	872 Ranch Hands 1,060 controls	Serum	0-617.8 0-54.8	— —	12.8 4.2
Phuong, 1989b	Vietnamese populations: 9 OB/GYN patients from a South Vietnam hospital	Adipose tissue	nd - 103	23	11.3

Table 7-50. Odds ratios for selected categories of birth defects for the telephone interview and hospital records study in the Vietnam experience study, 1989

Birth defects	Vietnam veterans rate/1,000	Controls rate/1,000	OR	95% CI
Telephone interview				
Total	64.6	49.5	1.3	1.2-1.4
Hospital records study				
Total	72.6	71.1	1.0	0.8-1.4
Major	28.5	23.5	1.1	0.7-1.8
Minor	32.4	34.3	1.00	0.7-1.5

Adapted from the Centers for Disease Control Vietnam Experience Study, 1988d.

Table 7-51. Results of the misclassification analyses for birth defects in the hospital records substudy, Vietnam experience study, 1989

Vietnam veterans		Non-Vietnam veterans	
PPV	24.8%	PPV	32.9%
NPV	95.2%	NPV	95.8%
Sensitivity	27.1%	Sensitivity	30.3%
Specificity	94.7%	Specificity	96.2%
% Agreement	90.6%	% Agreement	92.4%
Kappa index	20.9%	Kappa index	27.6%

PPV = Positive predictive value.
NPV = Negative predictive value.
Adapted from the Centers for Disease Control Vietnam Experience Study, 1989.

Table 7-52. Rates of miscarriage (per 1,000) by pre- and post-Vietnam tour status and time since tour of duty, among 1,475 Ranch Hands with >10 pg/g serum dioxin, Ranch Hand study, 1992[a]

Time of conception	Time since tour (years)	Miscarriage rate per 1000 (no./n) by current dioxin level			*p*-value
		10-14.9 pg/g	15-33.3 pg/g	>33.3 pg/g	
Pre-tour	≤18.6	142.0 (23/162)	146.8 (32/218)	48.8 (2/41)	0.014[b]
	>18.6	123.9 (14/113)	159.4 (33/207)	166.7 (16/96)	
Post-tour	≤18.6	92.1 (7/76)	136.6 (22/161)	168.5 (15/89)	
	>18.6	237.3 (14/59)	198.6 (29/146)	121.5 (13/107)	

[a]Adapted from Wolfe et al., 1992b.
[b]Comparison of pre- and post-tour data.

Table 7-53. Summary of effects observed in adults exposed to 2,3,7,8-TCDD

System	Acute	Chronic
Dermatologic	Conjunctivitis Red and irritated eyes Blepharitis	chloracne
Liver	Temporary enlargement	—[a]
Liver enzymes	↑ GGT ↑ AST ↑ ALT ↑ D-glucaric acid excretion	↑ GGT
GI other than liver	+\- RUQ[c] pain Loss of appetite Nausea	—
Urinary porphyrins	+/-[b] PCT Uroporphyrin Urobilinogen Coproporphyrin	—
Lipids	↑	—
Cholesterol	↑	—
Triglycerides	↑	—
Thyroid	↑ T_4 ↑ T_4/TBG in some studies	—
Diabetes	No data	+/-
Immune	No data	+/- ↑NK cells +/- ↑IgA
Neuro	+/- ↓ libido ↑ irritability ↑ nervousness ↓ pin prick sensation	—
Circulatory	—	+/-
Pulmonary	Irritation	—
Renal	—	—
Reproductive hormones	No data	+/- LH in ♂ +/- FSH in ♂ ↓ testosterone in ♂
Chromosome	+/-	no data

[a]No effect noted.
[b]Some positive and some negative studies.
[c]Right upper quadrant.

Table 7-54. Effects of exposure to 2,3,7,8-TCDD on serum glucose levels in nonhuman mammalian species

Author	Species	Route	Dose (μ/kg)	Duration	Percentage of serum glucose levels in control animals[a]
Zinkl et al., 1993	CD rat	oral	0.1 1.0 10.1	1x/day for 30 days	91[b] 71 51
Gasiewicz et al., 1980	Rats	ip (TPN) ip (chow-fed)	100[c]	1 time	29[d] 51[d]
Schiller et al., 1986	Fischer rat	gavage	30 60 90 180[c] 270[c] 360[c]	1 time	74[d,e] 54[d,e] 30[d,e] 43[d,e] 38[d,e] 39[d,e]
Gorski et al., 1990	Sprague-Dawley rat	ip	125[c]	1 time	day 4 75[b,d] day 8 67[b,d] day 16 50[b,d] day 21 31[b,d]
McConnell et al., 1978a	Rhesus monkey	gavage	70 350[c]	1 time	(decreased)[b,d]
DeCaprio et al., 1986	Hartley guinea pig	oral	0.01 0.06 0.44	90 days	NC[b,e,f] NC[b,e,f] NC[b,e,f]
Ebner et al., 1988	New Zealand rabbits	ip	1 50	1 time	NC 15 min NC 1 hour 125[d,e] 2 day 87 10 day 80[d,e]

[a]Relative to control values.
[b]Female animals.
[c]Lethal dose.
[d]Significantly different from controls.
[e]Male animals.
[f]Data not displayed.
ip = intraperitoneal.
TPN = total parenteral nutrition.
NC = no change.

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Chapter 8. Dose-Response Modeling for 2,3,7,8-TCDD

Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

Part II: Health Assessment for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds

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8. DOSE-RESPONSE MODELING

8.1. INTRODUCTION

8.1.1. Overview

This chapter describes concepts that embody the evaluation of dose-response relationships for the dioxins and related compounds and examines dose-response models for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). TCDD is the most potent form of a broad family of xenobiotics that bind to an intracellular protein known as the aryl hydrocarbon receptor (AhR) (Chapter 2). Other members of this family, in addition to the polychlorinated dibenzodioxins (PCDDs), include polyhalogenated hydrocarbons such as the polychlorinated dibenzofurans (PCDFs), polychlorinated biphenyls (PCBs), and polychlorinated naphthalenes (PCNs). In addition, there are other classes of chemicals that bind to the AhR, such as polynuclear aromatic hydrocarbons and naturally occurring compounds. A detailed discussion of the interactions of these chemicals and the concept of TCDD equivalence is presented in Chapter 9. The biological and toxicological properties of dioxins have been investigated extensively in more than 5,000 publications and abstracts since the identification of TCDD as a chloracnogen (Kimmig and Schulz, 1957). Some data sets on members of this family of compounds other than TCDD are clearly amenable to dose-response modeling. However, this chapter focuses exclusively on studies in laboratory animals that can be used to evaluate dose-response for TCDD. In addition, it evaluates human data where exposure to TCDD has been estimated and dose-response can be modeled quantitatively.

Most of the information presented in this introduction is found in more extensive detail later in this chapter or in the other parts of this reassessment. This introduction sets the stage for discussion of dose-response modeling of TCDD by briefly answering the questions, “what is dose?” “what is response?” and “what is modeling?” It then goes on to describe and, to a limited degree, compare different modeling approaches. This introduction also shows the reader the types of data and information available for TCDD that may have an impact on the development of dose-response models. Both in the introduction and throughout this chapter, gaps in knowledge relating to the evaluation of TCDD dose-response are identified. Understanding these gaps and their impact on the conclusions of this chapter can guide the design of new experiments that will add to our knowledge of TCDD action and clarify issues related to its dose-response.

8.1.2. What Is Dose?

When performing dose-response analyses, it is critical to understand what is meant by dose and how it applies to the response. The dose, in dose-response modeling, is an inclusive term. Examples of dose include the amount of TCDD given to an experimental animal by some specific route at some specific frequency, measured tissue concentrations in laboratory studies, body burdens attained in these studies, or daily exposure seen by workers in an occupational setting. In general, units of dose should reflect the magnitude of the exposure and the frequency over which it applies. Dose can be expressed in a multitude of metrics. Some of these metrics include daily intake (ng/kg/day), total body burden (ng/kg), body burden averaged over a given period of time, or tissue concentration. Depending on the particular endpoints to be compared, and in consideration of the half-life of elimination of TCDD (see Section 8.2), it may be possible to express dose in a form that allows comparison of response across various endpoints and species. Specific issues relating to dosage and comparison across species and endpoints are discussed in Section 8.2.

Most, if not all, of the effects elicited by TCDD are mediated by the ability of this chemical to bind to and activate the AhR. The activation of this protein leads to a series of molecular and biochemical events that ultimately contribute to particular biological responses (see Part II, Chapter 2). It is clear from the available human and animal data that TCDD can elicit many types of responses depending on the species, the age of the animal at exposure, and whether the exposure is acute or chronic. These responses vary from biochemical alterations such as enzyme induction, which may require only acute exposures, to developmental effects, which may require a level of exposure at a particular window of tissue development, to more complex responses such as cancer, which may require prolonged exposures (Section 8.1.3). To determine what might be the most sensitive endpoints, the species variation in sensitivity to these endpoints, and how these differences or similarities might be extrapolated to effects in humans, requires a comparison of the amount, or dosage, of TCDD that is present in particular tissues and/or the whole organism.

Dose is not always a known quantity. For humans, the actual dose is rarely known and best estimates are made on the basis of several assumptions and observations made at only a few time points, often many years after what may be believed to be the period of highest exposures. For these cases, models of exposure linked to response data may be used to develop a dose-response model. However, limited knowledge of the events that control tissue distribution (especially in humans at low levels of exposure) and those molecular and biochemical processes that ultimately lead to particular responses contribute uncertainty in these analyses.

8.1.3. What Is Response?

Response, in this context, generally relates to an observation seen in an animal or a human following exposure to TCDD. These responses cover a broad range of observations, ranging from early responses such as biochemical alterations that are closely coupled to activation of the AhR to more complicated responses such as cancer and developmental defects. The responses are sometimes species- and/or tissue-specific and have different degrees of variation across individuals. However, there is some commonality across species and there are known linkages between some responses (e.g., mRNA serves as a precursor molecule for the synthesis of protein). Dose-response modeling can address endpoints separately, provide insight into their quantitative similarity across species and tissues, and link responses in a mechanistically reasonable manner.

The binding of TCDD to the AhR is similar, although not identical, to the interaction of many steroid hormones with their intracellular receptors (Poellinger et al., 1987; Cuthill et al., 1991; DeVito et al., 1991; Lucier et al., 1993). An overall hypothesis for the mode of action of TCDD, put forth by several groups, is based on the transcriptional activation of expression of specific genes. This hypothesis has been most well characterized for transcriptional activation of the cytochrome CYP1A1 gene. There is also some evidence to indicate that activation of the AhR by TCDD may elicit responses by mechanisms that may not involve direct transcriptional activation of genes. The biological basis for these models of AhR action is outlined in Part II, Chapter 2. It is accepted by most researchers that most, if not all, cellular responses to TCDD require the initial interaction between TCDD and the AhR.

Although gaps in our knowledge remain, evidence to date is consistent with the hypothesis that binding of TCDD to the AhR and inappropriate activation of this protein represent the first steps in a series of biochemical, cellular, and tissue changes that define the toxicity observed. These changes are defined as responses to TCDD. Evidence to support this theory has been reviewed in several sections of this document as well as in the peer-reviewed literature (Safe, 1990; Birnbaum, 1994; Poland and Knutson, 1982). Many of the known biological activities of related PCDDs and PCDFs also appear to follow their rank order of binding affinity of the congeners and analogues to the AhR (see Part II, Chapters 2 and 9). This rank order holds for toxic responses such as acute toxicity and teratogenicity and for changes in concentration of several proteins, including the induction of cytochromes P-450 1A1 (CYP1A1), 1A2 (CYP1A2), estrogen receptor, and epidermal growth factor receptor (EGFR). The direct relationship between AhR binding and carcinogenicity of TCDD is less clear, although limited structure activity relationship studies on tumor promotion demonstrate a rank order in potency similar to binding to the Ah receptor (see Part II, Chapter 9).

The AhR has been identified in numerous mammalian species including humans (Okey et al., 1994; Roberts et al., 1985, 1986; Abbott, 1995; Manchester et al., 1987; Lorenzen and Okey, 1991; Cook and Greenlee, 1989), several non-mammalian vertebrates including chicken embryos

(Denison et al., 1986) and newts (Marty et al., 1989), and several aquatic species from whales to teleosts and elasmobranchs (Hahn, 1998). The broad phylogenetic distribution in vertebrate evolution (Hahn, 1998) and the phylogenetic conservation of this receptor also suggest that it has an important role in regulating cellular function in vertebrate animals. However, the physiological role or function of this receptor has yet to be determined.

Although the human data are limited, there is relatively good concordance for the biochemical/molecular effects of TCDD between laboratory animals and humans, indicating that animal models are generally appropriate for estimating human responses. Where wide species differences exist, understanding the relative sensitivity of human responses may not be possible at this time. However, many of the biochemical effects produced by TCDD and its analogues in animals also occur in humans. Data on effects of TCDD and its analogues in humans are based on in vitro (i.e., in cell culture) as well as epidemiological studies. Placentas from Taiwanese women exposed to rice oil contaminated with dioxin-like PCBs and PCDFs have markedly elevated levels of CYP1A1 (Lucier et al., 1987). Comparison of these data with induction data in rat liver suggests that humans are at least as sensitive as rats to enzyme-inductive actions of TCDD and its structural analogues (Lucier, 1991). Consistent with this contention, the in vitro EC_{50} for TCDD-mediated induction of CYP1A1-dependent enzyme activities is ~1.5 NM when either rodent or human lymphocytes are used (Clark et al., 1992). The human AhR appears to have greater than a twentyfold range in TCDD affinity (Okey et al., 1994). This range is comparable to that of the sensitive and resistant mouse strains as well as that of rats (see Chapter 2). It does appear that humans contain a fully functional AhR (Cook and Greenlee, 1989), as evidenced by significant CYP1A1 induction in tissues from exposed humans, and that this response occurs with similar sensitivity as observed in experimental animals.

One of the biochemical effects of TCDD that might have particular relevance to toxic effects is the loss of plasma membrane EGF receptor. There is evidence to indicate that TCDD and its structural analogues produce the same effects on the EGF receptor in human cells and tissues as observed in experimental animals. Incubation of human keratinocytes with TCDD decreases plasma membrane EGF receptor, and this effect is associated with increased synthesis of transforming growth factor-α (TGF-α) (Choi et al., 1991; Hudson et al., 1985). Placentas from humans exposed to rice oil contaminated with PCDFs also exhibited markedly reduced EGF-stimulated autophosphorylation of the EGF receptor, and this effect occurred with similar sensitivity as observed in rats (Lucier, 1991; Sunahara et al., 1989). The magnitude of the effect on autophosphorylation was positively correlated with decreased birth weight of the offspring.

Chloracne, a well-known response observed in highly exposed humans, has also been shown to occur in several animal species including nonhuman primates, rabbits, and hairless mice. However, it should be noted that in populations exposed to similar amounts of TCDD (e.g., Seveso,

Italy), some humans may exhibit chloracne while others do not. In mice, responsiveness to TCDD and related chemicals can be modified by genes as well as the AhR. For example, mice congenic at the hairless (*hr*) locus demonstrate altered sensitivity to the chloracnegenic and tumor-promoting effects of TCDD (Poland et al., 1982). These data suggest that there may be multiple factors (e.g., genetics) that may contribute to the development of a particular response both within and between species.

Several reports in the literature suggest that exposure of humans to TCDD and related compounds may be associated with cancer at many different sites, including malignant lymphomas, soft tissue sarcomas, hepatobiliary tumors, hematopoietic tumors, thyroid tumors, and respiratory tract tumors. These studies are evaluated in Part II, Chapter 7a, including discussion of confounding factors and strength of evidence. TCDD is a carcinogen in several species of laboratory animals (mice, rats, hamsters, fish) and the tumor sites include liver, thyroid, and the respiratory tract, as well as others.

Several noncarcinogenic effects of PCDDs and PCDFs show good concordance between laboratory species and humans (DeVito et al., 1995). For example, in laboratory animals, TCDD causes altered intermediary metabolism manifested by changes in lipid and glucose levels. Consistent with these results, workers exposed to TCDD during the manufacture of trichlorophenol showed elevated total serum triglycerides and cholesterol with decreased high density lipoprotein (Walker and Martin, 1979), similar to results seen in Air Force personnel following exposure to Agent Orange (Wolfe et al., 1990; Fallon et al., 1994). Another interesting finding of these studies was a positive relationship between TCDD exposure and diabetes (see Part II, Chapter 7b).

There are also differences between human and animal effects associated with TCDD. For example, chloracne has been observed in exposed humans but in only some animal species. Similarly, increases in humans of certain cancers such as soft-tissue sarcoma have not been observed in animals (see Part II, Chapters 6 and 7). Also, immunotoxic endpoints consistently seen in animals have rarely been demonstrated, or looked for, in humans (see Part II, Chapter 4). The recognition of these similarities and differences is essential when using animal data to estimate human effects. Understanding of these similarities and differences can substantially improve dose-response analysis.

The human-to-experimental-animal comparison is also complicated by several other factors:

(1) for most toxic effects produced by dioxin, there is marked species variation. An outlier or highly susceptible species for one effect (i.e., guinea pigs for lethality or mice for teratogenicity) may not be an outlier for other responses;

(2) human toxicity testing is based on epidemiological data comparing "exposed" to "unexposed" individuals. However, the "unexposed" cohorts contain measurable amounts

of background exposure to PCDDs, PCDFs, and dioxin-like PCBs. Also, the results of many epidemiological studies are hampered by small sample size, and in many cases the actual amounts of TCDD and related compounds in the human tissues were not examined; and

(3) In addition, it is often difficult, if not impossible, to assess in humans the same endpoints that might be determined in experimental animals (e.g., some immunotoxic effects and altered liver enzymes).

In summary, for many of the biological responses elicited by TCDD, animal models appear to be reasonable surrogates for estimating human risks. However, it must be kept in mind that the animal-to-human comparison would be strengthened by additional mechanistic information, especially the relevance of specific molecular/biochemical precursors to toxic responses. It is also important to note that the key events leading to carcinogenesis may be quite different at different sites (see Part II, Chapter 6).

8.1.4. What Is Modeling?

In the sciences, a model is a representation of how something works. Models are of several types, such as conceptual (e.g., a mental image of how something works), biological (e.g., transgenic mice as a surrogate for a human system), physical (e.g., a three-dimensional model of the human heart) and mathematical (e.g., a physiologically based pharmacokinetic model [PBPK]). Any model is defined by a set of parameters that make up its key components, and usually has inputs (e.g., dose) and outputs (e.g., response) that correspond to its real-world counterparts. Mathematical models of dose-response generally can be classed into two broad areas: empirical models and mechanism-based or mode-of-action models; these are described in the next two sections.

Modeling involves the application of a mathematical model to data as a tool to allow for analysis and prediction. Any modeling exercise requires the estimation of model parameters. The tools used to estimate parameters range from very simple techniques, such as estimating a slope of a straight line (linear regression), to extremely complicated approaches, such as estimation by maximizing a statistical likelihood function comprising unknown model parameters. In some cases, estimation of parameters in a model involves choosing a value based upon scientific judgment. The quality of any parameter estimate is dependent on the available data to characterize the model. The quality of the data and information used to develop a mathematical model is the major component in determining the confidence placed in any conclusions or predictions from that mathematical model.

Dose-response models for receptor-mediated events should use information on the quantitative relationships among ligand concentration, receptor occupancy, and biological response.

For example, Roth and Grunfeld (1985) state: "At very low concentrations of hormone receptor, occupancy occurs but may be trivial; i.e., the curve approaches 0% occupancy of receptors. But if there are 10,000 receptors per cell (a reasonable number for most systems), the absolute number of complexes formed is respectable even at low hormone concentrations. One advantage of this arrangement is that the system is more sensitive to changes in hormone concentration; at receptor occupancy (occupied receptors/total receptors) below 10%, the concentration of occupied receptors is linearly related to the concentration of hormone, whereas at occupancies of 10 to 90%, the concentration of HR is linear with log hormone concentration, a given increase in the concentration is more effective in generating occupied receptors at the lowest part of the curve than at the middle."

It is clear that multiple dose-response models are possible when considering ligand-receptor mediated events. For example, when there is a proportional relationship between receptor occupancy and biological response, occupancy of any number of receptors would produce a response, although it would be unlikely that the response could be detected if the number of receptors occupied was very low. Given this proportionality, a simple model, describing the response as a linear function of dose, may be adequate. However, such a simple relationship is unlikely to explain the diversity of biological responses that can be elicited by a single hormone utilizing a single receptor. For example, low concentrations of insulin produce much greater effects on fat cells than on muscle cells because fat cells have more receptors. These differences are due to cell-specific factors that determine the qualitative relationship between receptor occupancy and response. Similarly, it is expected that there are markedly different dose-response relationships for different effects of TCDD.

Coordinated biological responses, such as TCDD-mediated increases in cell proliferation, likely involve other systems, which means that the dose-response relationships for relatively simple responses (i.e., CYP1A1 induction) may not accurately predict dose-response relationships for complex responses such as cancer. Thus, it is necessary to consider what is known and observed regarding a biological response before a reasonable mathematical model can be applied to the data. Responses that include coordination of multiple steps that have linear dose-response relationships may ultimately produce markedly nonlinear dose-response relationships.

The goal of mathematical modeling should be to use as much data as possible to reduce uncertainties and to identify the areas where data gaps exist. Several important concepts have been generally accepted that may determine the types of mathematical models one might apply to responses due to exposure to TCDD:

(1) TCDD is a member of a class of xenobiotics (and probably natural products) that is not directly DNA reactive, binds to a cellular receptor, alters gene expression, and alters cell growth and development;

(2) a significant amount of information is available for estimating risks from exposure to this compound, and these data should be used to their fullest extent; and

(3) the biology of receptor-mediated events should be included to the greatest extent possible in any modeling exercise for TCDD, empirical or mechanism-based.

8.1.5. Empirical Modeling

By its very nature, data applicable to dose-response modeling can generally be expressed through groups of individuals (cells, animals, humans) exposed to a common level of a toxic agent (TCDD) for which some response is measured. Given sufficient numbers of exposure groups, it is possible to see a pattern arise, which indicates a change of that response as a function of increasing dose. Empirical dose-response modeling attempts to find a simple mathematical model that adequately describes this pattern. Empirical models generally have little or no direct linkage to the underlying mechanisms driving a given response, but instead focus on flexible mathematical forms that can fit a broad spectrum of data and allow comparisons across individual data sets. However, empirical models should be interpreted in light of information available on the biology of the modeled response and, in doing so, can provide qualitative insights into underlying mechanisms.

Examples of empirical models include linear functions (such as those used in linear regression), log-linear models, Poisson regression (commonly used in epidemiology), and Hill models (commonly used to analyze ligand-receptor data). Empirical models have the advantage of ease of use, the existence of "user-friendly" software tools capable of fitting these models to dose-response data , and a formal framework for hypothesis testing and interpolation between data points. In addition, empirical models can be used to estimate a point of departure for extrapolation. The major disadvantage of empirical models is their inability to quantitatively link multiple data sets in a mechanistically meaningful manner.

8.1.6. Mechanism-Based and Mode-of-Action-Based Modeling

In contrast to empirical modeling, mechanism-based modeling attempts to use an understanding of the mechanistic relationship between exposure and multiple endpoints to simultaneously describe the observed response. Mechanism-based modeling can be a powerful tool for understanding and combining information on complex biological phenomena (Lucier et al., 1993). Mechanism-based modeling commences from a series of experiments with a xenobiotic agent. The experimental results (data) can indicate a mechanism supporting the creation of a mathematical model. The predictions of that model are tested for consistency with the existing knowledge base for the agent and effect under study. Defects in the fit can suggest new experiments that may permit refinement of the model. On each iteration of this process, the model either gains additional credibility by predicting the new experimental results or it is modified to fit the new as

well as previous results. In either case, subsequent iterations of this process increase our confidence in accepting or rejecting a final model, although it may be difficult or impossible to quantify this confidence.

Mathematical models that incorporate parameters that correspond to actual biological structures or processes do not automatically constitute "mechanism-based models." The types of data available for the model and the method by which these data are incorporated into the model determine if a model truly reflects the biology. A parameter that specifies the activity of a xenobiotic metabolizing enzyme, for example, should have a biologically realistic value. Without careful attention to the representation of biological detail, confidence in the model and use of its results is reduced.

Ideally, the parameters in a mechanism-based model are derived from first principles in a "bottom-up" fashion. In this case, the structure of the model is an accurate mathematical representation of the known properties of the system being modeled, and the mechanistic parameters in the model are estimated directly from data. Such a model can increase confidence in extrapolating outside the range of the data as long as attendant uncertainties are carefully evaluated. In practice, it is generally impossible to completely develop a mathematical model for biological processes. At some point, processes by which the mechanistic events elicit the observed toxic effects must be deduced in a "top down" approach that uses some curve fitting. The concept of mode of action has been developed in response to this difficulty in implementing the "bottom up" approach (U.S. EPA Guidelines for Carcinogen Risk Assessment, EPA/600/Z96001). The term *mode of action* is defined as a series of key events and processes starting with interaction of an agent with a cell, through operational and anatomical changes resulting in cancer formation and other toxicities. "Mode" is contrasted with "mechanism" of action, which implies a more detailed molecular description of events. Operationally, the description of the mode of action should convey enough information to characterize the shape of the exposure-response curve. A risk assessment model based on the mode of action is preferable to empirical modeling when making inferences outside of the range of the effects data.

Without data (as is the case with extrapolated predictions), the statistical issue of the accuracy of a prediction cannot be easily addressed. Thus, while there may be greater biological confidence in extrapolated results, it is unlikely that an increased statistical confidence can be demonstrated. However, for each level and type of data, there are ranges of exposure beyond which it is impossible to demonstrate an effect because of limitations in the sensitivity of those assays. In general, effects can be demonstrated at lower exposures for mechanistic data (e.g., gene expression) than for toxicity data. Hence, use of a true mechanism-based approach should enable reliable and scientifically credible extrapolations to lower exposures.

Risk assessment typically involves extrapolations between species, from high to low doses, and between different patterns of exposure. Uncertainty in risk assessment is reduced to the extent that these extrapolations are based on mechanistic considerations. For TCDD, the mechanisms of three processes are of primary interest: (1) the dosimetry of TCDD throughout the body and specifically to target tissues; (2) the molecular interactions between TCDD and tissue proteins, emphasizing the activation of gene transcription and increases in cellular concentrations of growth-regulatory gene products and metabolic enzymes; and (3) the progressive tissue-level alterations resulting from these interactions that lead, eventually, to toxicity. Mechanism-based modeling for TCDD is the quantitative description of the mechanisms that define these processes. A model based on mechanistic understanding of the biochemistry of TCDD-induced toxicity and that accurately reproduces observed effects would permit more confident extrapolations to low doses and more reliable resultant risk estimates. As previously stated (Greenlee et al., 1991), "Neither the position taken by U.S. EPA or by Environment Canada (and several other countries such as Germany and the Netherlands) is based on any detailed mechanistic understanding of receptor-mediated interactions between TCDD and target tissues. In addition to their use in risk assessment, models of these processes can aid in the design of future experiments to clarify understanding of TCDD toxicity and support further risk estimation."

Several models ranging from very simple to complex have been developed to describe the toxicity of TCDD. It is obvious that the biology governing the toxicity of TCDD, beyond a few initial critical events, is not straightforward. These critical events, the first of which is binding to the AhR, are generally response-independent. The response-dependent events are species-, sex-, organ-, tissue-, cell- and developmental stage-specific. If binding to the AhR is essential but not sufficient for effects to occur, then the dose-response curve for this event (as well as the rate equations) should be a better predictor of biological action than external dose as long as the shapes of the dose-response curves for these subsequent actions are similar to those of receptor binding curves. In general, the available data indicate that receptor involvement is necessary for most if not all low-dose actions of TCDD. However, it is clear that for many responses, the dose-response curves are different from receptor binding curves. Furthermore, although the AhR has been detected in many kinds of cells, not all of these exhibit toxic responses. These data suggest that there must be other factors that are necessary for TCDD-induced toxicity. The roles of these cell-specific factors and how they affect the ultimate response must be elucidated before there is a complete understanding of TCDD action. However, a model may be developed for specific endpoints by using available data and biologically plausible assumptions.

TCDD can be considered as a prototype for exploring and examining the ability of mechanism-based modeling to improve the accuracy of quantitative risk assessment. The database for a mechanistic modeling approach to TCDD is extensive and contains a considerable amount of

information on low-dose behavior. In addition, there is some concordance between human data and experimental evidence in animals (see Section 8.3). On the other hand, some aspects of the mechanism by which TCDD induces its effects, such as binding of the AhR to accessory proteins, have not been modeled extensively because of lack of data. Because of this deficiency, several alternative mechanistic hypotheses may agree with the existing data. The role of mechanism-based modeling in this case is to identify a set of candidate biologically plausible models, rather than to provide a final description. This outcome is inevitable for the application of the technology of mechanism-based modeling to a new area. Reduction in the size of the candidate set and, eventually, identification of the preferred model must await additional results from the laboratory.

To reiterate an earlier point, mechanism-based modeling can aid in explaining and understanding experimental results, beyond its proposed use in risk assessment.

8.1.7. Elements of Chapter 8

The following sections of this chapter discuss the underlying science related to selection of appropriate dose metrics for dose-response modeling, empirical modeling of individual data sets, and mechanism-based dose-response modeling for biochemical responses and tissue responses. This modeling effort follows a natural progression related to the kind of information available at the time these models were developed. In addition, knowledge gaps have been identified throughout the chapter and have been consolidated in a section related to data gaps and research needed to address critical uncertainties that remain in the dose-response modeling of TCDD. Discussion of the strengths and weaknesses, assumptions and uncertainties, and implications of these TCDD dose-response modeling efforts follows. Detailed tables containing the outputs of the empirical dose-response modeling efforts are appended to this chapter for the benefit of those readers who wish a more detailed view of the data and analyses supporting the discussion and conclusions of this chapter. General conclusions are presented in a short summary statement that is found toward the end of this chapter.

8.2. DOSE METRICS

8.2.1. Introduction

One of the more perplexing issues in toxicology is animal-to-human dose extrapolation. To provide significant insight into differences in sensitivity among species, an appropriate animal-to-human extrapolation of tissue dose is required. Chemicals can produce many different types of responses depending on the exposure scenario and the response. Some responses are reversible (enzyme induction) whereas others are irreversible (death, cancer). Some responses require prolonged exposures (porphyria and cancer). Others have unique windows of susceptibility where an adverse effect (e.g., cleft palate) occurs only after a critical window of exposure (e.g.,

during development). The processes leading to particular toxic responses are highly divergent, with some responses requiring a continued exposure over a prolonged period of time and some requiring an exposure over only several hours. It is unlikely that a single dose metric will be adequate for interspecies and intraspecies extrapolation for all of these endpoints.

Estimating risk to various human populations is complicated by differences in exposure scenarios. Human exposures to high levels of dioxins have occurred in several different scenarios. There have been industrial accidents that have resulted in high exposures over a very short period of time, such as the explosion at the ICMESA trichlorophenol plant near Seveso, Italy, in 1976 (Ghezzi et al., 1982) and the BASF chemical plant in Ludwigshafen, Germany, in 1953 (Zober et al., 1990). Increased daily exposures over background to dioxins have occurred in occupationally exposed populations using some herbicides, for example, during the Vietnam War (Verger et al., 1994) and in agricultural workers (Kogevinas et al., 1995). Routine occupational exposures have occurred in several manufacturing facilities around the world. The final type of human exposure occurs in the general population, which is exposed daily to TCDD in the diet at a dose rate of approximately 0.14 to 0.4 pg/kg/day[1] (see Part I). One of the difficulties in examining and comparing these different populations is that the actual dose or exposure is rarely known. Estimates are often based on present serum TCDD concentrations, with extrapolation back to the initial time of exposure based on the half-life of TCDD in humans (Fingerhut et al., 1991; Scheuplein and Bowers, 1995).

In contrast, the exposures in animal experimentation are controlled and well defined. Animal studies use multiple dosing regimens including single acute exposures, chronic daily exposures, and biweekly exposures. Comparison across species sometimes requires extrapolation from one exposure scenario to another. Large differences between species and the half-life of TCDD, and quantitative differences in the tissue distribution of TCDD, must be considered (van der Berg et al., 1994).

Determining the most appropriate dose metric represents an additional difficulty when different endpoints and species are compared. Comparison of responses across species requires the expression of dose using an equivalent metric. Dose can be expressed in a multitude of metrics (DeVito et al., 1995) such as daily intake (ng/kg/day), current body burden (ng/kg), average body burden over a given period of time, plasma concentration, concentration of occupied AhR (Jusko, 1995), induced CYP1A2 (Andersen et al., 1997a; Kohn et al., 1993), and reduced EGFR (Portier and Kohn, 1996).

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[1]Calculated from human daily dietary dose of 10 to 20 pg/day TCDD and human body weights between 50 and 70 kg; it should be noted that, on a total TCDD equivalents (TEQ) basis, total daily intake equals approximately 70 pg/day (see Part I) (see Chapter 9 for discussion of TCDD equivalents).

Different dose metrics can lead to widely diverse conclusions. For example, the lowest dose with an increased tumorigenic response (thyroid tumors) in a rat (NTP, 1982a) is 1.4 ng/kg/day and the daily intake in humans is approximately 0.14 to 4 pg/kg/day. This implies that humans are exposed to doses 3,500 to 10,000 times lower than the rat dose. However, 1.4 ng/kg/day in the rat leads to a steady-state body burden of approximately 25 ng/kg, assuming a half-life of TCDD of 23 days and absorption from feed of 50%[2]. The current body burden of TCDD in humans is approximately 5 ng/kg lipid or 1.25 ng/kg body weight (assuming about 25% of body weight is lipid), suggesting that humans are exposed to about 20 times less than the minimal carcinogenic dose for the rat. The difference between these two estimates is entirely due to the approximately 100-fold difference in the half-life between humans and rats. At least for this comparison, the most appropriate metric for comparison is the steady-state body burden. (Note that current daily intake for humans is likely lower than historical levels and is biased downward because of unknown sources, leading to a discrepancy between body burdens and daily intake.

In addition to the uncertainty in the half-life of TCDD in humans, such calculations assume exposure to TCDD at a constant rate rather than the actual episodic exposure scenarios generally seen in the studied populations. In principle, a reliable PBPK model for humans could be used to compute body burden, tissue dose, or any other desired dose metric for any dosing scenario. However, as outlined in Section 8.4, the existing data are inadequate for this extrapolation. If time courses of TCDD in human blood were available for widely different doses, metabolic parameters for humans could be estimated. Inclusion of these quantities in a PBPK model would permit the calculation of a tissue dose or body burden to be used for risk assessment.

The developing embryo represents a very different complication in choosing a correct dose measurement. The susceptibility of a developing embryo or fetus to TCDD insult may be dependent upon the stage of development. For example, susceptibility to TCDD-induced cleft palate has a specific window of sensitivity. Once the palatal shelves fuse, cleft palates cannot be induced by TCDD. These windows of susceptibility are on the orders of hours to days. One of the difficulties is that the time span is often too short to clearly discriminate among dose metrics such as peak concentration, steady-state body burden, or average body burden. When these types of comparisons for TCDD are attempted, it appears that they are of equivalent utility, provided the dose metric was determined only during the window of sensitivity. In both animals and humans, the biological half-life of TCDD is much greater than the time span of the window of susceptibility. Hence, an average measurement or a peak measurement can be used as an appropriate dose metric.

[2] Steady-state body burden (ng/kg) = daily dose (ng/kg/day) [(half-life/ln(2)] (f where f is the fraction absorbed from the exposure route (unitless) and half-life is the half-life in days.

The windows of susceptibility for some of the developmental toxicities of TCDD have been identified (i.e., induction of cleft palate and hydronephrosis). Peak body burden may be a more appropriate dose metric for developmental effects because the window of susceptibility is undefined for several endpoints.

Ideally, the best dose metric is that which is directly and clearly related to the toxicity of concern by a well-defined mechanism. For mechanism-based cancer modeling, instantaneous values of a dose metric are used because these can be used as surrogates for mutational rates and growth rates within a two-stage cancer model. For epidemiology studies of lung cancer and all cancers combined, there is not enough information to develop a mechanistic approach. In this case the chronic exposures generally thought to be associated with the cancer process can be described by metrics that integrate dose over a specific time period., and an average body burden dose metric is acceptable for steady-state conditions. However, difficulties arise when this metric is applied to accidental high acute exposures. To allow for comparison across studies, it is sometimes useful to find a constant daily exposure or steady-state body burden that yields the same total exposure. Comparability of response over multiple species for a given dose metric can be used to assess the adequacy of that metric. It should be noted that for compounds like TCDD with very long half-lives, relative differences between doses expressed as steady-state body burden versus those expressed as total exposure may be small for humans, although the same may not be true in experimental animals where the half-life is much shorter.

8.2.2. Selection of Effective Dose Levels.

Comparisons across multiple endpoints, multiple species, and multiple experimental protocols are too complicated to be made on the basis of the full dose-response curve. Comparisons of this sort can be made by either choosing a given exposure and comparing the responses, or choosing a particular response level and comparing the associated exposures. In the analyses for the presentations in this chapter, responses are compared using estimated exposures associated with a given level of excess risk or response. To avoid large extrapolations, this common level of excess risk or response was chosen such that for most studies, the estimated exposure is in or near the range of the exposures in the studies being compared (Murrell et al., 1998; Gaylor and Zheng, 1996; Barton and Das, 1996; Allen et al., 1994a,b; McGrath et al., 1995), with extra weight given to the human data. A common metric for comparison is the effective dose, or ED_p, which is the exposure dose resulting in a excess risk in the studied population. Although effective dose reporting for the 2%, 5%, and 10% increased risks has been the suggested approach, these latter two levels are actually higher than those typically observed in the exposed groups in studies in humans. To illustrate, lung cancer mortality has a background lifetime risk of approximately 4% (smokers and nonsmokers combined), so that even a relative risk of 2.0 represents approximately a 4% increased

lifetime risk. On the basis of this observation, and recognizing that many of the endpoints studied in the laboratory include 1% effect levels in the experimental range, the dose resulting in a 1% effect above controls (ED_{01}) is presented.

Different measures can be used to present risks above and beyond the background risks encountered in the general environment or through genetic variables. For simplicity, a common measure will be used; the excess risk, defined as the effective dose for risk (p*100%), satisfying the relationship in equation (1):

$$p = \frac{R(d_p) - R(0)}{R(\infty) - R(0)} \qquad (1)$$

where $R(d_p)$ represents the response (either risk or other measure) at p at a given exposure or dose level d, and $R(\infty)$ is the maximum response possible (e.g., $R(\infty)$ =1 for quantal responses, such as cancer). In this exercise p is equal to 0.01.

The relative risk commensurate with a one percent excess risk can be calculated by rearranging the above formula:

$$\text{Relative Risk } (ED_{01}) = 0.99 + \frac{0.01}{R(0)}$$

Multiplying the relative risk by R(0), the background risk, gives the value of the absolute risk. If the background risk is 0 then the absolute risk equals the excess risk.

In the present analysis, the benchmark effect level has been specified as a 1% increase in the extra risk. Quantal data is determined as a probability on a scale of zero to one. Hence the difference between the probability of an adverse response at a given benchmark response level and the probability of a response at background is already on a standardized scale. In contrast, estimating the extra risk for continuous data is challenging. The changes in a continuous response that are considered adverse depend on the nature of the response that is determined. The change in effect that results in a significant public health problem is different for every response determined. In addition, the study design can influence this value. In order to have a consistent response level between endpoints, the measurement of response must be standardized between endpoints.

As outlined in Murrell et al (1998), there are several methods proposed to standardize continuous data. One method uses a specified change relative to background and is calculated according to the following equation:

$$E_{relative} = \frac{F_\theta(d) - F_\theta(0)}{F_\theta(0)}$$

where $F_\theta(d)$ is the function relating the response to dose *d*. There are some problems with this approach. $E_{relative}$ is now highly sensitive to the background response. For example, a small change in a response with a small background may seem more important compared to the same effective change in response with a large background. In addition, it is not clear that a certain percent change from background is an equivalent risk for all endpoints. For example, a 30% change in a heart rate may not be an equivalent risk as a 30% change in serum porphyrin concentrations. Therefore, using $E_{relative}$ does not result in a standardized risk level by which one could compare across endpoints.

Another proposed standardization method is to divide the change in effect by the standard deviation of the control group or from an assumed distribution of the mean effect for a particular dose group (Crump, 1984; Slikker et al., 1996). Because the standard deviation may vary for a variety of reason independent of the health importance of the effect, this method does not necessarily standardize across a variety of endpoints and experimental conditions.

Ideally, the benchmark effect level is one that separates a normal or no-effect level from abnormal or adverse effect levels (Crump, 1995). One of the difficulties in applying this approach are the assumptions that are made in the determination of the benchmark level. Often, there is not a clear consensus as to when a change in a continuous response becomes adverse. Because of the lack of a consensus on adversity levels for many of the effects examined in this analysis, this method was deemed inappropriate to use as a means of standardization across endpoints.

In the present analysis, the continuous data is standardized by the dynamic range of response for each effect (Murrell et al., 1998). Similar to quantal data, continuous data also has maximal response levels. Thus one can define extra effect as the change in the effect from background as standardized to the total range of the response. Dividing the change in effect by the theoretical or observed maximum produces a quantity that is standardized across endpoints with respect to scale.

8.2.3. Dose Corrections for Species Differences in Half-Lives

Considering the very large difference between half-lives of TCDD in various species, it is best to compare across species using body burden rather than daily intake (DeVito et al., 1995). Under steady-state conditions, it is possible to calculate total body burdens (ng/kg) for TCDD in equation (2).

$$ED_{01}(\text{ng/kg body burden}) = ED_{01}(\text{ng/kg/day}) * \text{half-life}/\ln(2) * f \qquad (2)$$

where f is the fraction of dose absorbed and is assumed to be 50% for absorption from food (Kociba et al., 1976) and 100% for other routes. Half-lives for converting between daily exposures and steady-state body burden are presented in Table 8-1.

In summary, the unit(s) of dose should appropriately reflect the magnitude of exposure and the frequency of this exposure. Given the various types of exposure scenarios and different types of responses, it is difficult to determine a single dose metric for TCDD that can be used to compare all endpoints and species. Nevertheless, for several types of specific endpoints, it is possible to express the dose of TCDD in a form that allows for a comparison of responses across various endpoints and species. For the analysis contained in this chapter, various measures of body burden will be used.

8.3. EMPIRICAL DOSE-RESPONSE MODELING OF INDIVIDUAL DATA SETS

8.3.1. Introduction

TCDD has been previously classified by EPA as a probable human carcinogen, and has more recently been classified as a known human carcinogen by the International Agency for Research on Cancer (IARC, 1997). In the Ninth Report on Carcinogens, the U.S. Department of Health and Human Services describes TCDD as "known to be a human carcinogen" (HHS, 2001). Epidemiological data have suggested increases in all cancers combined, respiratory system tumors, and soft-tissue sarcomas (see Chapter 7 for a detailed discussion of these findings).

TCDD is a carcinogen in all species and strains of laboratory animals tested (e.g., mice, rats, hamsters) with tumors detected in the liver, thyroid, respiratory tract, and other organs and tissues (see Part II, Chapter 6). Long-term rodent carcinogenicity studies have shown that TCDD is a potent carcinogen, with the most seriously affected organ being liver in female rodents (NTP, 1982a,b; Kociba et al., 1978; Portier et al., 1984).

8.3.2. Human Dose-Response Models

Despite the increasing amount of epidemiological data available for TCDD, it is generally difficult to find human data with sufficient information to model dose-response relationships. Unlike laboratory studies, human data can be affected by factors that are difficult to control. There exists the possibility of disease misclassifications, and measurements of exposure are often imprecise. However, risks studied in human populations do not require assumptions concerning species extrapolation and, as such, should be used maximally in studying dose-response. TCDD is no different in this regard, with several epidemiological studies providing varying degrees of utility for dose-response assessment. This section discusses those studies and the models that have been applied to them.

8.3.2.1. *All Cancers Combined and Lung Cancer*

There exist three studies of human occupational exposure that provide enough information to perform a quantitative dose-response analysis. These are the NIOSH study (Fingerhut et al., 1991; Steenland et al., 1999; Steenland et al., 2001), the Hamburg cohort study (Manz et al., 1991;

Flesch-Janys et al., 1995, 1998a; Becher et al., 1998), and the BASF cohort study (Zober et al., 1990).

8.3.2.1.1. ***NIOSH study*****.** NIOSH conducted a cohort study of 5,172 male workers at 12 plants in the United States that produced TCDD-contaminated chemicals (Fingerhut et al., 1991). They reported increased mortality for total cancers and for respiratory cancers for workers with greater than 1 year of exposure and more than 20 years latency since start of employment.

Steenland et al. (1999) performed an analysis of male workers from eight of the twelve plants in the NIOSH study (the plants with sufficient information on work histories and TCDD levels on the job) who had no exposure to pentachlorophenol. Exposure was measured using a job-exposure matrix. Cumulative TCDD exposure scores per day were assigned by multiplying TCDD concentration in industrial materials, fraction of work day spent working with TCDD-containing materials, and a qualitative degree-of-contact measure. The exposure scores for each day were added to get a cumulative exposure score, which cannot be interpreted as units of TCDD. Workers were divided into septiles by levels of this exposure score (with or without a 15-year latency taken into account).

SMRs were calculated by septile for all cancers and for lung cancer. SMRs for all cancers for 0 or 15 years latency showed a statistically significant ($p<=.05$) positive trend with exposure score, as did the SMRs for lung cancer with no latency. Cox regression analyses were also performed to compare high-exposure groups to the lowest exposure group. For the data with zero latency, rate ratios for all cancers did not show a significant positive trend with exposure. For data with 15-year latency, the analysis was performed for all cancers combined, lung cancers, smoking-related cancers, and non-smoking-related cancers. The rate ratios for all cancers and for non-smoking-related cancers showed a significant positive trend; ratios for lung cancer and for smoking-related cancer showed no significant trend with cumulative exposure, though they did show a significant trend with logarithm of cumulative exposure. ("Smoking-related cancer" here means cancer that has historically been associated with smoking; the smoker or nonsmoker status of workers was not itself included in the analysis.)

Steenland et al. (2001) extended their analysis of these workers to include estimated dioxin exposures. Serum lipid levels of TCDD in 1988 were measured in 193 workers at one of the eight plants in the study. First-order kinetics with a constant 8.7 year half-life were used to extrapolate back to serum level at time of last exposure. These serum levels were regressed on the exposure scores, using a first-order model for exposure between first exposure and last exposure (the resulting predicted serum level and the observed levels have correlation coefficient of 0.62). The formula derived by regression was used to estimate serum TCDD levels for all 3538 workers in the

cohort, and then to estimate serum TCDD areas under the lipid adjusted serum level curves over time (AUC).

Several different dose-response models were fit to these data to provide estimates of risk for dose-response assessment. The best-fitting model used the log(AUC) lagged by 15 years as the exposure metric. The analysis used Cox regression and had date-of-birth as a categorical variable (4 categories). Excess risk of cancer for intake of 1pg/kg/day for 75 years of exposure was estimated as 0.0094 for males and 0.0080 for females. This analysis assumes a background exposure of 0.5 pg/kg/day as background. The analysis was also carried out using log of TEQ AUC as a dose variable. Lifetime excess cancer risk using the TEQ model with an intake of 10 pg/kg/day TEQ was 0.0018 for males and 0.0015 for females.

A piecewise linear model fit nearly as well as the model using log AUC. Its risk estimates for an intake of 1 pg/kg/day TCDD for 75 years were 0.0005 for males and 0.0004 for females. When the background exposure included TEQ's, the risk estimates for an intake of 10 pg/kg/day TEQ for 75 years were 0.0005 for both males and females. These numbers appeared low and after discussing this with Dr. Steenland, he noted an error in the calculation and the corrected numbers are 0.0071 for males and 0.,0060 for females; in line with the numbers for the TCDD only analysis.

Aylward et al. (1996) presented a dose-response analysis using data from Fingerhut et al. (1991), considering only cancers occurring after 20 years of exposure. This analysis is superceded by the extended follow-up and exposure matrix used in Steenland et al (2001).

8.3.2.1.2. ***Hamburg cohort study*****.** Another cohort studied consisted of 1,189 men who worked at a herbicide plant in Hamburg, Germany (Becher et al., 1998; Manz et al., 1991; Flesch-Janys et al., 1995, 1998a). Flesch-Janys et al. (1995) used an estimate of TCDD levels in workers in their analysis. Levels of TCDD were measured in blood or adipose tissue for 190 male workers in the cohort. Levels at the end of employment were estimated using a first-order kinetic model, and the contribution of each of several job areas was estimated by regression of the TCDD level on time worked in the job areas. The regression results were used to calculate TCDD concentrations (ng/kg of blood fat) at the end of the occupational exposure for each member of the entire cohort. The cohort was divided into the lower four quintiles and ninth and tenth deciles of the calculated value. Cox regression was used to calculate relative risks for cancer mortality. Relative risks were calculated using either an external reference group (control group of gas workers) or the lowest two quintiles of the Hamburg cohort combined as internal reference. Variables used in the regression were TCDD level (categorized by quintiles), total duration of employment, age, and calendar year of first employment. A test for trend of the relative risks with increasing TCDD concentration was conducted. In the calculations using either reference group, the trend test was significant at $p<0.05$. Standard mortality ratios (SMRs) were calculated on the basis of the national mortality data

available from the German Federal Office of Statistics using standard methods (Breslow and Day, 1987). The SMRs for the tenth decile of TCDD concentration were significantly elevated, whereas none of the SMRs for lower TCDD concentration categories were significantly elevated in the comparison with the lowest two quintiles combined. In the comparison with the gas worker controls, SMRs were 129 or higher. The increase was significant for three of the five categories.

Flesch-Janys et al. (1998a) extended this analysis using mortality up to 1992 and calculating time courses for TCDD concentration in blood lipid. Workers were divided into quartiles by integrated blood concentrations over time and SMRs were calculated. For total cancer mortality, the mortality was significantly increased for the highest quartile (SMR 173; 95% CI=121-240) and for all workers combined (SMR 141, 95% CI=117-168). The overall cancer SMR is increased over the results of Manz et al. (1991), which included mortality only up to 1989. For all workers combined, lung cancer mortality was significantly increased (SMR 151, 95% CI= 107-208), but the SMRs were not significantly over 100 for any of the individual quartiles. A linear trend test on the SMRs by quartile was significant for total cancer deaths (p=0.01) but not for lung cancer deaths.

Another recent article (Becher et al., 1998) gave a dose-response analysis of the Hamburg cohort for all cancers combined. A Cox regression was used for the dose-response modeling. Three response models were used: a multiplicative model, an additive model, and a power model. The response variable in the analysis was SMR for total cancer mortality. The dose variable was the integrated blood levels for TCDD concentration (AUC) as calculated by Flesch-Janys et al. (1998a). Year of entry into employment, age at entry, duration of employment, and an exposure metric for beta-hexachlorocyclohexane were also used as covariates in the model. The models were calculated with latency times of 0 and 10 years. The dose-response was modeled using three classes of models. The "multiplicative model" had relative risk (RR) equal to $\exp(\beta d)$, where the dose d is the AUC. The "additive model" had $RR=1+\beta d$, and the "power model" had $RR= \exp(\beta \log(kd+1))=(kd+1)^{\beta}$. The value β and k are estimated parameters. The multiplicative model gave the best fit, but the fits for the three classes of models were so close that Becher et al. found no statistical reason to select between them. In all cases, the value of β was significantly different from 0 ($p<0.05$). The model results were used to calculate unit risk estimates, i.e., estimates for (risk of cancer death through age 70 given a daily dose of 1 pg/kg body weight of TCDD) – (risk given no exposure to TCDD). These calculations were based on background German mortality rates. The unit risks for intake of 1pg/kg/day of TCDD ranged from 0.0011 (risk for females under the multiplicative model with 10-year lag) to 0.0084 (risk for males under the power model with no lag).

Becher also gave results for a Cox regression for lung cancer deaths using the multiplicative model. The resulting risk (value of β) was close to that for the model of all cancer deaths.

8.3.2.1.3. ***BASF cohort study*****.** Zober et al. (1990) studied a cohort of 247 workers from a 1953 accident at a BASF factory in Germany that released TCDD into the factory. Overall cancer mortality for all workers combined was not significantly increased. However, for the 127 workers who developed either chloracne or erythema, and for a 20+ year latent period, mortality from all cancers was increased (SMR=201; 90% CI=122-315). There was also an increase in cancer mortality with a 20+ year latency for a subcohort of 153 workers who were considered most likely to have been exposed to TCDD (SMR 198; 90% CI=122-305).

Another study of the BASF cohort (Ott and Zober, 1996a) included 243 male workers. Chloracne status and estimated TCDD concentration (μg/kg body weight) at time of exposure were used as metrics of exposure. The concentration was calculated by a first-order kinetics model using a regression procedure. Subjects were divided into 3 or 4 groups by concentration. SMRs were calculated by dose group. Standardized incidence ratios were calculated by dose group for all cancers and for cancers at various sites. Neither total cancer mortality nor respiratory system cancer mortality was significantly increased overall, although respiratory cancer mortality was increased in the highest of three TCDD concentration groups (SMR 240, 95% CI=100- 500). The incidence was not significantly increased for all cancers or respiratory cancers, either overall or in any concentration subgroup. This study also included a dose-response analysis by a Cox proportional hazard model, which calculated relative risks, with cigarette smoking, body mass index, exposure to asbestos, exposure to aromatic amines, age, and date of first exposure included as explanatory variables. TCDD dose was found to be marginally significantly related to total cancer deaths (conditional risk ratio for 1 μg TCDD/kg body weight = 1.22; 95% CI=1.00-1.50), but not significantly related to respiratory cancer deaths or to incidence of either. There also appeared to be a trend for increasing total cancer deaths by TCDD level in smokers and in all workers, but not in nonsmokers or ex-smokers.

8.3.2.1.4. ***Other studies.*** Hooiveld et al. (1998) studied former workers at an herbicide factory in the Netherlands. A back-calculation and regression method was used to estimate peak TCDD concentration for all workers. A total of 1,031 male workers were divided into groups of low, medium, or high estimated peak TCDD level (cutpoints were 7.7 and 124.2 ppt). These groups were approximately tertiles of the TCDD level. Relative risks (RR) of mortality were calculated for the high and medium groups versus the low group, with adjustment for age, time of follow-up, and time since first exposure. Relative risks for total cancer deaths were significantly increased for both medium (RR 1.9, 95% CI=1.2-2.8) and high (RR 1.9, 95% CI=1.3-2.8) exposure groups, but with no apparent trend. Some relative risks for specific cancer types were marginally significant, but with no apparent trend from medium to high exposure. Not enough information is given in this

study to calculate average body burden. In the cohort of residents from Seveso, Italy (Bertazzi et al., 1993), a single episode of exposure to TCDD occurred following an explosion at a local chemical plant. Men, women, and children from this community have been followed for cancer mortality for 15 years. However, this study could not be included in this analysis because the limited exposure information is not sufficient at present to calculate average body burden. Two other studies were also not included in this analysis for various reasons. Kuratsune et al. (1998) reported increased lung cancer mortality in male victims (SMR = 330, based on eight cases) from the Yusho PCB and PCDF contaminated rice-oil poisonings. Although there are serum measurements and 37 total TCDD equivalents (TEQ) estimates available for this cohort, there was no TCDD in the contaminants reported. Because this chapter has focused primarily on the effects of TCDD, this cohort will not be included in the modeling effort. In addition, Collins et al. (1993) reported increased mortality for both lung cancer and all cancers combined for a subcohort of 122 U.S. workers who developed chloracne following exposure to TCDD at a chemical plant during a 1949 accident. Their analysis, however, attributes this increase in mortality to co-exposure to 4-aminobiphenyl. As that chemical plant is included in the NIOSH study cohort (Fingerhut et al., 1991), it is discussed in Chapter 7.

8.3.2.2 *ED and Unit Risk Calculations*

Life table data (total death risk by age and percent of deaths due to cancer by age) from 1995-1997 were obtained from the National Center for Health Statistics (NCHS, 1999). Cancer deaths through age 75 due to TCDD exposure of 1 ppt body burden over background (background assumed to be a steady-state lipid concentration of 5 parts per trillion; 1 ppt body burden above background equals 4 ppt lipid concentration over background) were calculated using the best-fitting models for the NIOSH data (Steenland et al., 2001), the Hamburg data (Becher et al., 1998), and the BASF data (Ott and Zober, 1996). In these calculations, exposure was assumed to be at steady-state TCDD body burden.

The models literature used by Steenland et al. and Becher et al. use TCDD or TEQ lipid concentration in calculating the AUC; lipid concentrations were converted to body burdens by dividing by 4. For those models, the exposure levels were used to calculate AUCs with a time lag included as specified by the model.

The model used by Ott and Zober (1996) gives risk in terms of conditional risk ratio per unit TCDD dose. Units for TCDD were μg/kg body weight at time of initial exposure to TCDD. For purposes of the current analysis, it is necessary to convert from units of steady-state body burden to Ott and Zober's units of initial dose. Assuming a constant half-life of 2593 (approximately 7.1 years) as in Table 8-1, an initial body burden of B_0 will yield a body burden at time t of

$B(t) = B_0 e^{-k_e t}$, where k_e is an elimination constant equal to ln(2)/(half-life in years). This implies that the AUC at time T after initial exposure is $AUC = \frac{B_o}{k_e}\left(1 - e^{-k_e T}\right)$. T in this case will be 39 years (time from the accident in 1953 to the followup in 1992). Dividing by a lifetime of 71 years (mean age in 1954, 33 years, plus 38 years from 1954 to the followup in 1992) gives the lifetime mean body burden as:

$$B_{mean} = \frac{B_o}{71 k_e}\left(1 - e^{-k_e T}\right)$$

.

In the risk calculations, therefore, the steady-state body burden will be converted to units of equivalent initial dose by dividing by the constant $\frac{1}{71 k_e}\left(1 - e^{-k_e T}\right)$. With the given values for half-life and T, that constant is 0.1411 and 1/(the constant) is 7.0851. The model from Ott and Zober has risk proportional to $e^{\beta \times dose}$ with β=ln(1.22). The corresponding slope for the mean (steady-state) body burden is 7.0851*log(1.22)*0.001 (the 0.001 converts nanograms to micrograms) and the slope for steady-state lipid concentration is that value divided by 4.

ED_{01}, ED_{05}, and ED_{10} values were calculated by finding the dose giving the specified excess risk. All estimates were calculated using the same methods as the original author with estimates of risk from the background exposure subtracted from the mortality data.

ED values are given below in Table 8-2. The values are exposures above background exposure which will produce the given level of excess risk. The table also gives unit excess risks: the excess risk for a unit exposure above background, given for exposure of 1 ppt body burden above background. Steenland et al. (2001) provide sufficient information to develop confidence bounds for the calculations using their models. Confidence limits for the models using the Hamburg data could not be calculated due to insufficient detail in the manuscript. Because the lower confidence limit for the risk value in the Ott and Zober (1996) model is zero (conditional risk ratio of 1.00), the lower confidence limits for unit risk are zero and the upper confidence limits for the ED values are infinite. The power model from the Steenland et al. (2001) data predicted that an unrealistically large fraction of the tumors seen in humans was due to background dioxin exposure.

8.3.2.3. *Noncancer Endpoints*

8.3.2.3.1. ***Cardiovascular disease***. A pattern of increased risk of cardiovascular and ischemic heart disease mortality was observed by Flesch-Janys et al. (1995) across six exposure categories. There was a statistically significant trend (p=0.04) in relative risk for mortality for all cardiovascular diseases when gas workers were used as the reference population, but in no single class of TCDD exposure was there a significantly increased relative risk. There was no statistically significant trend for death from ischemic heart disease (p=0.1), but the highest TCDD group (344.7-3,890.2 ppt) showed a significant relative risk of 1.99 (CI=1.05-3.75). When national rates were used for the reference population, there were no statistically significant trends for either disease, and all confidence intervals included 1. Information about time-average body burden could be obtained from Flesch-Janys et al. (1998 a,b). With these data, an excess body burden over background (95% lower bound) for 1% excess risk was calculated as 11.2 ng/kg (3.1 ng/kg) for all cardiovascular disease, assuming a lifetime risk of 25%. No statistically significant increase of cardiovascular diseases was observed for the NIOSH cohort (Steenland et al., 1999) or for the BASF cohort (Zober et al., 1990, 1994).

8.3.2.3.2. ***Effects on infants***. One major public health concern is the potential effects of environmental chemicals on the developing fetus, infants, and children. TCDD and related chemicals produce a broad range of effects in experimental animals exposed in utero ranging from alterations in biochemical parameters to overt toxicity and lethality (see Chapter 5 for a review). Few studies have examined the effects of TCDD and related chemicals in humans following in utero exposures. Studies in the Netherlands (Huisman et al., 1995; Koopman-Esseboom, 1996; Weisglas-Kuperus et al., 1995) have examined infants for thyroid hormone status, mental and psychomotor development, and immunological status. Exposures were assessed by determining the concentrations of PCBs, PCDFs, and PCDDs in maternal and umbilical blood and maternal breast milk. Exposures were then categorized by total TCDD equivalents (TEQs), Planar-PCB TEQ, nonplanar-PCB TEQ and total dioxin-PCB TEQs. (For a discussion of the TCDD toxic equivalency concept, refer to Chapter 9.) These studies are discussed in greater detail (design, analysis, and limitations) in Chapter 7. There is an indication that these data would be amenable to dose-response analysis for complex mixtures of PCDDs, PCDFs, and PCBs, but not for TCDD exposure alone.

8.3.2.4. *Uncertainties in Estimates From Human Epidemiology*

There are many uncertainties associated with risk estimates derived from epidemiological studies, both in hazard identification and in dose estimation. The estimates of dose, although based on actual body measurements, may not be fully representative or precise. Although 253 subjects were sampled in the Fingerhut et al. (1991) study, the blood samples were all taken decades after

last exposure and were from 2 of a total of 12 plants. Subjects from the larger of these two plants had the higher TCDD levels but a lung cancer SMR=72 based on seven deaths, whereas the smaller plant had only one death from lung cancer (SMR=155). Thus, while serum TCDD levels correlated well with duration of occupational exposure for the 253 individuals sampled, and cancer response correlated well with duration of exposure for the 12 plants overall, correlation of serum TCDD levels with cancer response in this study is far less certain. Analysis by plant in the Fingerhut et al. (1991) study would have been possible if body measurements at these other 10 plants had been available.

The choice of half-life is another element of uncertainty. In the literature, average body burden was calculated on the basis of a one-compartment model with first-order elimination. Half-life assumptions in the literature vary. Some data, however, suggest a shorter half-life of as little as 5.8 years (Ott and Zober, 1996b) while others suggest a longer half-life of 11.3 years (Wolfe et al., 1994). A recent study (Portier et al., 1999) suggests a half-life of 9.5 years. However, the assumption of a single half-life is uncertain because it is possible that in humans the apparent half-life may be shorter at higher levels of exposure, as has been observed in rat liver (Walker et al., 2000). If this were the case, the actual initial exposure may have been higher than predicted using a single half-life. In addition, it is assumed that the apparent half-life for TCDD is independent of exposure to other dioxin-like compounds. In the rodent, apparent half-life is in part determined by binding to CYP1A2, which is inducible via the AhR. In humans, while neither the dose response for induction of CYP1A2 by TCDD nor the effect this may have on disposition of TCDD is known, it is likely that the half-lives for dioxin-like compounds are not independent.

The fraction of TCDD absorbed could have an impact on the risk estimates derived from the epidemiological data. In our calculations, we have either directly assumed a 50% absorption fraction or relied upon analyses by the original authors that used a 50% absorption fraction. In the analyses applied in this chapter, changes in absorption fraction result in a proportional change in steady-state body burden. Hence, a 10% change in absorption would result in a corresponding 10% change in steady-state body burden.

Another uncertainty is possible interaction or confounding between TCDD and tobacco smoking. In mice, TCDD and 3-methylcholanthrene (3-MC, one of the many polycyclic aromatic hydrocarbons in tobacco smoke) have been shown to be cocarcinogenic (Kouri et al., 1978). Other studies of mouse skin tumors have shown that TCDD can have anticarcinogenic properties when administered before initiation with either 3-MC or benzo(a)pyrene. Furthermore, dioxin's tumor-promoting ability suggests that two-stage models would be more appropriate if individual smoking histories were known. Smoking histories and analyses are presented only for the Zober et al. (1990) cohort; for the 37 cancer cases, only 2 were stated as being nonsmokers. Of the 11 men with lung cancer, only 1 reported never smoking. The Ott and Zober (1996b) analysis, which includes

smoking as a covariate, did appear to show an effect of smoking on TCDD dose-response. Although similar SMRs from other smoking-related diseases in the two subcohorts in Fingerhut et al. (1991) suggest similar smoking prevalence across this multifactory cohort, the effects with higher levels of TCDD could be synergistic for cancer. Steenland et al. (1999) point out that confounding by smoking is likely to be reduced in an exposure-response analysis comparing highly-exposed workers to workers with lower exposure.

Other potential confounders in all three studies include exposures concomitant with TCDD exposures, other chlorinated hydrocarbons in the case of Zober et al. (1990) and Manz et al. (1991) and miscellaneous chemicals including 4-aminobiphenyl, a known human bladder carcinogen, in the case of Fingerhut et al. (1991). These confounders raise the question of whether the increased SMRs are due to exposure to TCDD or to the confounders. However, it is important to note that within this context, 4-aminobiphenyl does not increase tumors overall, and there is no evidence that TCDD induces the incidence of bladder cancers.

Another source of uncertainty is the choice of model for analysis. The Becher et al. (1998) analysis of data from the Hamburg cohort used three models for dose-response for total cancer mortality, of which only one was linear. The risk estimates they derived using different models varied by as much as a factor of five. The risk estimates of Steenland et al. (2001) for their best-fitting model (Cox proportional hazards model) fall above the range of risk estimates given by Becher et al. The risk estimates for Steenland et al.'s second best fitting model (piecewise linear) are more than an order of magnitude lower than those for their best fitting model.

When interpreting the risk estimates presented in this section, a few additional caveats and potential biases must be kept in mind.

All observed risk is attributed to exposure to TCDD, even in the presence of exposure to other confounding chemicals. In particular, this analysis ignores exposure to PCDDs, PCDFs, and other dioxin-like chemicals. The extent to which exposure to other agents increases the total exposure on a TEQ basis (see Chapter 9) also increases the potential bias of calculated risk estimates. In general, exposure to these compounds is correlated with the exposure to TCDD, although differences in relative contribution of different dioxin-like compounds to the total TEQ have been observed and are briefly discussed for the epidemiological data. This issue is especially important for agents with shorter half-lives than TCDD (some will be longer; some shorter). Analysis of blood samples analyzed years after exposure may fail to adequately measure an initial exposure to dioxin-like compounds with shorter half-lives. For example, a current lipid level of 1 ppt for an agent with a half-life of 7 years, e.g., TCDD, would imply a lipid level of a little less than 8 ppt 20 years ago. On the other hand, an isomer with a current lipid level of 1 ppt and a half-life of 2 years would imply a lipid level of 1,024 ppt 20 years ago.

In any epidemiological study, misclassification can bias estimates of risk. In this case, recent exposures to TCDD, changes in the lipid fraction of body weight or presence/absence of genetic differences in humans that alter the distribution and metabolism of TCDD could cause misclassification bias, resulting in higher or lower risk estimates depending upon the direction of the misclassification.

Selection bias may be another factor. For example, it is possible that the subpopulation used for the biomonitoring of TCDD levels in human blood is not representative of the entire cohort used for risk estimation. There is also a potential bias due to a healthy worker effect in these occupational populations.

8.3.2.5. *Conclusions for Human Cancer Dose-Response Modeling*

Epidemiological studies of occupational exposure suggest a TCDD-mediated increase in all cancers and also suggest that the lung in the human male is a sensitive target for TCDD. Smoking and other factors (discussed above) may be modifiers for these cancers. Caution should be used in interpreting the overall risk estimates and care should be taken to understand them in the context of the entire weight-of-evidence concerning the potential toxicity of TCDD. The data obtained from two occupational studies were sufficient to calculate risk estimates. Estimates derived from the human data suggest an ED_{01} based on body burden in the range of 1.4-62 ng/kg for all cancers combined.

8.3.2.6. *Additional Knowledge Gaps in Human Cancer Dose-Response Modeling*

One major knowledge gap in the epidemiological data is a complete exposure history for each individual in the cohort. This includes lack of a realistic exposure matrix (areas and their exposure potency and time spent in such areas of occupational exposure) and TCDD concentrations measured over time during exposure. At present, only a few measurements per individual are available to estimate a time course ranging over many years of human life.

Different dose metrics have been discussed in Section 8.2, and others may arise if more information about the exposure process becomes available. Neither comparisons of the dose metrics applicable at present to available data sets nor simulation studies on artificial data sets have been performed to clarify the strengths and weaknesses of different metrics under different scenarios.

More information is needed on factors determining individual differences in half-life of TCDD such that these can be included into the calculation of individual time-average body burdens. Age, sex, and portion of body fat have been discussed and used as factors of influence. The existence of a more complex model for TCDD kinetics in humans may be possible, but no systematic usage of these factors in risk estimation has been made so far.

Information about confounders of human carcinogenesis, such as smoking or other behavioral cancer risk factors, was sparse in these studies. Future studies must reduce this lack of information by use of appropriate design measures, or by inclusion of appropriate biomarkers of coexposure. Exposure to related dioxin-like compounds clearly complicates the estimates of the effective dose of TCDD. For example, in the Hamburg cohort, the mean TCDD concentration for 236 males was 108.3 ppt, whereas the mean TEQ concentration based on all other PCDDs and PCDFs (except TCDD) was 142.0 ppt. Other coexposure-based confounders have been described above. Although TEQ values can be calculated for each person using half-life estimates of each individual PCDD and PCDF congener, it is unclear how an interaction of different congeners in the individual organism determines the concentration levels over a long time period in humans. Long-term studies, even of a small cohort of individual persons, would have the potential to clarify basic pharmacokinetics of these complex mixtures. One question to be addressed would be potential changes in half-life of TCDD in the presence of other dioxin-like compounds in different concentrations.

The ED_{01}s presented are based on simple dose-response models. The analyses uses the crude endpoint of all cancers combined. No mechanistic information was available for these cohorts to strengthen this analysis. This prohibited cancer modeling using parameters other than TCDD blood serum concentration. For a mechanism-based cancer risk estimation, such information would be required. If such information cannot be obtained for the entire cohort, investigators should consider statistically appropriate subcohort sampling as a possible source of information.

Risk estimates could not be calculated for infant or nonadult exposure. This is to some extent due to insufficiencies in study design for risk estimation for the total population and missing information in the reporting of the results. Similarly, it is not possible at present to identify subpopulations that may be at increased risk. Effects of limited but high exposure at an early age have not been investigated under conditions where dose-response analyses can be done. In addition, dose-response data are almost completely missing for human noncancer endpoints. Although the cohorts considered above are large (with a few thousand individuals), given the size of the effects to be expected, the statistical power of some analyses is quite small and larger studies with thorough epidemiological design consideration are required.

8.3.3. Rodent Dose-Response Models: Cancer Endpoints

8.3.3.1. *Animal Cancer Studies for Dose-Response Modeling*

Mathematical modeling can be a powerful tool for understanding and combining information on complex biological phenomena. Modeling of carcinogenicity can be accomplished using simple techniques (Portier et al., 1984) and can be improved by taking the results of an existing mechanism-based model on receptor-based effects of TCDD within the context of a physiologically based pharmacokinetic (PBPK) model (Kohn et al., 1993) and using these results in a detailed multistage model of carcinogenesis (Portier et al., 1996). Both approaches have been attempted. For a mechanism-based approach see Section 8.4.3.2.

Portier et al. (1984) used a simple multistage model of carcinogenesis with up to two mutation stages affected by exposure to model the five tumor types observed to increase in the 2-year feed study of Kociba et al. (1978) (Sprague-Dawley rats) and the eight tumor types observed to increase in the 2-year gavage cancer study conducted by the National Toxicology Program (1982a) (Osborne-Mendel rats and B6C3F$_1$ mice). The findings from this analysis are presented in Table 8-3. The ED_{01}s were calculated based on Portier et al. (1984). Excess risks were then calculated from the ED_{01} using equation (1) in Section 8.2.2. All but one of the estimated ED_{01} values are above the lowest dose used in the experiment (approximately 1 ng/kg/day) and are thus within the experimental range. The exception, liver cancer in female rats from the Kociba study, is very near the lowest dose used in this study. Steady-state body burden calculations were also used to derive doses for comparison across species (see Section 8.2). Absorption was assumed to be 50% for the Kociba et al. (1978) study (feed experiment) and 100% (Rose et al., 1976) for the NTP study (1982a) (gavage experiment). Also presented in Table 8-3 are the shapes of the dose-response curves as determined by Portier et al. (1984).

The predominant shape of the dose-response curve in the experimental region is linear; this does not imply that a nonlinear model such as the quadratic or cubic would not fit these data. In fact, it is unlikely that in any one case, a linear model or a quadratic model could be rejected statistically (Hoel and Portier, 1994). These studies had only three experimental dose groups; hence these shape calculations are not based upon sufficient doses to guarantee a consistent shape estimate; they should be viewed with caution. The body burdens at the ED_{01} values range from a low value of 14 ng/kg based upon the linear model associated with liver tumors in female rats, to as high as 1,190 ng/kg based upon a cubic model associated with thyroid follicular cell adenomas in female rats.

8.3.3.2. *Conclusions From Animal Cancer Dose-Response Modeling*

The animal studies show an increase in cancer incidence in rats and mice at various sites. The ED_{01} estimates of daily intake level obtained from an empirical linear model range from 0.8 to 43 ng/kg body weight/day depending on the tumor site, species, and sex of the animals investigated. These are equivalent to steady-state body burdens of 14 to 1,190 ng/kg body weight. By way of comparison, the ED_{01} estimate obtained from a linear mechanistic model of liver tumor induction in female rats (Section 8.4.3.2) was 0.15 ng/kg body weight/day, equivalent to a steady-state body burden of 2.7 ng/kg body weight (Portier and Kohn, 1996).

8.3.3.3. *Knowledge Gaps in Animal Cancer Dose-Response Modeling*

The dose-response data for cancer in animals following TCDD exposure are limited to three exposure groups. Although nonlinear models could be applied to these data (Portier et al., 1994), the estimates of the shape of the dose-response curve should be viewed with caution. Studies with more dose groups and sufficient animals per dose group are needed for distinguishing between different shapes of dose-response curves. Furthermore, mechanism-based cancer modeling could be improved if physiological, biochemical, and tissue response information were obtained from the same experiment.

Hepatocellular carcinomas have been the main focus for much of the research on the carcinogenicity of TCDD, although there has been increased tumor incidence in other organs. With respect to extrapolation to humans, the investigation of lung and thyroid cancer should be studied further. Animal cancer studies using other PCDDs, PCDFs, PCBs and complex mixtures reflecting human exposure patterns have rarely been done and may add information to the problem of complex human exposure.

8.3.4. Rodent Dose-Response Models: Noncancer Endpoints

8.3.4.1. *Methodology*

Risk assessments for noncancer endpoints traditionally have not used endpoint-specific mathematical models. Instead they have relied on safety assessment involving determination of a dose that is likely to be without risk, taking both data and model uncertainties into account. Although many of the same biochemical effects involved in carcinogenesis are also involved in many other toxicities, biologically based mathematical models for noncancer endpoints are not as developed as are the cancer risk models. In the interim, we will use a simple empirical modeling scheme to estimate effective doses and to discuss dose-response curve shape for the biological and toxicological effects induced by TCDD. The models and the statistical details follow similar analyses done by McGrath et al. (1995) and Murrell et al. (1998). In brief, two different models

were applied to the continuous data depending upon the number of dose groups used and the overall quality of the data. First choice was to use a Hill model of the form

$$R(d) = b + \frac{vd^n}{k^n + d^n} \quad (4)$$

where *R(d)* is the response at dose *d*, and *b*, *v*, *k*, and n are model parameters to be estimated from the data. The parameters each describe a different aspect of the dose-response curve: *b* is the background response, *v* is the maximum attainable response, *k* is the dose yielding half of *v*, and *n* is the Hill coefficient describing the curvature of the dose-response. As the shape of the dose-response curve is critical for risk assessment, it is of interest to consider important classifications based on *n*. When n is near or below 1, risk is predicted to be approximately proportional to dose or climbing more rapidly than proportional. When *n* is much larger than 1 ($n > 1.5$), the dose-response is sigmoidal and has been described as appearing to have a threshold. For these reasons, n will also be referred to as the shape parameter.

In the present exercise, *n* was not allowed to vary below 1, and thus the model as used does not predict supralinearity. Estimates of n were restricted to be greater than 1 to avoid instability. Estimates for the ED_{01} are sensitive to the slope of the dose-response curve evaluated at dose=0, and when $n<1$, this slope becomes infinite. This infinite slope is not biologically realistic and is difficult to tie down accurately to these data. This makes the estimates of the ED_{01} unstable and, worse, makes their lower confidence bounds very unstable. The net effect of this restriction is a possible bias towards higher-than-expected ED_{01} value and a truncation in the distribution of observed shapes. The first effect cannot be avoided, but the second should not be a problem because unrestricted estimates of $n<1$ will yield restricted estimates of $n=1$ and the shape will be classified into a grouping of risk approximately proportional to dose.

The second model used here is the power function:

$$R(d) = b + sd^n \quad (5)$$

where *b* and *n* have similar descriptions and *s*, referred to as the scale parameter, describes the magnitude of the effect per unit of dose. Unlike the Hill model, this model has no fixed maximum and is used in this chapter for data with either no experimentally evident maximal response or with few dose groups. This poses a considerable problem in defining effective doses, and caution should be used in applying effective doses derived from the power function model. Quantal data were modeled using the Weibull model given by

$$R(d) = c + (1 - c)[1 - exp(-ad^k)] \quad (6)$$

where *R(d)* is the probability of response at dose *d*, *c* is the expected response in untreated animals ($0 \leq c \leq 1$), *a* is the magnitude of response per unit dose raised to the k^{th} power ($a \geq 0$), and *k* is the shape parameter ($k \geq 1$). The Weibull model as used in this analysis estimates threshold-like behavior when *k* is large. In addition, *k* was not allowed to be less than 1 to avoid instability in the analysis. The ED_{01} values from quantal data satisfy the excess risk relationship described in equation (1) in Section 8.2.2 where $R(\infty)$ is equal to 1 for quantal endpoints.

The data sets examined in this exercise are found in the published literature. The studies analyzed provided dose-response information on TCDD using at least three dose levels of TCDD and a control. In addition, the mean and an estimate of the variance of the data had to be presented in tabular form in the manuscript. Attempts to estimate the means and variances of data presented in graphical forms proved unreliable, thus publications where the data were presented only in graphs were not included in the analysis. Model fits, calculation of the ED_{01} and ED_{10} and the 95% lower bound on the estimated ED_{01} were carried out using the U.S. Environmental Protection Agency (EPA) Benchmark Dose Software (BMDS) version 1.1b (U.S. EPA, 1999). In some cases, the BMDS software failed to locate a lower confidence bound on the ED_{01}.

The model fits were evaluated with regard to the observed data. The goodness of the model fit was determined as "good" if the model curve included nearly all of the data point means, "marginal" if the model curve was within one standard deviation of the data point means, or "poor" if model fit was not within one standard deviation of the means. There were 242 endpoints for which dose-response analyses could be made (approximately 200 continuous endpoints and approximately 30 quantal effects), obtained from more than 36 published manuscripts (see Appendices). The number of data sets, categorized by species, gender and study type, is shown in Table 8-4. Poor fits were not evaluated further and were not included in the overall assessment of the ED_{01} values.

For the Hill model fits, the Vmax estimates from "good and "marginal" model fits were subjectively evaluated for stability and biological plausibility with regard to the observed data. This evaluation identified some potential problems with some of the Vmax estimates. In some cases the error associated with the Vmax could not be calculated by the BMDS software. In these cases if the Vmax model estimate was similar to the "observed Vmax" (i.e. the difference between the highest dose response level and the control response level) then the Vmax estimate was considered biologically plausible and was used for the calculation of an ED_{01}. Otherwise the "observed Vmax" was used for calculation of the ED_{01}.

In other cases the error associated with the model Vmax estimate was high, indicating a potentially unstable estimate that may not be biologically plausible. The Vmax estimate was considered unstable if the error associated with the Vmax estimate was greater than the Vmax itself.

In these cases an "alternate Vmax" was calculated as 3 standard deviations of the observed control response. If the maximum response associated with the use of this "alternate Vmax" was within 3 standard deviations of the observed highest dose response then this new Vmax value was considered to be biologically plausible and was used for subsequent ED_{01} calculations.

However, if the maximum response was not within 3 standard deviations of the observed highest dose response then this "alternate Vmax" value was considered to not be biologically plausible and was not used. In these cases an "observed Vmax" was determined for use in the ED_{01} calculations. The "observed Vmax" was calculated as the difference between the observed highest dose response and the observed control response.

In all cases where the model estimated Vmax was replaced with a new surrogate Vmax a new ED_{01} was recalculated using this new Vmax. In all cases, the original shape, and ED_{50} parameters were used for calculation of the ED_{01}, i.e. the data were not remodeled using the new assigned Vmax as fixed parameter in the Hill model. Because the data were not remodeled, estimates of the lower confidence interval are not available for these data sets.

There were 284 dose-response data sets found in the peer-reviewed literature that fit the inclusion criteria described above. The Hill, Power or Weibull models were fit to these 284 data sets. Good or marginal fits were attained for 242 of these data sets. The data sets that had poor fits were not included in the synthesis of the modeling results. All fits to the 284 data sets are presented in Appendices I through III.

The analyses of the data are presented as summaries of the endpoint categories in Figure 8-1, Figure 8-2, Figure 8-3, Table 8-5, and Table 8-6. The data are divided into several categories on the basis of exposure regimen and endpoint. Exposure categories are grouped as either single exposures or multiple exposures. For simplicity, effects were categorized as biochemical, hepatic, immune, endocrine, tissue, or toxicity (Table 8-7). Biochemical changes included alterations in mRNA, protein, or enzyme activities. The category of hepatic changes included responses of hepatotoxicity, such as serum enzymes and histological effects. Immune responses included alterations in lymphocyte phenotypes and functional alterations such as altered responses to antigen challenge. Alterations in tissue and body weights were classified as a tissue response. Developmental, reproductive, and tissue toxicities were classified as toxic responses. Finally, there were limited studies on the effects of TCDD on serum thyroid hormone concentrations and alterations in either serum or tissue retinoid concentrations; these studies were categorized as endocrine effects.

Comparison of the ED_{01} between studies can be problematic for several reasons. The effective dose is dependent upon the sensitivity of the endpoint examined and the dosing regimen employed. For example, in studies examining the effects of TCDD following a single exposure, the time after the initial exposure when the determinations were made varied from days to weeks. For

some effects, the differences in the time after the initial exposure probably influence the effective dose. Similarly, in studies employing multiple doses, investigators used a variety of regimens including daily exposure, weekly exposures, and loading/maintenance regimens. These differences in dosing regimens may influence the dose response relationships. In addition, investigators used a variety of exposure routes including dietary, oral gavage, subcutaneous, and intraperitoneal. The different routes and vehicles (diet vs. oil solution) have different absorption rates and percentage absorbed. These differences may result in different tissue concentrations and may influence the dose-response relationships. In order to compare the multiple-dose studies using different routes of exposure, the average daily dose was estimated for each study by calculating the total dose administered to the animal over the course of the study and dividing by the length of the study in days. In addition, for the multiple-dose studies, average steady-state body burden at the ED_{01} was calculated using the equation in Section 8.2.2 and the percentage of dose adsorbed and the half-lives for TCDD in Table 8-1.

In applying a consistent modeling approach across all endpoints, some uncertainty is introduced for those data sets where this approach provides only a marginally adequate fit. In some cases, no trend was apparent below the highest dose examined, thus reducing the confidence that can be placed in accurately estimating the dose associated with a change as small as 1%. In other cases, it appeared that other models could provide a better fit to the data, with a significantly different ED_{01}. For example, sometimes the Hill model gave a dose-response curve with sharp changes in slope, but a Weibull model could have provided a better fit to the data with a smoother curve and a lower ED_{01}. In addition, the ED_{01} and the 95% lower confidence interval (LED_{01}) were sometimes quite far apart (differing by more than tenfold), suggesting that little confidence can be placed in some ED_{01} values as a precise index of toxicity. In such cases, it is useful to look at the LED_{01} as a bound. Whenever the modeling results were problematic for these or other reasons, we noted it and gave less emphasis to those results in our overall synthesis of the data. In this way, the overall conclusions are based on the strongest results.

8.3.4.2. ***Multiple-Dose Studies***

Of 139 endpoints examined from multiple-dose studies, 108 data sets had fits described as good or marginal. Thirteen of the data sets had statistically significant fits designated as poor and 18 data sets did not have statistically significant fits to the models. Data sets with poor fits or non-statistically significant fits were not included in the following analysis. The estimates of the Vmax were unstable in 43 of the 108 data sets with good and marginal fits. Of the 43 data sets with unstable Vmax estimates, five of the modeled Vmax values were accepted as the estimate. The Vmax was set at three standard deviations from controls for 25 of the data sets. For 13 data sets, the Vmax was set as the difference between the response of the highest dose tested with those of the controls.

In the studies examining the effects of TCDD following multiple exposures, the range of the ED_{01} values is highly variable within and across response categories (Figure 8-1). For the multiple dose exposure studies, the ED_{01} values were modeled using the average daily dose from each study. When examined by category, the median values for the ED_{01} for biochemical responses are lower than the median ED_{01} for other types of response by almost an order of magnitude. Biochemical responses have a median ED_{01} of approximately 1 ng/kg/d and hepatic, immune and tissue responses have median ED_{01} values of 10 ng/kg/d or greater. Of the 108 endpoints examined from studies using multiple exposures, ten have ED_{01} values less than 0.1 ng/kg/day. Six of the ten endpoints with an ED_{01} below 0.1 ng/kg/day are markers of immune response. However, the ED_{01} for markers of immune function range over six orders of magnitude, decreasing the confidence of any particular ED_{01} value for this response. In general these ED_{01} values represent dose-response information from female rats and mice, with few studies examining male rats and mice or other species. These knowledge gaps decrease our confidence in making extrapolations between species and gender.

ED_{01}s for single dose exposures were also estimated using body burden as the dose metric (Figure 8-2). Biochemical responses had a median ED_{01} of approximately 13 ng/kg. Hepatic, immune and tissue response had median ED_{01}s greater than 200 ng/kg. Background human exposure to dioxin-like chemicals is approximately 5 ng TEQ/kg. The margin of exposure between the median ED_{01}s for humans is approximately 3 for biochemical effects and approximately 40 for hepatic, immune and tissue responses. Of the 108 data sets for which ED_{01}s were estimated, 42 are less than 50 ng/kg and include responses in the biochemical, endocrine, immune and hepatic categories. There are 11 responses with ED_{01}s of 5 ng/kg or lower. Six of these responses are immune, three are biochemical and one each is endocrine and tissue. These data indicate that a number of the ED_{01}s are at or below present background exposures.

The ED_{10} was also estimated for these data sets and similar trends were observed compared to the ED_{01}. The median ED_{10} for biochemical responses was approximately 200 ng/kg and the

other response categories were 5-10 times higher (Figure 8-3). There were 14 data sets with ED_{10}s less than 50 ng/kg and 9 of these data sets had ED_{10}s that were less than 5 ng/kg. This data suggests that the ED_{10} for a number of endpoints is within an order of magnitude of background exposures. In 44 of the multiple-dose data sets analyzed the ED_{10} was less than 2 times the ED01. In 28 of the data sets the ED_{10} was between 10 and 2 times greater than the ED_{01}.

One measure of the degree of confidence of the ED_{01} estimate is the ratio of the ED_{01} to the lowest dose used in the study from which it was derived (Table 8-5). A ratio of 1 or greater indicates that the ED_{01} is above the lowest dose examined. Ratios between 1 and 0.1 are within one order of magnitude of the lowest dose tested and indicate that the ED_{01} may provide a realistic value. Ratios less than 0.1 indicate that the estimate was more than an order of magnitude below the lowest dose used in the study and should be viewed with caution. Forty-seven of the 108 values had ratios of the ED_{01}/lowest-dose less than 1. However, of these 47 only 37 were less than one order of magnitude below the lowest dose used in the study. Another measure of the stability of the ED_{01} is the ratio of the LED_{01} to the ED_{01} of the 59 data sets for which the LED_{01} was estimated, the median ratio of the LED_{01}/ED_{01} is 0.39. Only 17 of the 59 data sets had an LED_{01} that was an order of magnitude or more less than the ED_{01}.

In general, an estimated shape parameter that is less than 1.5 indicates that the shape of the dose-response curve tends to be linear at low doses, and those with shape parameters greater than 1.5 tend to be threshold-like. Of the 108 endpoints for which an estimate was obtained, 48 had shape parameters less than 1.5, indicating linear dose-response relationships (Table 8-6). Approximately half of the biochemical and half of the tissue responses indicated a linear dose-response relationship. In contrast, only 19% of the immune function responses were linear.

Although there is some consistency of shape within certain categories of these endpoints, in general about half of the responses could be classed as either linear or nonlinear. These observations do not strongly support linearity for TCDD dose-response, nor do they strongly support the existence of thresholds within the observable range.

8.3.4.3. *Single-Dose Studies: Adult Animals*

There were 98 data sets examining the effects of dioxin in adult rats and mice following a single exposure. Good or marginal fits were assigned to 75 of these data sets. The Hill model was used in 58 of these data sets and the Weibull model was applied to 17 of these data sets. The Vmax was considered unstable in 17 out of the 58 data sets with good or marginal fits to the Hill model. The Vmax was set at three standard deviations from control for 5 data sets and the response at the high dose minus the control response was used as the Vmax for 10 data sets. For two of the data sets with unstable Vmax estimates, the modeled estimate was considered acceptable based on the criteria outlined above.

The median ED_{01} is above 1 ng/kg for all endpoints examined (Figure 8-2). Biochemical and immune responses had the lowest median ED_{01} estimates, 207 and 133 ng/kg, respectively. Hepatic and toxic responses gave median ED_{01}s greater than 10,000 ng/kg. Once again there was large variability in the ED_{01}s for a given category. In general the ED_{01}s varied over three orders of magnitude within each category. There were 14 data sets from the immune, tissue and biochemical response categories with ED_{01} values less than 50 ng/kg. The ED_{01} estimates were below the lowest dose tested for 21 of the 74 endpoints for which an estimate was obtained. Of these 21 estimates, the ED_{01} was less than one order of magnitude lower than the lowest dose tested for 13 of the values (Table 8-5). An LED_{01} was estimated for 70 data sets. The median ratio of the LED_{01}/ED_{01} was 0.36 with only 11 out of 70 data sets with ratios less than 0.1.

Estimates of the ED_{10} produced similar trends (figure 8-3). The immune and biochemical response categories had the lowest median ED_{10} values. There are four data sets with ED_{10} values less than 50 ng/kg and all are in the immune response category. There are four response categories that overlap between the single acute studies and the multiple dose studies. The ED_{10}s for the biochemical, hepatic and tissue response categories are higher in the single dose studies than in the multiple dose studies. In contrast, the ED_{10}s in the immune response categories are approximately 4 times less in the single dose studies compared to the multiple dose studies.

In studies examining the effects of dioxin in adult rats and mice following a single exposure, the median ED_{01} is above 1 ng/kg for all endpoints examined Figure 8-2. Biochemical and immune responses had the lowest median ED_{01} estimates, 207 and 133 ng/kg, respectively. Hepatic and toxic responses gave median ED_{01}s greater than 10,000 ng/kg. Once again there was large variability in the ED_{01}s for a given category; in general they varied over three orders of magnitude within each category. The ED_{01} estimates were below the lowest dose tested for 21 of the 74 endpoints for which an estimate was obtained. Of these 21 estimates, the ED_{01} was less than one order of magnitude lower than the lowest dose tested for 13 of the values (Table 8-5).

Following a single exposure to TCDD, 30 of the 74 endpoints examined (40%) had shape parameters less than 1.5, indicating linear dose-response relationships (Table 8-6). There was no consistent pattern in the shape of the dose-response relationships for the biochemical, immune, and tissue response categories. In these categories both linear and threshold-like dose-response relationships were observed. In contrast, all endpoints in the toxicity category exhibited threshold-like dose-response relationships.

8.3.4.4. *Single-Dose Studies: Developmental Studies*

There were 90 data sets classified as developmental studies following a single exposure. The model fits were described as good or marginal for 60 data sets. The Hill model was fit to 55 data sets. Thirty data sets were not included in this analysis because the model fits were either not

statistically significant or were described as poor. The model estimates of the Vmax was considered unstable in 18 out of the 55 data sets with good or marginal fits to the Hill model. In 7 of these data sets, the model estimate of the Vmax was considered acceptable based on the criteria describe above. Vmax was set at 3 standard deviations from controls in 11 of the data sets and for 5 of the data sets Vmax was set as the response at the high dose minus the response in the controls.

Following a single exposure, a number of developmental effects have been examined. These effects have been categorized as biochemical, tissue, or toxic. The majority of the effects examined were considered tissue responses. The range of ED_{01} values was more than five orders of magnitude, and the median values for all response categories were greater than 10 ng/kg, with an overall median of 139 ng/kg (Figure 8-2). The median ED_{01} values for the response categories were lower for developmental effects following a single dose compared to ED_{01} estimates for effects observed in adults after a single dose. The tissue response category was the only category with sufficient studies to compare between the developmental studies and the multiple dose studies in adults. In this case the median ED_{01} for the developmental effects was approximately an order of magnitude less than the median ED_{01} for the multiple dose studies. There were 18 out of the 60 data sets that had ED_{01} values of less than 50 ng/kg and 8 of these were less than 5 ng/kg. ED_{10}s were also estimated for the developmental effects and similar trends were observed. The ED_{10} values for 12 of the developmental data sets was below 50 ng/kg and only one of the data sets had an ED10 less than 5 ng/kg. Decreases in epididymal sperm counts on PND 49 had and ED_{01} of 1.7 ng/kg based on data from Gray et al. (1997).

The ED_{01} values for developmental effects were below the lowest dose tested in 38 out of 60 endpoints for which an estimate was obtained. Of the 28 estimates that were below the experimental range, approximately half (18) were less than an order of magnitude below the lowest dose tested. There were 37 endpoints for which the LED_{01} was estimated. The median ratio of the LED_{01}/ED_{01} was 0.19 and there were 8 endpoints with ratios less than 0.1. The shape parameter for the developmental effects was less than 1.5 (i.e. linear) for only 18 of 60 endpoints analyzed.

The results of the analysis of the single exposure studies had similarities to those of the multiple dose studies. There was a large range of ED_{01} values within response categories which in some instances reached over five orders of magnitude. Similar to the analysis of multiple-dose studies, the biochemical and immune response categories had the lowest ED_{01}s. The median values for all response categories were greater than 10 ng/kg, with an overall median of 139 ng/kg (Figure 8-2).

8.3.4.5. *Summary of the Dose-Response Modeling for Noncancer Endpoints*

The activation of the AhR by TCDD initiates a cascade of events resulting in alterations in growth factors and their receptors, hormones and their receptors, and proteins involved in numerous

cellular functions such as cell cycle regulation and intermediary metabolism (see Chapter 2 for a more detailed discussion of these processes). Many of these biochemical changes, particularly the alterations in growth factors and their receptors, may mediate the toxic effects of TCDD. The role of other biochemical changes, e.g., induction of aldehyde dehydrogenase, is less certain. One can consider the biochemical and toxicological effects of dioxins as a continuum, starting with biochemical changes leading to toxicological events. Hence, understanding the shape of the dose-response relationship for the biochemical effects may provide insight into the shape of the dose-response relationship for toxic responses, particularly in the low-dose region.

Consistent with the hypothesis that the biochemical effects are precursors of the toxic effects is that, in general, the biochemical responses tend to have lower ED_{01} estimates than other types of endpoints examined. However, few of the biochemical changes examined have been directly linked to toxic responses. For example, the induction of CYP1A proteins is perhaps the best-characterized response to TCDD and related chemicals. Despite their known role as modulators of intermediary metabolism for a number of classes of environmental chemicals in both activation and elimination pathways, the direct relevance of these proteins to the toxic effects of TCDD remains uncertain. Induction of CYP1A proteins has been proposed as a dose surrogate for the carcinogenic effects of TCDD (Portier and Kohn, 1996). One of the best examples of biochemical changes leading to toxicities is the TCDD-induced decreases in circulating thyroid hormones. This is likely a result of TCDD-mediated induction in hepatic glucuronosyltransferases (UGTs), which metabolize these hormones and increase their elimination. van Birgelen et al. (1995a) determined total and free plasma thyroxine concentrations and hepatic thyroxine glucuronidation (T_4UGT) in rats exposed to TCDD for 90 days in the diet. The ED_{01} values for total plasma thyroxine, free plasma thyroxine, and T_4UGT are 33, 4.9, and 1.6 ng/kg/day. The increased sensitivity of T_4UGT is consistent with the mechanism by which the plasma concentrations of these hormones are decreased. In female Sprague-Dawley rats exposed biweekly to TCDD for 30 weeks, Sewall et al. (1995) examined the effects of TCDD on UGT mRNA, serum total thyroxine, and serum TSH. All three responses had shape parameters greater than 1.5 and the ED_{01} values were 0.37, 1.3, and 26 ng/kg/day for UGT mRNA, total serum thyroxine, and serum TSH, respectively. Similar to the data of van Birgelen, the induction of UGT is more sensitive than changes in total serum thyroxine, which in turn is more sensitive than are changes in serum TSH. These data indicate that simple biochemical responses have lower ED_{01} values than more complex phenomena such as decreases in thyroxine and alterations in the homeostasis of thyroid hormones.

One concern in the interpretation of the data is whether the study design can affect the ED_{01} or the shape parameters. One example of this is the studies by Diliberto and co-workers. Diliberto et al. (1995) examined both dose-response and time course for CYP1A1-associated hepatic ethoxyresorufin deethylase (EROD) activity at 7, 14, 21, and 35 days after a single exposure to

TCDD. In these studies, the ED_{01} values and the shape parameters increased with time after dosing. The increase most likely stems from the decreasing tissue concentrations of TCDD and the subsequent decreases in enzyme induction from day 7 to day 35. The shape parameter ranged from 1 at 7 days after dosing to 6.5 at the 35-day time point. The ED_{01} increased from 27 ng/kg at 7 days after dosing to 740 ng/kg at the 35-day time point. These data indicate that both the shape parameter and the ED_{01} are sensitive to the study design. Comparisons of studies that determined EROD activity within 7 days of administration of TCDD demonstrate considerable consistency. Four studies examined EROD induction in rats or mice within 7 days of dosing and the ED_{01} values ranged from 16 to 84 ng/kg. The estimated shape parameter is 1 for the Diliberto et al. (1995), Abraham et al. (1988), and Narasimhan et al. (1994) studies and 1.8 for the van Birgelen et al. (1995a) study. It should be noted that two of these studies are in mice and two are in rats, suggesting similar dose-response relationships for enzyme induction between these species.

Another variation in study design that may affect dose-response modeling is dose selection. The dose-response relationship for induction of hepatic EROD activity was modeled for six studies (van Birgelen et al., 1995a,b; DeVito et al., 1994; Johnson et al., 1997; Schrenk et al., 1994; Vogel et al., 1997). Only the data from DeVito et al. (1994) and Johnson et al. (1997) had shape parameters greater than 1.5. While most of the ED_{01} values were approx 1 ng/kg/day, the data of Vogel et al. (1997), resulted in an ED_{01} more than 100-fold lower. Vogel et al. (1997) used a loading/maintenance dosing regimen, and the low dose used was 100 times lower than those of the other studies. The highest dose in the Vogel study was approximately 50-100 times lower than the highest dose used in the other studies. The much lower ED_{01} from this study may be a consequence of the dose pattern and dose selection in this study compared to the other studies.

Another factor to consider is species and strain selection in the studies. The developmental effects of TCDD have generated concern, particularly the developmental reproductive toxicities observed in rats and hamsters (Mably et al., 1992a,c; Gray et al., 1997). These studies demonstrated decreases in epididymal sperm counts on postnatal day 63. However, the shape parameters vary between 1 and 11 and the ED_{01} values vary between 0.65 and 140 ng/kg. The studies used different strains of rats, and perhaps this may account for some of the differences between the data sets. The decreases in the epididymal sperm counts were greater in the Holtzman rat used by Mably et al. (1992a) when compared to the Long Evans rat used by Gray et al. (1997) Overall, the study by Gray et al. (1997) demonstrated smaller effects than the study by Mably et al. (1992a). Also, the data from Gray et al. (1997) demonstrate highly nonlinear responses (shape parameters greater than 2 for all but 3 out of 32 responses examined). In contrast, the effects observed in Mably et al. (1992a) were larger, the shape parameters indicate a more linear dose-response, and the ED_{01} is almost two orders of magnitude lower than those estimated from the data of Gray et al. (1997).

One of the apparent observations of this exercise is the limited number of studies examined compared to the vast literature on the health effects of 2,3,7,8-TCDD. There are thousands of research articles examining health effects of TCDD. Of these articles, less than 50 were analyzed. There are a variety of reasons why only a limited number of articles could be included in this analysis. First, only studies in experimental animals were included, omitting many articles on in vitro studies. Second, only studies providing dose-response data that included a minimum of three dose levels and a control were included. Third, the data had to be presented in tabular form with means, standard deviations or standard error, and the number of samples for which the mean was calculated. It is likely that given the vast number of data sets available, some were inadvertently excluded. However, most of the studies found in the literature did not fit these criteria, either because of inadequate dose-response information or graphical presentation. For some studies that provided adequate dose-response information but presented the data in graphical format, the authors were asked to provide means and standard deviations and kindly did so. One of the conclusions of this exercise is that when preparing data for publication, authors conducting dose-response studies should consider the use of their data and present it in such a way that it is usable in future independent analyses.

Care should be taken in interpreting these analyses. There tends to be a large variation in both the shape parameter and the ED_{01} values for a given endpoint. Most of the studies examined were designed to determine a no-observed-effect-level (NOEL) or lowest-observed-effect-level (LOEL) and, as such, these data contain limited dose-response information. The limited information contributes to the observed variation in the estimates of both the shape parameters and the ED_{01} values. This should not be taken as a critique on the quality of the study designs. In almost all instances, the authors of the studies used analysis of variance as a statistical tool and the studies were designed for such an analysis. In contrast, the present exercise attempts to examine the dose-response relationships using nonlinear regression analysis as a statistical tool. Because of the limited dose-response data available, particular caution should be used when extrapolating to dose levels outside the experimental design. If this situation is to be improved and uncertainties in data interpretation reduced, studies will need to be designed and data produced that are more suitable for nonlinear regression analysis. Second, and perhaps more disappointing, was the frequency of inadequate reporting of the data. Many studies would present a mean and some measure of variance without describing whether the variance was presented as a standard deviation, a standard error of the mean, or some confidence interval. These variables can be adjusted for use in modeling if the proper number of animals/group is provided. However, often the number of animals/group was presented as a range.

Although ED_{01} values are intended as a common measure across studies and endpoints, they must be interpreted in relation to their respective maximal responses. For example, if enzyme

induction varies over a considerably greater range in one strain than another (for example, hepatic EROD induction in the studies by DeVito et al. [1994] compared to that observed in the study of Vogel et al. [1997]), then their respective ED_{01} values will represent different levels of induction. The biological significance of these responses may not be commensurate with their respective ED_{01} values. In addition, comparisons across endpoints must proceed cautiously. A 1% increase in response for decreased body weight may not necessarily be comparable to a 1% excess effect on immune function or enzyme induction.

Several studies have demonstrated that control rats and mice have detectable amounts of TCDD and related chemicals (Vanden Heuvel et al., 1994a; DeVito et al., 1998). The concentrations of these chemicals are at or near the quantification limits. In the present analysis, the background exposures of the control animals were not considered. The inclusion of background exposure levels or tissue concentrations in the dose-response analysis may alter the shape of the dose-response curves and is some cases may possibly increase the ED_{01} estimate and/or the model estimate of the shape parameter. However, it is unlikely that any effect of the estimates would substantially change the observed trends in the estimates or the main conclusions of this dose-response chapter.

An important finding in this analysis is that the biochemical effects tend to have lower ED_{01} values compared to more complex effects such as immunotoxicity or tissue weight loss. This finding is consistent with the hypothesis that the biochemical responses are precursors to the toxic responses of these chemicals. Another difference between the biochemical and toxicological responses is that the biochemical responses tend to have lower shape parameters. Thus, the dose-response relationships for the biochemical responses tend to be linear more often than the toxicological responses. Because of the limited dose-response data available for many of these analyses, caution must be taken when making some of these generalizations. For example, the decrease in thymus weight tends to have estimated shape parameters of 1.

Finally, the present analysis focused on the ED_{01}. This effect level was chosen because it would allow the comparison between the human epidemiological data and the animal data. Typically, the ED_{01}, ED_{05} or ED_{10} is used as the point of departure in risk assessments. Use of either of these alternative risk estimates would result in some differences. Obviously choosing higher effect levels will result in higher dose levels compared to the ED_{01}. Also the estimates of the ED_{10} would most likely be more stable than the estimates of the ED_{01}. However, in the present analysis several data sets had ED_{01}s and ED_{10}s that were less than 50 ng TCDD/kg. Based on a background human exposure at 5 ng TEQ/kg, using either the ED_{01} or ED_{10}s would result in a number of effects with margin of exposures less than an order of magnitude from background human exposures.

8.4. MODE-OF-ACTION-BASED DOSE-RESPONSE MODELING

8.4.1. Introduction

Mode-of-action-based modeling for TCDD encompasses PBPK models for estimating tissue dose and biochemical/tissue response models that describe the consequences of tissue dose. The distinction between tissue dose and response is often maintained in developing mechanism- or mode-of-action-based models. A number of PBPK models for TCDD have been developed. These models have provided insights into key determinants of TCDD disposition in TCDD-treated animals, such as diffusion-limited movement of TCDD between blood and tissue and induction of hepatic binding. PBPK models may be extended to generate predictions for biochemical consequences of the tissue dosimetry of TCDD. The molecular steps leading to observed responses form a causal sequence that describes the mode of action by which pathology is produced. Examples of carcinogenic modes of action include enhanced mutation by direct DNA reactivity, increased cell proliferation related to toxicity or mitogenic stimulation, or diminished apoptosis in a population of altered cells. The predictions of a PBPK model can be used to describe parameters in the mathematical representation of this mode of action. The goal of mode-of-action-based modeling is to express quantitatively the relationships between TCDD exposure, TCDD tissue kinetics, and the biochemical alterations leading to effects on these integrated responses. This section discusses models for dosimetry, biochemical, and tissue responses, and how they ultimately lead to adverse effects of TCDD.

Risk assessments where mechanistic dosimetry models have been used without any attempt to describe the mechanism of tissue response are a viable intermediate stage in the development of mechanism-based risk assessments. This approach to risk assessment also reflects the paucity of mechanistic models of tissue response, relative to models of tissue dosimetry. The more ambitious modeling of the entire exposure-tissue response continuum (Section 8.4.2) carries with it the greater requirement for mechanistic understanding of tissue response. When our understanding of mechanisms of tissue dosimetry and response are different, careful consideration should be given to the sources of uncertainty in the overall modeling effort. The realization that dosimetry and response submodels can contribute unequally to overall model uncertainty can help to guide the choices made in developing the final risk model and the allocation of resources for additional research.

8.4.2. Model Structures and Model Development

8.4.2.1. *PBPK Models*

8.4.2.1.1. ***Issues pertaining to PBPK models***. Tissue dosimetry encompasses the absorption of an administered chemical and its distribution among tissues, metabolism, and elimination from the body (ADME). TCDD dosimetry depends on physicochemical properties of TCDD (e.g., tissue

permeation constants, partition coefficients, kinetic constants, and biochemical parameters) and physiological parameters (e.g., organ volumes and blood flow rates). The mathematical structure that describes the relationship between these factors and ADME constitutes a model for the tissue dosimetry of dioxin. These models describe the pharmacokinetics of TCDD by a series of mass-balance differential equations in which the state variables represent the concentration of TCDD in anatomically distinct regions of the body. These tissue "compartments" are linked by a physiologically realistic pattern of blood perfusion, called a PBPK model. Several research documents discuss the development of PBPK models for general use (Gerlowski and Jain, 1998), and use in risk assessment (Clewell and Anderson, 1985).

PBPK models have been validated in the observable response range for numerous compounds in both animals and humans, making them useful for risk assessment, especially for cross-species extrapolation. In addition, they aid in extrapolation from one chemical to other structurally related chemicals because many of the components of the model are the same or can be deduced for related compounds. The tissue concentrations of several cellular proteins are known to be modified by TCDD, making them useful as dose metrics. A model can be used to predict the concentrations of these proteins as well. If one of these proteins is mechanistically linked to a toxic endpoint, the protein could also serve as a dose metric of toxic effects.

The time course of behavior in each compartment of a PBPK model is defined by an equation containing terms for input and loss of chemical. The specific structure of a PBPK model and the assumptions used to develop the model are encoded in the equations. A careful evaluation of any PBPK model must involve the adequacy of its fit to the data, the relationship of its structure to the underlying biology, and the mathematical details linking the two. Several PBPK models have been developed for TCDD and related chemicals (see Part II. Chapter 1 for a brief overview). Models have also been developed for polychlorinated biphenyls (Lutz et al., 1984; Matthews and Dedrick, 1984; Parham et al., 1997, 1998) and polychlorinated dibenzofurans in several species (King et al., 1983), including humans.

There are four levels of complexity in PBPK models for the effects of TCDD. First is the traditional PBPK model by Leung et al. (1988) with the added complexity of protein binding to CYP1A2 in the liver. The next level of complexity are the models by Andersen et al. (1993) and Wang et al. (1997) using diffusion-limited modeling and protein induction by interaction of DNA binding sites. The third level is represented by the model of Kohn et al. (1993) with extensive hepatic biochemistry and the model for zonal induction of cytochromes P-450 (Andersen et al., 1997b). Finally, there are the models that include coordination of responses in multiple organs (Kohn et al., 1996) for hormonal interactions, and Roth et al. (1994) with its detailed description of gastrointestinal uptake, lipoprotein transport, and mobilization of fat (Figure 8-4).

8.4.2.1.2. ***Initial attempts to include protein induction***. Leung et al. (1988) developed a PBPK model for TCDD disposition in mice, for Sprague-Dawley rats (Leung et al., 1990a) and for 2-iodo-3,7,8-trichlorodi-benzo-*p*-dioxin in mice (Leung et al., 1990b). These initial models considered tissue partitioning, protein binding in blood, specific binding of TCDD to inducible hepatic proteins, binding of TCDD to the AhR, and activation of gene transcription by the Ah-TCDD complex. Subsequent PBPK models have refined the representations of these processes as more biological information became available.

This early PBPK model (Leung et al., 1990a) contained five flow-limited tissue compartments, including blood, liver, fat, and slowly perfused and richly perfused tissues. TCDD binding in blood was described by an effective equilibrium between the bound and free TCDD given by a constant ratio. TCDD also binds to two liver proteins: one corresponding to the high-affinity, low-capacity AhR and the other to a lower affinity, higher capacity microsomal protein inducible by TCDD, now known to be CYP1A2. The predictions from this modeling exercise prompted a series of experiments to examine the nature of these binding proteins in mice (Poland et al., 1989a,b). In the PBPK model (Leung et al., 1990a), the concentration of the AhR is held constant and the concentration of CYP1A2 is calculated using a Michaelis–Menten equation for the instantaneous extent of induction as a function of hepatic TCDD concentration.

In various studies, TCDD has been administered by intravenous, intraperitoneal, or subcutaneous injection; feeding; or by oral intubation (gavage). In the PBPK modeling framework, intravenous injection can be represented by setting the initial amount in the blood compartment equal to the injected dose. Oral intubation and subcutaneous injection were modeled as first-order uptake from the site of administration, with TCDD appearing in the liver blood after oral administration and in the mixed venous blood after subcutaneous injection. Feeding was modeled (Leung et al., 1988, 1990a) as a constant input rate on days that TCDD was included in the diet. With 2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin, the estimated rate constant for oral absorption was considerably larger in TCDD-induced than in naive animals. The physiological basis of this change is unknown, but it may be a consequence of increased hepatic lipid synthesis and elevated plasma lipid following TCDD treatment (Gorski and Rozman, 1987).

The descriptions of the routes of uptake are clearly not defined in specific physiological terms, and this lack of detail represents a common limitation in all of the PBPK models for TCDD. These descriptions of the oral, subcutaneous, and skin routes are simply empirical attempts to estimate an overall rate of uptake of TCDD into the PBPK model. This is one area in which additional research could improve dose-response modeling for TCDD.

Partition coefficients for TCDD were estimated from measurements of tissue and blood concentrations in exposed animals. Leung et al. (1990a) also modeled metabolic clearance as a first-order process with the rate constant scaled inversely with $(\text{body weight})^{0.3}$. In the mouse with

the iodo-derivative, TCDD pretreatment at maximally inducible levels caused a threefold increase in the rate of metabolism, probably through loss of iodine. However, Olson et al. (1994) found that pretreatment of rats with 5 µg TCDD/kg body weight increased metabolism in isolated hepatocytes only when at least 1 mM TCDD was present in the medium. Induction of its own metabolism by TCDD appears to be a minor high-dose effect.

Leung et al. (1990a) kept all physiological parameters (e.g., organ perfusion rates and tissue volumes) constant over the lifetime of the animal. Subsequent PBPK models have included growth of the animals over time and changes in organ size due to growth and toxicity. TCDD and TCDD analogues have dose- and time-dependent kinetics in both rodents (Kociba et al., 1976, 1978; Rose et al., 1976; Abraham et al., 1978; Poland et al., 1989b; Tritscher et al., 1992) and humans (Carrier and Brodeur, 1991; Pirkle et al., 1989). As the exposure level increases in single and short-duration exposures, the proportion of total dose found in the liver increases. This initial model served as the basis of later models as new data were published on dose and time dependence of TCDD tissue concentrations (Abraham et al., 1988 Tritscher et al. 1992).

In discussing the components that form the basis for a mechanistic model for TCDD, we focus on aspects of the model that could lead to nonproportional response for low environmental doses (nonlinear behavior). The model of Leung et al. (1990a) predicted slight nonlinearity between administered dose and tissue concentration in the experimental dose range. In the low-dose range, the model predicts a linear relationship between dose and concentration. The authors argue, however, that tissue dose alone should not be used for risk assessment for TCDD because of the large species specificity in the ability of TCDD to elicit some toxic responses. They suggest instead that use of time-weighted receptor occupancy linked with a two-stage model of carcinogenesis is a better approach to risk estimation. The time-weighted receptor occupancy predictions derived from the Leung et al. (1990a) model are linear in the low-dose region, reaching saturation in the range of high doses used to assess the toxicity of TCDD. This discussion represented one of the early attempts to define a dose metric for the carcinogenic action of TCDD.

8.4.2.1.3. ***Refinements with DNA binding of Ah-TCDD complexes***. Andersen et al. (1993a) modified the model of Leung et al. (1990a) to include Hill kinetics in the induction of CYP1A1 and CYP1A2 and to treat tissue uptake of TCDD as diffusion limited instead of blood flow limited as done by Leung et al. (1990a). Diffusion limitation was incorporated by replacing the blood flow term in the expression for tissue uptake of TCDD by a permeability factor equal to the diffusion coefficient times the cell membrane surface area accessible to the chemical. Andersen et al. (1993a) assumed this quantity to be proportional to the tissue perfusion rate, with a constant of proportionality less than 1. In the model used by Andersen et al. (1993a) each tissue has two subcompartments, the tissue blood compartment and the tissue itself.

This revised model eliminated allometric scaling of the metabolic rate constant used in the model of Leung et al. Instead, it treats TCDD as inducing its own metabolism, with a maximal increase of 100%. The increase is a hyperbolic function similar to that for binding of TCDD to the AhR. This induction led to an improved fit to observed liver and fat TCDD concentrations. Subsequent research (Olson et al., 1994; McKinley et al., 1993) revealed no induction of metabolism of TCDD suggesting that this is likely to be a minor high-dose effect.

Most of the physiological constants and many of the pharmacological and biochemical constants used by Leung et al. (1990a) were modified for the Andersen et al. (1993a) model because Wistar rats instead of Sprague-Dawley rats were used in the experiments they simulated. The parameters in the model were optimized to reproduce tissue distribution and CYP1A1-dependent enzyme activity in a study by Abraham et al. (1988) and liver and fat concentrations in a study by Krowke et al. (1998). For the longer exposure regimens and observation periods, changes in total body weight and the proportion of weight as fat compartment volume were included via piecewise constant values (changes occurred at 840 hours and 1,340 hours).

Induction of CYP1A1 proteins in the model was modeled by including interaction between the Ah-TCDD complex and presumed DNA binding sites. The concentrations of CYP1A2 and CYP 1A1 were modeled as a function of hepatic AhR–TCDD concentration. Although the revised model represented the kinetics with a Hill equation, the Hill exponent was 1, similar to the Michaelis–Menten model used by Portier et al. (1993) for the independent induction of CYP1A2. The Hill exponent for CYP1A2 (2.3) introduced marked sigmoidicity in the computed dose-response of this protein.

Andersen et al. (1993a) noted that the liver/fat concentration ratio changes with dose because of an increase in the amount of microsomal TCDD-binding protein (CYP1A2) in the liver. For high doses in chronic exposure studies, this introduces a nonlinearity into the concentration of TCDD in the liver. In the low-dose region, because the Hill coefficients for CYP1A2 concentration and for TCDD binding to the AhR are equal to 1, the liver TCDD concentration as a function of dose is still effectively linear. In the observable response range, there is a slight nonlinearity in the concentration of TCDD in the liver as a function of dose under chronic exposure (Andersen et al., 1993a). The dose-dependent changes in liver/fat ratio are consistent with animal data and limited human data (Carrier and Brodeur, 1991), and are a necessary part of the modeling for TCDD.

Andersen et al. (1993b) provided a simple comparison of the induction of CYP1A1 and CYP1A2, the concentration of free TCDD in the liver, and the total concentration of TCDD in the liver to tumor incidence (Kociba et al., 1976) and to the volume of altered hepatic foci (Pitot et al., 1987). The computed cumulative hepatic concentrations of TCDD and induced proteins were used as summary metrics of internal exposure. Tumor promotion correlated more closely with predicted induction of CYP1A1 than with the other dose metrics. The choice of an independent induction

model for CYP1A1 and a Hill coefficient greater than 1 leads to nonlinear low-dose behavior. These correlations were not based on any mechanistic considerations of the role of induction of CYP1A1 in hepatocarcinogenesis.

8.4.2.1.4. ***Improving the physiological characteristics of the TCDD models***. Kohn et al. (1993) modeled the binding of TCDD to the AhR using explicit rate constants for association and dissociation of ligand instead of dissociation equilibrium constants. However, large unidirectional specific rates were used, leading to a predicted TCDD–AhR complex concentration similar to that computed by Leung et al. (1990a) and Andersen et al. (1993a). Other binding reactions in the model were handled similarly (e.g., TCDD binding to CYP1A2 and TCDD binding to blood protein). This approach avoids having to solve for the concentration of TCDD in the liver using the mass conservation relationship described in Leung et al. (1990a) as mass balance is automatically achieved. The physiology described in the Kohn et al. (1993) model is dependent on the body weight of the animal. Body weighs as a function of dose and age were recorded by Tritscher et al. (1992) and directly incorporated into the model by cubic spline interpolation among the measured values. Tissue volumes and flows were calculated by allometric formulas based on work by Delp et al. (1991). To allow the model to fit data at both low and high doses (Tritscher et al., 1992), this model includes loss of TCDD from the liver by lysis of dead cells, where the rate of cell death was assumed to increase as a hyperbolic function of the cumulative amount of unbound hepatic TCDD. This assumption is based on the observation of a dose-response for cytotoxicity in livers of TCDD-treated rats (Maronpot et al., 1993) and is consistent with observed tissue burdens of TCDD. No information regarding the rate of TCDD release from lysed cells is available; therefore, this feature of the Kohn et al. (1993) model predicts a net contribution of TCDD clearance by TCDD-induced cell death.

A further extension of this model, incorporating effects on thyroid hormones (Kohn et al., 1996), included tissue blood compartments similar to those used by Andersen et al. (1993a). Blood was distributed among these compartments and a compartment for the major blood vessels, instead of supplementing a generalized blood compartment with the tissue blood. The GI tract was separated from the rapidly perfused tissues compartment to permit a more realistic representation of uptake of TCDD and perfusion of the liver. The allometrically scaled metabolic rate constant used in the Kohn et al. (1993) model was replaced by a Hill rate law, and parameters were estimated to reproduce the kinetic data of Abraham et al. (1988) and the dose-response data of Tritscher et al. (1992).

Transthyretin (also known as prealbumin) can bind hydroxylated PCDDs, (McKinney et al., 1985) and single doses of TCDD can cause prolonged decrease in this protein (Albro et al., 1978). A dose-dependent decrease was included in the model and the algebraic equation for blood binding

was replaced by a differential equation. The revised model, incorporating blood binding, correctly predicted blood TCDD data not used in constructing the model. Ignoring production of binding protein led to serious underestimation of the low-dose data, and ignoring inhibition led to overestimation of the high-dose data. This revised model also differed from the earlier version in its treatment of loss of TCDD from the liver consequent to cytotoxicity. Instead of simply disappearing from the model, TCDD from lysed cells was assumed to pass via the bile into the gut, where it was reabsorbed and redistributed to tissues. This model also explicitly accounted for background exposures of TCDD equivalents in the feed, as observed by Vanden Heuvel et al. (1994a).

The above models have been applied in developing dose metrics for biochemical and tissue-response models. They do not necessarily include every aspect of the distribution of TCDD within the mammalian organism. The following two efforts expand on issues related to TCDD distribution. However, at this time they have not been included in the dose-response models and are unlikely to dramatically change estimates of dose metrics.

8.4.2.1.5. ***Lipid metabolism and sequestration in blood***. The above PBPK models empirically represent sequestration of TCDD in blood without reference to the nature of the pools of TCDD in the blood compartment. Animals exposed to high doses of TCDD and related compounds exhibit alterations in lipid metabolism characterized by mobilization of fat stores and resulting in wasting, hyperlipidemia, and fatty liver. Roth et al. (1993, 1994) constructed a PBPK model of the distribution of TCDD in the rat over a 16-day period following an oral dose. The model did not include tissue blood compartments but did consider diffusion limitation in uptake by multiplying tissue perfusion rates by a fractional extraction, mathematically identical to the formulations of Andersen et al. (1993a) and Kohn et al. (1996). A unique feature of this model was the division of the GI tract into five subcompartments—stomach, duodenum, jejunum, cecum, and colon—with sequential passage of ingested material. The model also separates the rapidly perfused tissues compartment into its constitutive organs and separates white and brown adipose tissue because of their different perfusion rates and differences in ability to mobilize lipid stores. The model included an earlier submodel of fatty acid metabolism in liver and adipose tissues, triglyceride transport via lipoprotein particles in blood plasma, and uptake of lipoprotein by liver and fat (Roth et al., 1994). Regulation of food consumption and lipolysis in white adipose tissue were assumed to be regulated by a cytosolic receptor that binds TCDD.

The model included the possibility for loss of body weight, muscle mass, and fat weight and hypertrophy of the liver subsequent to TCDD administration. It matched data for the initial increases and subsequent declines of TCDD in liver and brown and white fat. Fecal and urinary excretion data also were reproduced. The model included induction of CYP1A2 binding sites for

TCDD. The measured concentration of TCDD in white adipose tissue shows a paradoxical increase at 16 days postdosing despite the fact that TCDD was being cleared from the body. The model of Roth et al. (1994) failed to reproduce this effect, but the concentration in the lipid portion of the tissue did increase because the mass of lipid was decreasing in highly exposed animals. Roth et al. suggested that barriers to uptake and efflux of TCDD may not be symmetrical.

Roth et al. (1994) cited evidence that TCDD is absorbed from the gut, dissolved in dietary fat, carried into the bloodstream by chylomicrons, and secreted into the gut lumen from the intestinal mucosa. There does not appear to be a significant first-pass extraction of these unprocessed lipoprotein particles by the liver. Several tissues (e.g., heart, spleen, and fat) have high levels of receptors for such very-low-density lipoprotein vesicles. So TCDD transport may be regulated by endocytosis of these particles and not be under equilibrium control, as has been assumed in all other pharmacokinetic models. Such a process may reflect the mechanistic origin of diffusion-limitation in TCDD tissue uptake. Further research may be required to resolve this point. Another feature of the Roth et al. (1994) model that suggests additional research is the assumption that white adipose tissue contains a cytosolic TCDD receptor (adipose tissue does express the AhR) which mediates effects on lipid metabolism.

8.4.2.1.6. ***Diffusion limitations in multiple tissues***. Assessment of diffusion limitation in tissue uptake has been hampered by a lack of data at short times after dosing with TCDD. Wang et al. (1997) obtained time-course data for TCDD in blood, several tissues, and the remaining carcass following a single oral dose. They fit an eight-compartment (blood, lung, liver, kidney, spleen, fat, skin, carcass) PBPK model to these data, estimating the values of gut absorption rate, tissue permeability, partition coefficients, AhR concentrations, and CYP1A2 induction parameters by an ad hoc method (no formal optimization). The terminal TCDD half-lives in liver and kidney were assumed to reflect metabolism and were used to calculate an effective first-order rate constant. Time courses in highly vascularized tissues (lung, spleen) could be fit with flow-limited kinetics, but diffusion restriction was required for other tissues, especially kidney. The model by Wang et al. was also used to predict induction of CYP1A1 and CYP1A2 protein in liver and CYP1A1 and CYP1A2 enzyme activity in liver, kidney, lung, and skin (Santostefano et al., 1998). This model has recently been shown to predict the TCDD tissue concentrations from a study by Krowke and coworkers using a loading dose/maintenance dose exposure regimen (Wang et al., 2000). However, it was not demonstrated that the model could reproduce responses to chronic exposure to TCDD.

8.4.2.1.7. ***Modeling of dose-dependent tissue disposition in humans***. Carrier et al. developed a simple empirical model to account for dose-dependent hepatic sequestration of dibenzofurans and other TCDD-like compounds (Carrier et al., 1995a,b). This description had two primary

parameters: a maximum proportion sequestration of body burden in the liver (F_{max}) and a half-saturation constant (K_d)(in units of µg TEQ/kg) for enhanced sequestration with increasing dose. These two parameters were estimated by fitting the model to data on the dose-dependent sequestration in the liver presumed to occur in the livers from human poisoning incidents in Japan and China. The model was also used to derive similar empirical constants from the rat data (Abraham et al., 1988). These two fitting parameters do not contain specific information about the biology of TCDD and related compounds. A PBPK model for TCDD was used recently to infer the relationship between specific biological factors and these two empirical parameters (Evans and Anderson, 2000). With sensitivity analyses, the half saturation constant (K_d) was found to be related to characteristics of the binding of TCDD to the AhR and the AhR-TCDD complex binding to dioxin response elements on DNA. In contrast, the maximum proportion in liver is determined by fat:blood partition coefficients and binding parameters for the interaction of CYP1A2 with TCDD. The composite parameters of Carrier's models (1995a,b) have no obvious relationship to specific biological processes.

In principle, it is possible to convert a PBPK model of disposition of TCDD in a laboratory rodent into one for a human by substituting human parameter values for rodent values. (Andersen et al., 1997c). Although values for anatomical and physiological parameters are available for humans, the biochemical parameters (e.g., TCDD metabolism, binding to the AhR and CYP1A2, and induction of the various proteins cited above) are generally not available for humans. Parameters for protein binding (K_d and basal B_{max}) could be determined in vitro from samples of human tissues obtained either postmortem or from surgical patients, but estimating parameters for induction of proteins would require tissue samples from living individuals exposed to dioxin. Alternatives to measuring human parameter values include allometric scaling of rodent values by the 2/3 or 3/4 power of body weight. This tactic is suspect, as species differences in expression of proteins do not follow a simple pattern for all proteins.

8.4.2.2. *Biochemical, Tissue, and Endocrine Response Models*

The next step after the modeling of the disposition of TCDD within the body is the modeling of effects of TCDD on biological responses that are plausibly linked with activation of the AhR.

8.4.2.2.1. ***Generic receptor-mediated response models***. Looking at one aspect of modeling of TCDD's effects, Portier et al. (1993) examined the relationship between tissue concentration and the response of three liver proteins by TCDD in intact female Sprague-Dawley rats. The effects studied included the induction of two hepatic cytochrome P-450 isozymes, CYP1A1 and CYP1A2, and the reduction in maximal binding of EGF to its receptor in the hepatic plasma membrane.

Portier et al. (1993) modeled the rate-limiting step in the induction of CYP1A1 and CYP1A2 following exposure to TCDD using a Hill equation. Hill equations are commonly used for modeling ligand-receptor binding and enzymatic kinetics data. Consequently, these models could be applied to other receptor-mediated effects and are not specific to TCDD and the AhR. The Hill equation allows for both linear and nonlinear response below the maximal induction range. A complete discussion of Hill kinetics and other models for ligand-receptor binding is given by Boeynaems and Dumont (1980). Examples of the use of Hill kinetics for ligand-receptor binding include the muscarinic acetylcholine receptors (Hulme et al., 1981), nicotinic acetylcholine receptors, opiate receptors (Blume, 1981), the AhR (Gasiewicz and Rucci, 1984), estrogen receptors (Notides et al., 1985), and glucocorticoid receptors (Sunahara et al., 1989). The Hill model can be thought of as a very general kinetic model that reduces to hyperbolic kinetics when the Hill exponent is 1. Portier et al. (1993) also modeled the reduction in maximal binding to the EGF receptor with Hill kinetics, assuming that TCDD reduces expression of the receptor protein from the rate observed in control animals. For all EGFR, CYP1A1, and CYP1A2, proteolysis was assumed to follow Michaelis–Menten kinetics. The proposed models fit the data in the observable response range. The major purpose of this paper by Portier et al. was to emphasize the importance of the mechanism of basal (i.e., uninduced) expression on the curve shape of tissue concentration of protein vs. dose of TCDD. For each protein, they considered two separate models of steady-state protein production.

In the first model, the additional expression of protein induced by TCDD is independent of the basal-level expression. In their second model, basal expression of these proteins is mediated by a ligand of endogenous or dietary origin that competes with TCDD for binding sites on the AhR. Using these simple models, Portier et al. (1993) see virtually no difference in predicted protein concentrations between the independent and additive models in the observable response range, even estimating almost equal Hill coefficients in the two models for all three proteins. In the low-dose range where risk extrapolation would occur, the models differed depending on the value of the Hill coefficient. An estimated Hill exponent exceeding 1 yielded a concave upwards dose-response curve, especially for the independent model. This behavior implies diminished increases in responses at very low doses followed by an accelerated response as the dose increases. For CYP1A2, the Hill exponent was estimated to be about 0.5. When the estimated Hill exponent is less than 1, the dose-response curve was convex upwards, indicating greater than linear increases in response at low doses. Finally, for the EGF receptor, the Hill exponent was approximately 1, in which case the two models are identical.

The additive model is expected to exhibit low-dose linearity because each additional molecule of TCDD adds more ligand to the pool available for binding and, under subsaturating conditions, proportionally increases the concentration of protein. Similar observations have been

made with regard to statistical (Hoel, 1980) and mechanistic (Portier, 1987) models for tumor incidence. Thus, even though these two basic models show almost identical response in the observable response region, their low-dose behavior is remarkably different. If either CYP1A1 or CYP1A2 levels had been used as dose surrogates for low-dose risk estimation, the choice of the independent or additive model would yield differences of several orders of magnitude in the risk estimates for humans. Using CYP1A1 as a dose surrogate, the independent model would predict much lower risk estimates than the additive model. For CYP1A2, the opposite occurs. For EGF receptor, there would be no difference.

8.4.2.2.2. ***Specific biochemical responses to TCDD***. Kohn et al. (1993) have provided an extensive model of the biochemistry of TCDD in the liver to explain TCDD-mediated alterations in hepatic proteins in the rat, specifically considering CYP1A1, CYP1A2, and the Ah, EGF, and estrogen receptors over a wide dose range. The model describes the distribution of TCDD to the various tissues, accounting for both time and dose effects observed by other researchers. A description of the PBPK portion of this model is described above. Earlier PBPK models (Andersen et al., 1993a, Leung et al., 1990a) relied on several single-dose data sets (Rose et al., 1976; Abraham et al., 1988) and were validated against dosimetry results from longer term subchronic and chronic dosing regimens (Kociba et al., 1976; Krowke et al., 1989). These and other studies (Tritscher et al., 1992; Sewall et al., 1993) were used to model the pharmacokinetics and induction of gene products in female Sprague-Dawley rats (Kohn et al., 1993). Among the data reported were concentrations of TCDD in blood and liver, concentrations of hepatic CYP1A1 and CYP1A2, and EGF receptor binding capacity in the hepatocyte plasma membrane. The tissue dosimetry for the model (Kohn et al., 1993) was validated against single-dose and chronic dosing regimen experimental data not used in estimation of model parameters.

In the biochemical effects portion of the model the AhR-TCDD complex upregulates four proteins: CYP1A1, CYP1A2, the AhR, and an EGF-like peptide (treated nominally as transforming growth factor-alpha, TGF-alpha). The induction of an EGF-like peptide is deduced from observations on human keratinocytes (Choi et al., 1991; Gaido et al., 1992) and is quantified on the basis of a presumed interaction with the EGF receptor, resulting in a downregulation and internalization of the EGF receptor. However, TCDD-mediated induction of TGF-alpha or of other EGF-like peptides has not been demonstrated in liver. For all four proteins, synthesis is defined explicitly as a function of occupied AhR concentration. Constitutive rates of expression for CYP1A2, AhR, and EGF receptor are substantial and were assumed independent of the induced expression. The Hill coefficients for the induction of these proteins were estimated to be 1.0, indicating low dose linearity in this response irrespective of the mechanism of basal expression.

Estimated ED_{01} values for TCDD-regulated responses predicted from the dose-response model is shown in Table 8-8.

The model included a background of dioxin-like AhR agonists, which compete with TCDD for binding to the receptor. Induction of CYP1A1 was assumed to be based on additive induction because this enzyme is poorly expressed in the absence of an inducer and expression in control animals is likely due to the background exposure. Again, the Hill exponent was estimated to be 1, leading to low-dose linearity under either additive or independent assumptions. This model predicts that the induction of all gene products appears to be a hyperbolic function of dose without any apparent cooperativity. The discrepancy in the estimates of the Hill exponents between this model and the other models discussed (Andersen et al., 1993a,b; Portier et al., 1993; Kedderis et al., 1993) is probably related to the inclusion only in the Kohn et al. (1993) model of induction of the AhR. The effects of TCDD on the AhR concentration are uncertain. In acute studies, the AhR is decreased following TCDD exposure (Pollenz et al., 1998), whereas in subchronic studies, there is some evidence that the AhR is increased (Sloop and Lucier, 1987). Further studies are required to better understand the regulation of the AhR following TCDD exposure.

The AhR-TCDD complex is assumed to downregulate the EGF receptor in the Kohn et al. (1993) model. It was assumed that the estrogen receptor-estrogen complex synergistically reacts with the AhR-TCDD complex to transcriptionally activate gene(s) that regulate synthesis of an EGF-like peptide. This term was introduced to partially account for the observation of reduced TCDD tumor-promoting potency in ovariectomized females as compared to intact female rats (Lucier et al., 1991). This mechanism of TCDD regulation of these proteins, although supported by some data (Sunahara et al., 1989; Clark et al., 1991), is speculative.

Vanden Heuvel et al. (1994b) provided data on the production of CYP1A1 mRNA and protein following a single oral dose of TCDD. These observations were used to extend the Kohn et al. model and resulted in a model that predicted two critical DNA binding sites for the liganded AhR with different affinities (Vanden Heuvel et al., 1994; Kohn et al., 1994). Both sites had to be occupied in order to activate transcription. This rate equation led to a sigmoidal dose-response curve for the message. Protein synthesis on the mRNA template was modeled by a Hill equation. The optimal Hill exponent was less than 1 and the computed overall dose-response was hyperbolic, as in the Kohn et al. model. This result suggests that the supralinear response of protein to mRNA production compensates for the sublinear response of the message to AhR-TCDD complex formation. It is possible that this reflects the greater sensitivity of the RT-PCR method to detect CYP1A1 mRNA than measurement of CYP1A1 protein. Within this context it is of note that there are more than two DREs within the human CYP1A1 promoter region that may be occupied (Kress et al., 1998).

8.4.2.2.3. ***Tissue response models: zonal induction model***. The mechanistic model of Kohn et al. treats the TCDD-treated liver as a single homogeneous unit. With regard to the induction of cytochromes P-450 in the liver, Tritscher et al. (1992) used antibody staining techniques, showing that the induction of CYP1A1 and CYP1A2 by TCDD in the liver exhibits a regiospecific pattern of induction characterized by increased areas of staining around the central vein of the liver lobule. The size of the induced region in the centrilobular region increased with increasing dose of TCDD. This sharp demarcation in observed induction within hepatocytes could be due to an insensitivity in detection of low levels of CYP proteins in the cell using immunohistochemical techniques: alternatively, it may indicate differences in the sensitivity of hepatocytes to TCDD across the liver. In an attempt to model this regiospecific pattern of induction, Andersen et al. assumed that the observed sharp demarcation in CYP1A expression between induced and noninduced regions indicated that individual hepatocytes were either fully induced or noninduced (Anderson et al., 1997a,b). In this model the liver lobular structure was divided the into five concentric zones with a threefold difference between adjacent zones, in the affinity of DREs for the liganded AhR. The model also further used Hill kinetics for induction, with a Hill exponent of 4. The model reproduced the qualitative features of expanding zonal induction and, with parameters selected to yield a fit to time-course data (Abraham et al., 1988) and CYP1A1 mRNA data (Vanden Heuvel et al., 1994), produced a fit to P-450 data comparable to that obtained with the homogeneous liver model of Kohn et al. (1993). The mRNA data were fitted without proposing multiple DRE binding sites for transcriptional control of message. However, the low-dose extrapolated responses predicted by the regional induction model exhibited greater low-dose sublinearity than a comparable homogeneous liver model. The model predicted an 81-fold difference in AhR-TCDD binding between periportal and centrilobular zones and utilized steep Hill kinetics; these two issues drive the low-dose nonlinearity of this model and are important areas for further research.

8.4.2.2.4. ***Endocrine models: thyroid hormones.*** In addition to models of whole-tissue responses such as that seen in the liver, attempts have also been made to model endocrine effects that encompass changes that may occur in multiple tissues. This is demonstrated in the thyroid hormone model of Kohn et al. (1994). TCDD induces thyroid tumors in male rats and female mice at lower doses than those that induce liver tumors in female rats (NTP, 1982a). Sewall et al. (1995) found increased circulating thyrotropin (TSH) and thyroid hypertrophy and hyperplasia in TCDD-treated rats, suggesting that thyroid tumors may be a consequence of chronically elevated serum TSH (Hill et al., 1989). Because this may be a sensitive endpoint for TCDD carcinogenesis, the Kohn et al. (1993) model was extended (Kohn et al., 1996) to include effects of TCDD on thyroid hormones.

The extended model added compartments for tissues involved in the production (pituitary and thyroid glands) and storage (e.g., kidney, brown fat) of thyroid hormones as well as equations

for secretion and metabolism of the hormones. It reproduced the data used in the original model, blood levels of thyroid hormones and TSH (Sewall et al., 1995), and mRNA (vanden Heuvel et al., 1994b) for the thyroxine metabolizing enzyme UDP-glucuronosyl-transferase-1*6 (UDPGT). It also reproduced experimental data for induction of this enzyme that were not used in the construction of the extended model. In the model, induction of UDPGT by TCDD and subsequent endocrine changes in thyroid hormone homeostasis can lead to chronically elevated serum TSH. This may be related to increased thyroid cancer risk. The estimated dose-response relationships were hyperbolic in the experimental range, supporting a linear dose-response at lower doses.

8.4.2.2.5. ***Dose-response behavior of biochemical/tissue dose-response models*****.** The models of Kohn et al. (1993, 1996) are based on the concept that tissue-level responses are emergent properties that arise from the accumulated molecular effects of exposure to TCDD. Thus, the models were constructed in a bottom-up fashion starting from these more elementary steps, e.g., binding to the AhR, transcriptional activation, translation of mRNA, and the enzymatic functions of the induced proteins. The calculated responses that can serve as dose metrics include altered expression of CYP1A1, CYP1A2, and UDPGT. Because TCDD induces expression of the AhR, lower computed doses are required to obtain the same responses as estimated by models that ignore this effect. The critical steps are binding of the liganded AhR to DREs and translation of the mRNA into protein. The most important lesson of this modeling exercise is that lack of significant sigmoidicity in the dose-response curves calculated for these proteins arises from saturation of protein synthesis at low concentrations of mRNA, compensating for possible sublinearity in transcription. Similar compensatory effects led to low-dose linearity in the more complex responses of EGF receptor internalization and elevation of plasma TSH.

Any of the above responses can serve as indices of toxicity or pathology, and which is selected for such use depends on the hypothesized origin of the endpoint. Use of CYP1A2 as a marker for indirect DNA damage is based on the hypothesis that the catalytic properties of this enzyme lead to the generation of free radicals or DNA-reactive quinones (Yager and Liehr, 1996). Use of the internalized EGF receptor as a marker for promotional effects in the liver is based on the hypothesis that TCDD induces growth factors that are ligands of this receptor. Use of TSH as a marker for promotional effects in the thyroid is based on the goitrogenic properties of this hormone. Further experiments are required to determine if these postulated events are causally related to the pathological responses. Nevertheless, if the computed responses are used as dose metrics, the model indicates that linear extrapolation from the experimental dose range can be used to estimate low-dose effects.

The main hepatic response motivating the regional induction model was the pattern of staining within hepatic lobules in TCDD-treated rats (Tritscher et al., 1992). On the basis of

geometric considerations, hepatic lobular structure was described as a series of concentric lobular regions with differing affinities of DNA binding sites for the Ah-TCDD complex (Andersen et al., 1997a). A main underlying assumption was a linear correspondence between mRNA concentrations and protein levels, modeled by an inducible rate of synthesis and a first-order degradation. The rate of message production was modeled with Hill kinetics with respect to receptor complex concentration. The successful parameterization required differences in binding affinity between adjacent zones and very steep dependence on TCDD and Ah-receptor complex concentration (i.e., the estimated Hill coefficients were large) in order to reproduce experimental data. A single-compartment liver model was also examined. It could reproduce all data except the heterogeneous distribution and low-dose mRNA levels. The major inference drawn from this analysis was that induction should be considered on the level of the cell, not the gene. The effects appear to be coordinate, cooperative expression of a battery of gene products and emergence of new cellular characteristics. This behavior, if true, might be regarded as a reversible differentiation of TCDD-transformed phenotype, rather than induction of single genes in isolation. Overall linear behavior in the entire liver arises from composite responses of individual cells with differing thresholds for induction. The sensitivity of cells in the centrilobular region of the liver would determine the low-dose behaviors.

In the present model the low-dose behavior of this small group of cells would be distinctly nonlinear. The ED_{01} with this regional induction model was about 1.4 ng/kg/day (Table 8-8). This value is close to the estimate of 0.34 for the induction of CYP1A2 estimated by Kohn et al. More significant than the differences in ED_{01} values are the inferences drawn with regard to the shape of the curve in the low-dose region by the two models. Specific studies on regional induction and cellular level responses should be vigorously pursued to discriminate between these two model structures. Regional induction of mRNA needs to be studied on a more quantitative level and methods need to be developed for studying induction in primary hepatocytes. Recent data in rats exposed to TCDD demonstrate that the hepatocytes in the centrilobular region accumulate TCDD to a greater extent in the low-dose region and are more responsive to TCDD than are the periportal hepatocytes (Santostefano et al., 1999).

8.4.3. Application of Models

The goal of biochemical response models is to link TCDD-regulated responses to adverse effects associated with TCDD exposures. In principle, these models could be applied to a variety of adverse responses. The focus of the application of these models has been to carcinogenic endpoints. Much less attention has been given to the application of mathematical models to the development of noncancer pathologies.

TCDD is a potent carcinogen in all animal species tested (see Part II, Chapter 6). TCDD is an operational promoter, as defined in assay systems of skin and/or liver in mice and rats (Schrenk et al., 1994; Maronpot et al., 1993; Clark et al., 1991; Pitot et al., 1980; van Birgelen et al., 1999; Buchman et al., 1994) (see Chapter 6). Mathematical modeling can be a powerful tool for understanding and combining information on complex biological phenomena such as carcinogenesis. For the analysis of tumor promotion by TCDD, much of the focus on the use of mathematical and mechanistic models has been on understanding the mechanism of hepatocarcinogenesis induced by TCDD. Specifically, the focus has been on modeling the development of putatively preneoplastic altered hepatocellular foci (AHF) that exhibit altered expression of marker enzymes such as placental glutathione-s-transferase (PGST), or gamma-glutamyl transpeptidase (GGT). Mechanism-based modeling of carcinogenicity can be accomplished by incorporating linkages between cell growth and mutation and the biochemical/tissue responses of TCDD, within the context of the quantitative dose-response models described above. In addition, analysis of changes in hepatocyte replication has been used to estimate of parameter values for in some models.

8.4.3.1. *Modeling Preneoplastic Lesions*

Within the framework of a two-stage model of carcinogenesis, these models treat AHFs as an initiated phenotype produced by conversion of a normal cell by a mutational event. Models for the numbers of normal and initiated cells also incorporate parameters related to the relative birth rates and death rates of the respective cell populations. These growth and mutational parameters may or may not be directly related to biological processes altered by TCDD. Three research groups have evaluated growth and development of AHFs, using different mathematical approaches, different assumptions of the phenotypic distribution of the AHFs, and different linkages of biological processes to the model parameters.

8.4.3.1.1. ***Models with a single initiated phenotype.*** Portier et al. (1996) estimated the parameters in the first half of a two-stage mathematical model of carcinogenesis from the initiation-promotion data (Maronpot et al., 1993) using previously developed methods (Dewanji et al., 1989). This analysis used daily average dose as the dose metric for examining dose dependent effects of TCDD on model parameters. Maronpot et al. (1993) quantified the number and size of liver AHF lesions expressing the placental form of glutathione-S-transferase (PGST). The modeling results indicate that TCDD stimulates the production of PGST-positive AHF (which could indicate a mutational effect) and promotes the growth of PGST AHF (as a result of either increases in birthrate or decreases in the death rate). Data on cell replication indices and liver weight could not explain the mutational effect of TCDD. Following upon the work of Kohn et al. (1993), Portier et al. (1996)

suggested this finding could be due to an increase in the metabolism of estrogens to catechol estrogens, leading to subsequent increase in free oxygen radicals and eventually to mutations. The analysis also indicated an interaction between DEN and TCDD that results in dose-related formation of initiated cells throughout the study period. Portier et al. (1996) also found that best-fitting curves (using maximum likelihood methods) for the effect of TCDD on the mutation and birth rates reached saturation levels at doses below 3.5 ng/kg/day.

As a validation exercise, Portier et al. (1987) used the same methods to analyze focal lesion data from Pitot et al. The two studies utilized different initiation protocols. In the Maronpot experiments, a necrogenic DEN dose (175 mg/kg) was used, whereas in the Pitot experiments a non-necrogenic dose of DEN (30 mg/kg) was given 24 hours after partial hepatectomy. These two initiation protocols lead to differences in background tumor rates and differences in time course for tumor development following TCDD exposure.

In the Pitot experiment, three types of enzyme-altered AHF were quantified using the marker enzymes gamma-glutamyltranspeptidase (GGT), canalicular adenosine triphosphatase (ATP) and glucose-6-phosphatase (G6P). Portier et al. (1996) found that all four types of AHF from the two different studies produced similar qualitative results; TCDD had effects on both mutation and birth rates. The effect of dose on the birth rates for both data sets produced similar patterns, with an almost identical unexposed birthrate for all of the four lesion types, a maximal increase over the background rate between 33% and 300%, saturation of the increased birthrate at low doses, and a small increase in birthrate because of DEN initiation. The pattern of dose-related changes in the mutation rate is slightly different in the ATP, GGT, and G6P AHF than for the PGST AHF, tending more toward linearity than the hyperbolic response seen for the PGST AHF. However, for all four lesions, the maximal induction rate tended to be the same.

Moolgavkar et al. (1996) analyzed data from Buchmann et al. (1994) on ATP AHF in female Wistar rats exposed to 2,3,7,8-TCDD as well as 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (HCDD). The initiation protocol was a non-necrogenic dose (10 mg/kg) for 5 consecutive days. In addition to the mathematical analysis developed by Dewanji et al. (1989), Moolgavkar et al. (1996) used a modification that allowed for cellular replication focused on the edge of the AHF. Although Moolgavkar et al. (1996) did not have information on multiple dose groups, the results of their analysis for TCDD concur qualitatively with those of Portier et al. (1996). In essence, they observed no effect on the birthrate of initiated cells, a significant (sevenfold in noninitiated and twofold in initiated) effect of TCDD on the mutation, and a prolonged effect of DEN following initiation (similar to the interaction effect observed by Portier et al. [1996]). The observed lack of change in birthrates is similar to that of the nonsignificant increase observed by Portier et al. (1996) for PGST+, GGT, and G6P foci, but smaller than that for ATP foci in the Pitot et al. (1980) study. In the DEN-initiated groups, the associated increases in the mutation rates were quantitatively

similar to those observed for PGST lesions in the Portier et al. (1996) study (2.2-fold at 100 ng/kg/day in Moolgavkar et al. (1996), 2.5-fold at 125 ng/kg/day for PGST), but much smaller than those observed for the ATP, GGT, and G6P lesions from the Pitot et al. (1980) study (9.9-fold for ATP, 4.5-fold for GGT and 5.8-fold for G6P). The observed increase in the mutation rate in noninitiated animals was much larger in the Moolgavkar et al. (1996) analysis than that for the Portier et al. (1996) analysis. This study was conducted at a single dose and the comparison is simply treated versus control.

8.4.3.1.2. ***Models with two initiated phenotypes*.** Conolly and Andersen (1997) developed a model for focal lesion growth based upon two types of initiated cells, applying the negative selection mechanism for hepatic tumor promotion proposed by Jirtle et al. (1991a,b). In this model, even though the two types of initiated cells express the same biochemical marker, they respond differently to promotional stimulation in the liver. The model presumes that a promotional stimulus to the liver is countered by mitoinhibitory signals generated by the liver to constrain proliferation. One set of mutated cells is sensitive to this mitoinhibition whereas the other set of mutated cells is insensitive and responds only to the promotional stimulus. The result is that, under increasing doses of the promoter, one group of focal lesions is decreasing in size, and hence number of cells, while the other group is increasing in size.

Conolly and Andersen's model is different from those of Portier et al. (1996) and Moolgavkar et al. (1996) in that it can result in U-shaped dose-response curves for the total number and mean size of observable focal lesions without using U-shaped parametric forms for the mutation rates or the birthrates. Number and size of focal lesions were estimated using the stochastic resampling methods outlined in Conolly and Kimbell (1994), with deterministic growth replacing stochastic growth when colonies exceeded 1,000 cells. Twenty-five replicates for each model output were compared to the data for the combination of all three focal lesion types from the study by Pitot et al. (1980) to obtain parameter estimates for the birth and death rates of the two types of mutated cells. This analysis used administered dose as the tissue dose metric.

The two-cell model adequately fit the data with biologically reasonable parameter values. An alternative model including an effect of TCDD on mutation rates was not considered. Similarly, the earlier analyses of Portier and Moolgavkar did not consider two types of initiated cells, so comparisons between models with one type of initiated cell versus two types of initiated cells relating to the issue of the effect of TCDD on mutation rates cannot be made. This is an area that could use additional research. The birthrates (combined for the two mutated clones in the Conolly and Andersen model) for all three sets of models (Portier et al., 1996; Moolgavkar et al., 1996; Conolly and Andersen, 1997) are comparable in the control groups but differ substantially for the higher dose groups, with the two clone models having much larger rates. This difference is

partially due to the assumption in the Conolly and Andersen model that there is no increase in mutation rate following initiation and partially due to the use of an increasing death rate with exposure to TCDD. Portier et al. (1996) used a fixed death rate in their final model and Moolgavkar et al. (1996) varied the death rate with the birth rate. Results from a study of Stinchcombe et al. (1995) indicate a lack of significant effects of TCDD on cell replication in PGST foci, but remarkable suppression of apoptosis within PGST-positive AHF. This study, however does not supply information on dose dependency of these parameters. Given the lack of sufficient data, it is not possible to simultaneously estimate both the birthrates and death rates for the initiated cell phenotypes.

8.4.3.1.3. ***Alternative dose metrics in promotion studies.*** In the above models, oral dose of TCDD was essentially used as the dose metric. In contrast, Conolly and Andersen used the fraction of the maximum possible induction of CYP1A1 and CYP1A2 calculated from the zonal induction model (Andersen et al., 1997a) as a dose-surrogate for the effect of TCDD on the clonal expansion of both mutated cell types within the framework of a two-cell multistage model. Andersen et al. (1997a) fit their multicompartment geometric model of hepatic zonation (Andersen et al., 1997b) to data derived from several studies on the expression of CYP1A2 in rats (Abraham et al., 1988; Tritscher et al., 1992; van den Heuvel et al., 1994b). The zonal induction model is described previously in this review. The model was linked to the previous PBPK model (Andersen et al., 1993a) with modifications (Andersen et al., 1997b) to account for the regional induction of CYP1A2, rather than to the original model which was based upon uniform expression throughout the liver. Formal optimization methods were not used to obtain model parameters; however, graphical comparisons of the model predictions to these data did not appear to be obviously different from previous descriptions and provided adequate fits. The dissociation constants for binding of the TCDD-AhR complex to dioxin-responsive elements for CYP1A1 (0.6 to 2 nM for compartment 3) and CYP1A2 (0.08 to 1.0 nM for compartment 3) were fit separately for each data set and varied by a factor of 3 from compartment to compartment. This produced a model that fit the fraction of liver volume occupied by focal cells, but failed to fit the number of foci per volume of liver as well as the original analysis. These analyses used percent of liver expressing CYP1A2 as an indicator of the dose metric.

8.4.3.2. *Estimation of Cancer Risks*

Portier and Kohn (1996) combined the biochemical response model of Kohn et al. (1993) with a single initiated phenotype two-stage model of carcinogenesis to estimate liver tumor incidence in female Sprague-Dawley rats from the 2-year cancer bioassay of Kociba et al. (1978). In the simplest of several models tested, the initial mutation rate to the initiated phenotype was

proportional to the instantaneous concentration of CYP1A2 as predicted by the biochemical model of Kohn et al. The birthrate of mutated cells was a linear function of loss of EGFR. All death rates were held constant, as was the second mutation rate from the initiated to the malignant phenotype. This model adequately fit the tumor data, although it overestimated the observed tumor response at the lowest dose in the Kociba et al. (1978) study. The shape of the dose-response curve was approximately linear and the estimated ED_{01} value for this model (0.15 ng/kg/day) is presented in Table 8-8. The corresponding body burden giving a 1% increased effect was 2.7 ng/kg. The use of CYP1A2 as a dose metric for the first mutation rate is consistent with its role as the major TCDD-inducible estradiol hydroxylase in the liver (Hayes et al., 1996; Dannan et al., 1986) and with the hypothesized role of estrogen metabolites leading to increased oxidative DNA damage and increased mutation (Yager and Liehr, 1996; Roy et al., 1992; Cavalieri et al., 1997) .

Even though the thyroid hormone model of Kohn et al. (1996) has not been strictly used for modeling of thyroid neoplasia induced by TCDD, it is important to note that the hypothesis for induction of thyroid neoplasia consequent to growth stimulation by chronically elevated serum TSH is highly plausible. In contrast there is weaker evidence in the liver that alteration in CYP1A2 and EGFR are causally linked to carcinogenesis. Given that the alteration in thyroid hormone homeostasis as a consequence of TCDD induction of UDPGT can be effectively modeled provides an excellent opportunity to mechanistically link activation of gene expression by TCDD with thyroid cancer risk.

8.4.4. Knowledge/Data Gaps

Knowledge gaps still exist with each of the models. All the PBPK models have biological structure and encode hypotheses about the modulation of protein concentrations by TCDD. However, each of them falls between curve fitting and mathematical representations of known biology. Parameters in empirical equations representing overall production of the protein gene products, for example, were estimated using dose-response data for protein concentrations and enzyme activity. Although protein level is a direct consequence of gene expression, this empirical approach constitutes curve fitting. In the cases of CYP1A1 and UDGPT induction, information about both mRNA and protein levels was available, permitting a more realistic, although still empirical, representation of the mechanism of induction. Similarly, equations for metabolism of TCDD and thyroid hormones in the model of Kohn et al. (1996) and of lipids in the model of Roth et al. (1994) are not based on detailed studies of the enzymatic kinetics but are greatly simplified representations. Nonetheless, the structure of the physiological models was specified by information on anatomy, physiology, and qualitative effects of TCDD. These PBPK models reproduce protein concentrations in data sets that were not included in the construction of the model

and that were obtained from experimental designs different from those used to define the model. This constitutes at least a partial mechanistic validation of these models.

Models for tissue response including lipid metabolism and hepatic lobular effects also have aspects that need confirmation. The Roth et al. (1994) model has not been validated for chronic exposures or low doses. Even though the Wang et al. (1997) model has examined CYP1A1 and CYP1A2 induction, it has not been validated for chronic exposures. The regional induction model (Andersen et al., 1997a,b) creates a hypothesis concerning regional induction that should be further studied. An alternative to altering the affinity of DREs to the liganded AhR is a gradient in the receptor concentration across the liver acinus. The concentration of the receptor in centrilobular hepatocytes was found to be more than 40 times that in periportal hepatocytes (Lindros et al., 1997). The use of Hill kinetics to describe at least some of the binding (or metabolic) reactions is a convenience to allow flexibility in estimating dose-response relationships.

The models for estimating values of the dose metrics for exposure or effects differ in their mathematical representations of the same physiological processes while providing comparable fits to the observed responses. The endocrine response model includes TCDD induction of the AhR, binding to multiple DREs, and saturation kinetics for protein synthesis on the mRNA template. This sequence of steps can potentially lead to nonlinear kinetics for the overall responses, but the nonlinearities in the individual steps appeared to compensate for each other, leading to approximately linear low-dose responses. The regional induction model (Andersen et al., 1997a) collapses this sequence into a single overall process and uses Hill kinetics to represent the potential overall nonlinearity. A high Hill exponent was required to reproduce the sharp edge detected for the induced region of the liver, leading to sublinear predicted responses below the experimentally accessible range of doses. Thus, emphasizing different aspects of the underlying biology leads to different mathematical structures with different predicted low-dose behavior. Which of these processes are most important in producing the overall responses cannot be resolved by existing data.

The biochemical and tissue response models were linked to a two-stage cancer model (Portier and Kohn, 1996). Although TCDD is not a mutagen in in vitro systems commonly used to detect mutation through DNA damage, inferences drawn from biochemical data and mechanistic modeling supported a secondary mechanism for TCDD-induced mutations (Portier et al., 1996; Moolgavkar et al., 1996). Another approach, with secondary pathways leading to mutations and two cellular phenotypes, also fit these data but does not require this secondary effect on mutation rate (Andersen et al., 1997a,b; Conolly and Andersen, 1997). Even though this secondary mechanism of mutation is still speculative, these studies present challenges to the application of general models for cancer risk assessment based on direct chemical mutagenesis as a fundamental mechanism for chemically induced or radiation-induced cancer and the notion of a single cellular phenotype as a precursor for cancer.

8.4.5. Summary

The development of PBPK models describing the disposition of TCDD within experimental animals has proceeded through multiple levels of refinement, with newer models incorporating ever-increasing levels of biological complexity. The two most complete PBPK models give similar predictions about TCDD tissue dose metrics. It is unlikely that additional refinement of the current models will have a major impact on the model predictions within the observable dose range. However, further work could better characterize the biological processes involved in disposition.

Despite their availability, these PBPK models have been highly underutilized in aiding empirical dose-response analyses for the effects of TCDD observed in laboratory studies. Differences in dosing regimens in experimental animals, such as exposure duration, route of exposure, time after dosing to necropsy, use of maintenance-loading dose regimen, etc., complicate the use of a simple metric based on administered dose for comparative analyses between studies (Section 8.3). The use of the current PBPK models could provide a more scientifically credible description of a body burden dose metric and may reduce some of the uncertainties introduced when converting a daily averaged dose ED_{01} to a body burden dose metric.

Similarly, the application of these models to human dose-response data, while possible has also not been pursued. The current level of detail in rodent PBPK modes for TCDD has not been included in any current human PBPK model for TCDD. Human exposure assessment for use in dose-response modeling utilizes either back-extrapolation based on a single measurement of a tissue (plasma/serum) concentration or a dose metric based on an estimated external exposure. Although extrapolation of the current generation of rodent PBPK models to humans would have uncertainties, it is unlikely that predictions from such a model would be any less uncertain that current methodologies used for estimating human body burdens.

With regard to the extension of PBPK models to biochemical response, tissue response, and toxicological responses, the differences in interpretation of the mechanism of action of a TCDD-dependent response lead to varying estimates of the dose-dependent behavior for similar responses. In addition, the hypotheses and assumptions used in different models may restrict the shape of the dose-response curves that are calculated and lead to differences in their low-dose behaviors.

The use of specific biochemical/tissue responses as dose metrics for the evaluation of the dose-response for toxicity are based upon hypotheses regarding specific linkages between these responses and toxicity. A greater understanding of the mechanism of linkage of these dose metrics to the toxicological endpoint of concern is required before an interpretation of the shape of the dose-response curve or estimation of low-dose risk is credible.

In summary, the state of the science for mechanism-based modeling has been greatly improved by these newer PBPK models and incorporation of knowledge of the mode of action of

TCDD. These models may allow qualitative assessment of modes of action, i.e., low-dose behavior; however, differences exist in the low-dose expectations of current models. Expanded use of current PBPK models could reduce uncertainty in quantifying actual internal dose following different dosing regimens.

8.5. DATA GAPS

This chapter identified several important data and knowledge gaps. Information to fill these gaps would substantially improve dose-response analysis and risk assessment. The most substantial gaps are summarized below.

There are similarities and differences, both qualitative and quantitative, in responses to TCDD between laboratory animals and humans. These are due to a variety of factors, including disposition of TCDD, AhR properties and regulation, and tissue- and species-specific biochemical responses and specific factors regulating these responses. A better understanding of these factors could substantially improve dose-response analysis and risk assessment.

There are differences between AhR binding curves and dose-response curves for specific toxic endpoints. This suggests that factors in addition to the AhR contribute to these toxic endpoints. For complex endpoints, including frank toxicities, there are likely to be earlier biochemical events, initiated by receptor binding, that lead ultimately to the toxic responses. Detailed quantitative knowledge of this sequence of events would increase reliability in response and species extrapolation, mechanistic modeling, and extrapolation to lower doses.

Also, tissue disposition of TCDD plays a critical role in the approach to risk assessment for this chemical. Knowledge about the disposition of TCDD at or near the background exposures experienced by the general population is limited. PBPK models can make predictions about tissue disposition at these low levels of exposure, though these predictions tend to be below the dose ranges for which the models have been validated. Lack of knowledge of disposition of low doses is especially applicable to human exposures and exposures that may occur in the embryo at critical time points. Furthermore, there is uncertainty about half-life in humans and about the heterogeneity in this half-life among individuals. These factors add to the difficulty in determining the proper dose metric for different endpoints and across different species. PBPK modeling could help to address this problem if the existing models developed for laboratory rodents were extrapolated to humans. Although there would be uncertainty associated with this extrapolation, it would not necessarily be greater than, nor even as great as, the uncertainty associated with the current approach.

In animals, more information is needed about background levels of exposure and how they may affect dose-response analyses. This is especially true because greater emphasis is being placed

on low levels of exposure in animal experiments. Including background exposure data may alter the shape of the dose-response curve and affect the estimate of the ED_{01}.

Quantitative mechanism-of-action-based models can provide insights into the complex interrelationships of the molecular and biochemical events that comprise a mechanism or mode of action. However, the level of confidence in the models and their predictions should not be greater than the level of confidence in the quality of the database and degree of scientific consensus about the mechanism or mode of action that the model describes. This is particularly true when the model is to be used for risk assessment. It is possible to use alterations in the concentrations of proteins known to be altered by TCDD as potential dose metrics. However, more information is needed about the mechanistic linkages of these proteins to toxic endpoints to improve estimations of shapes of dose-response curves and estimates of low-dose risks.

8.6. SUMMARY

Data available for several biochemical and toxicological effects of TCDD, and on the mechanism of action of this chemical, indicate that there is good qualitative concordance between responses in laboratory animals and humans. For example, human data on exposure and cancer response appear to be qualitatively consistent with animal-based risk estimates derived from carcinogenicity bioassays. These data would suggest that animal models are generally an appropriate basis for estimating human responses. Nevertheless, there are clearly differences in responses between animals and humans, and recognition of these is essential when using animal data to estimate human risk. The level of confidence in any prediction of human risk depends on the degree to which the prediction is based on an accurate description of these interspecies extrapolation factors.

Almost all data are consistent with the hypothesis that the binding of the TCDD to the AhR is the first step in a series of biochemical, cellular, and tissue changes that ultimately lead to toxic responses observed in both experimental animals and humans. As such, an analysis of dose-response data and models should use, whenever possible, information on the quantitative relationships between ligand (i.e., TCDD) concentration, receptor occupancy, and biological response. However, it is clear that multiple dose-response relationships are possible when considering ligand-receptor mediated events. For example, dose-response relationships for relatively simple responses, such as enzyme induction, may not accurately predict dose-response relationships for complex responses such as developmental effects and cancer. Cell-specific factors may determine the quantitative relationship between receptor occupancy and the ultimate response. Indeed, for TCDD there is much experimental data from studies using animal and human tissues to indicate that this is the case.

One of the most difficult issues in risk assessment is the dose metric to use for animal-to-human extrapolations. The most appropriate dose metric should reflect both the magnitude and frequency of exposure, and should be clearly related to the toxic endpoint of concern by a well-defined mechanism. However, considering the variety of endpoints in different species, it is unlikely that a single dose metric will be adequate for interspecies extrapolation for all of these endpoints. Furthermore, the use of different dose metrics with respect to the same endpoint may lead to widely diverse conclusions. Nevertheless, it is possible to express dose in a form that allows for comparison of responses for selected endpoints and species. This can be done by either choosing a given exposure and comparing responses or choosing a particular response level and comparing the associated exposures. For particular endpoints, and considering the large differences in half-lives for TCDD across multiple species, it is best to compare the dose metric as body burden rather than daily intake. A useful and common metric for comparison is the 1% effective dose or ED_{01}, which is the exposure dose resulting in 1% change in a particular endpoint. The possibility that existing PBPK models could be used to a greater extent to compare tissue doses across experimental designs and between species deserves further study.

TCDD has been classified as a known human carcinogen, and is a carcinogen in all species and strains of laboratory animals tested. However, it is generally difficult to find human data with sufficient information to model dose-response relationships. For those data that are available, the uncertainties involved in the modeling of these data are considerable, and notably include extrapolation of occupational exposure many years after it took place, and the type and shape of the curve for the dose-response model used in the extrapolation. A linear model is often used because the number of exposure groups for analysis is too small to support more complex models. On the other hand, analysis of animal data suggests that many complex responses to TCDD are nonlinear (Figures 8-1, 8-2, 8-3). Nevertheless, with these qualifications, it is possible to apply simple empirical models to studies in which exposure data for TCDD are available in human populations. An analysis of epidemiological studies of two studies of occupationally-exposed individuals suggests an effect of TCDD on all cancers at body burden ED_{01}s for total cancers ranging from 1.4 ng/kg to 40 ng/kg. This was slightly smaller than the estimates from empirical modeling from the animal studies which ranged from 14 ng/kg to 1190 ng/kg (most estimates were in the range from 14 to 500 ng/kg), and in most cases slightly above the 2.7 ng/kg estimate from the single mechanism-based model. The two lowest human ED_{01} values (1.4 and 1.8 ng/kg) were associated with the power model used by Steenland et al. (2001) which predicts an unrealistic risk for the background exposure; the next lowest value was 6 ng/kg.

At this point, sufficient data are not available to model noncancer endpoints in humans. Many studies are available to estimate ED_{01} values for noncancer endpoints in animals. However, there are a number of difficulties and uncertainties that should be considered when comparing

endpoints across species. Some of these include differences in sensitivity of endpoints, times of exposure, exposure routes, species and strains, use of multiple or single doses, and variability between studies even for the same response. The estimated ED_{01} values may be influenced by experimental design, suggesting that caution should be used in comparing values from different designs. In addition, caution should be used when comparing studies that give ED_{01} estimates outside the experimental range. Furthermore, comparing values between different categories of inducible responses may result in misleading estimates of a potential health risk. For example, the human health risk for a 1% change of body weight may not be comparable to a 1% change in enzyme activity. Finally, background exposures are not often considered in these calculations simply because they were not known. The latter consideration is particularly important as the inclusion of these may alter the shape of the dose-response curve, possibly increasing the shape parameter so that the responses would demonstrate more threshold-like effects. Nevertheless, given these considerations several general trends were observed. The lowest ED_{01} values tended to be for biochemical effects, followed by hepatic responses, immune responses, and responses in tissue weight. An analysis of shape parameters implies that many dose-response curves, for a variety of responses, were consistent with linearity over the range of doses tested. This does not imply that the curves would be linear outside this range of doses. The lower shape parameters, suggesting linearity, were for biochemical responses, whereas the higher values for shape parameters, suggesting nonlinearity, were for tissue responses. Overall, these data suggest that biochemical responses to TCDD are more likely to be linear within the experimental dose range, while the more complex responses including frank toxicity are more likely to assume a nonlinear shape. For cancer, the shapes were split between linear (eight analyses) and nonlinear (five analyses).

The tissue weight changes seen for animals (using only data sets with good or moderate empirical fits to the model) yielded a median ED_{01} of 510 ng/kg in the multidose studies (range 11 to 28,000 ng/kg) and a median ED_{01} of 160 ng/kg (range 0.0001 to 9,700 ng/kg) in the single- dose studies. Toxicity endpoints from the single-dose studies resulted in a median value of 4,300 ng/kg (range 1.3 to 1,000,000 ng/kg). For tissue weight changes, 43% of the dose-response curves exhibited linear response. In contrast, the toxicity endpoints from the single-dose studies exhibited predominantly nonlinear responses (80%). All multidose studies demonstrated a greater degree of linear response (41%) than did single-dose studies (37%), especially for tissue weight changes and toxicity endpoints (50% linear for multidose versus 34% for single dose). In general it is not possible to specify the differences between cancer and noncancer dose-response as being due to differences in endpoint response or to differences in the length of dosing and exposure. Also, a greater percentage of the noncancer ED_{01} values were below the experimental dose range (42%) than was the case for the cancer endpoints (8% in animals and no extrapolations in humans). However, many more noncancer data sets were examined compared to the cancer endpoints.

Empirical models have advantages and disadvantages relative to mechanism-based models. Empirical models provide a simple mathematical model that adequately describes the pattern of response for a particular data set and can also provide the means for hypothesis testing and interpolation between data points. In addition, empirical models can provide qualitative insights into underlying mechanisms. However, the major disadvantage is their inability to quantitatively link data sets in a mechanistically meaningful manner. On the other hand, comprehensive mechanism-based models can be powerful tools for understanding and combining information on complex biological systems. Use of a truly mechanism-based approach can in theory enable reliable and scientifically sound extrapolations to lower doses and between species. However, any scientific uncertainty about the mechanisms that the models describe is inevitably reflected in uncertainty about the predictions of the models.

PBPK models have been validated in the observable response range for numerous compounds in both animals and humans. The development of PBPK models for disposition of TCDD in animals has proceeded through multiple levels of refinement, with newer models showing increasing levels of complexity by incorporating data for disposition of TCDD and its molecular actions with the AhR and other proteins, as well as numerous physiological parameters. These have provided insights into key determinants of TCDD disposition in treated animals. The most complete PBPK models give similar predictions about TCDD tissue dose metrics. The PBPK models have been extended to generate predictions for early biochemical consequences of tissue dosimetry of TCDD such as induction of CYP1A1. Nevertheless, extension of these models to more complex responses is more uncertain at this time. Differences in interpretation of the mechanism of action lead to varying estimates of dose-dependent behavior for similar responses. The shape of the dose-response curves governing extrapolation to low doses is determined by these hypotheses and assumptions. In the observable range around 1% excess response, the quantitative differences are relatively small. Below this response, the different mechanisms can diverge rapidly. The use of predicted biochemical responses as a dose metric for toxic responses is considered a potentially useful application of these models. However, greater understanding of the linkages between these biochemical effects and toxic responses is needed to reduce the potentially large uncertainty associated with these predictions.

8.7. CONCLUSIONS

Once an environmental agent has been deemed a health hazard, the two main questions to be addressed in any dose-response assessment are: (1) What can be said about the shape of the dose-response function in the observable range, and what does this imply about dose-response in the range of environmental exposures? and (2) What is a reasonable limit (critical dose or point of departure) at the edge of the observable range, and what risk is associated with this exposure? For

the dose-response assessment of TCDD, these questions are complicated by the multiplicity of responses observed and the complexity of the mechanisms known to impact upon those responses. In the dose-response evaluation conducted for this chapter, we have attempted to use the best available analytic procedures to provide insight into the answers to these questions. This includes both the critical assessment of formal empirical dose-response analyses of the available data and, where appropriate, predictions of dose-response behavior using mechanism-based models of TCDD.

Many different shapes of dose-response curves were seen in the observable range. Although human data were available, the data were not adequate for addressing curvature of the dose-response relationship. Consequently, the main conclusions on the shape of the dose-response for TCDD are based on animal models.

Under simple empirical dose-response models, about half of the cancer endpoints observed in animals were linear in the observable range and about half were not. Noncancer endpoints had a greater degree of nonlinearity, with only 40% of the observed responses being linear. Biochemical endpoints (more closely coupled to activation of the AhR) tended to exhibit linear dose-response curves, whereas TCDD-inducible responses, which are likely more complex and involve multigene interactions, exhibited more nonlinear behavior. Mechanism-based modeling provided two different answers depending upon the approach used in the analysis and the assumptions used in the approaches. The variability in the available data for mechanism-based modeling did not allow us to clearly decide upon any one given model in favor of another. For intermediate biochemical endpoints and preneoplastic lesions in the rat liver, we saw model fits that strongly supported nonlinear dose-response shapes in the observable range. This was based upon the assumptions of a nonlinear expression of proteins in the liver and upon multiple types of focal lesions responding differently to the effects of TCDD. In contrast, using an alternative model resulted in effectively linear dose-response (defined as response proportional to dose in the low-exposure region, not necessarily the higher experimental doses) for both endpoints and the proposition of a secondary effect of TCDD on increasing mutations through changes in estrogen metabolism.

All humans tested contain detectable body burdens of TCDD and other dioxin-like compounds that are likely to act through the same mode of action. This consideration, together with the high percentage of observed linear responses, suggests that a proportional model should be used when extrapolating beyond the range of the experimental data rather than using a margin-of-exposure analysis. However, this decision would have to be based upon a policy choice because this analysis dose not strongly support either choice.

Because we had human data for dose-response analysis and a strong desire to stay within the range of responses estimated by these data, the risk chosen for determining a point of departure was the 1% excess risk. Doses and exposures associated with this risk (the ED_{01}s) were estimated from

the available data using both mechanistic and empirical models. Comparisons were made on the basis of body burdens (either averaged, steady-state or administered dose) to account for differences in half-life across the numerous species studied. In humans, restricting the analysis to dose-response models from the literature for two occupational cohorts resulted in body burden ED_{01}s for total cancers ranging from 1.4 ng/kg to 40 ng/kg. This was slightly smaller than the estimates, from empirical modeling from the animal studies which ranged from 14 ng/kg to 1190 ng/kg (most estimates were in the range from 14 to 500 ng/kg), and in most cases slightly above the 2.7 ng/kg estimate from the single mechanism-based model. The two lowest human ED_{01} values (1.4 and 1.8 ng/kg) were associated with the power model used by Steenland et al. (2001) which predicts an unrealistic risk for the background exposure; the next lowest value was 6 ng/kg. Estimates for non-cancer endpoints showed much greater variability. In general, the noncancer endpoints displayed lower body burdens at the ED_{01} for longer term exposures versus short-term exposures, and for simple biochemical endpoints versus more complex endpoints such as tissue weight changes or toxicity. In addition, the noncancer endpoints generally displayed higher estimated body burdens at the ED_{01} than the cancer endpoints, with most estimates ranging from 100 ng/kg to 100,000 ng/kg. For some endpoints, however, the body burdens at the ED_{01} were below the range of the cancer endpoints. The mechanism-based models for noncancer endpoints gave a lower range of body burdens at the ED_{01} (0.17 to 105 ng/kg). While most of these estimates were based upon a single model, the estimate from the hepatic zonal induction model gave a body burden for the ED_{01} for CYP1A2 induction of 51 ng/kg and hence was within the same range.

These estimates, although highly variable, suggest that any choice of body burden, as a point-of-departure, above 100 ng/kg would likely yield greater than 1% excess risk for some endpoints in humans. Also, choosing a point-of-departure below 1 ng/kg would in general only be supported by analyses that gave estimates that were below the range of these data, and would likely represent a risk of less than 1%. Any choice in the middle range of 1ng/kg to 100 ng/kg, would be supported although the data provide the greatest support in the range of 10 ng/kg to 20 ng/kg.

This Chapter has produced an extensive summary of dose-response relationships as is feasible at this time. The analyses and discussions synthesize a considerable breadth of data and model types, drawing upon this information to highlight strengths and weaknesses in the information base, gaps in our qualitative and quantitative understanding and the uncertainties inherent in making a decision concerning a point-of-departure for risk characterization. While such an extensive evaluation may not be necessary for most environmental contaminants, the concepts envisioned here can serve as a framework for evaluation in other settings. This unique document hopefully marks the beginning of more objective, quantitative reviews of information pertaining to risk decisions for environmental agents.

Table 8-1. Estimated half-lives for species considered in the analyses to follow and used for converting between daily exposures and steady-state body burdens

Species	Half-life (days)
C57BL/6N mice	10
All other mouse strains	11
Golden Syrian hamster	12
Wistar rats	22
All other rat strains	25
Human	2,593

TABLE 8-2: Total cancer risk in humans through age 75 (units are constant body burden in ng/kg not adjusted for lipid). Upper and lower 95% confidence limits (where available) are in parentheses after ED values

Study	Model and Sex	ED_{10}	ED_{05}	ED_{01}	Unit excess risk for 1 ppt body burden above background
Steenland et. al, (2001)	power male	500 (46.4, 2.91 x 10^7)	33.9 (8.23, 1.59 x 10^4)	1.38 (0.71, 8.95)	0.0079 (0.0027, 0.0132)
	power female[1]	1315 (84.4, 4.5 x 10^8)	64.5 (12.6, 2.50 x 10^4)	1.84 (0.92, 14.9)	0.0064 (0.0022, 0.0107)
	piecewise linear male	• (92.9, •[3])	83.6 (51.8, •[3])	18.6 (11.5, 48.3)	0.00052 (0.00020, 0.00084)
	piecewise linear female[2]	•[8] (108.9, •[3])	100.7 (62.39, •[3])	23.1 (14.3, 59.8)	0.00042 (0.00016, 0.00067)
Becher et al., (1998)	power-male	120.3	41.17	5.971	0.0018
	power-female[4]	170.9	55.44	7.580	0.0014
	additive-male	192.8	93.35	18.22	0.00055
	additive-female[5]	239.1	116.2	22.75	0.00044
	multiplicative-male	258.9	144.4	32.16	0.00030
	multiplicative-female[6]	304.4	173.8	39.82	0.00024
Ott and Zober (1996)	multiplicative-male	411.7 (201.9, □)	229.0 (112.3, □)	50.9 (25.0, □)	0.00019 (0, 0.00039)
	multiplicative-female[7]	478.0 (234.4, □)	272.1 (133.4, □)	62.1 (30.5, □)	0.00015 (0, 0.00032)

[1] Relative risk RR proportional to $(AUC)^{0.097}$, with 15 year lag

[2] Relative RR proportional to exp (0.000015 AUC). This is based on the linear function in the lower range of the piecewise linear model.

[3] When body burden exceeds 133 ng/kg, the AUC years exceeds 40,000 ppt years and the model cannot achieve the prescribed risk level

[4] Relative risk RR proportional to $(0.00017\ AUC + 1)^{0.326}$

[5] Relative risk RR proportional to (1+0.000016 AUC)

[6] Relative RR proportional to exp (0.00000869 AUC).

[7] Relative RR proportional to exp (0.0003522 x lipid concentration).

Table 8-3. Doses yielding 1% excess risk (95% lower confidence bound) based upon 2-year animal carcinogenicity studies using simple multistage models

		ED_{01}	
Tumor	**Shape**	**Intake for 1% excess risk (ng/kg/day)**	**Steady-state body burden (ng/kg) at ED_{01}**
Liver cancer in female rats (Kociba)	Linear	0.77 (0.57)	14 (10)
Squamous cell carcinoma of the tongue in male rats (Kociba)	Linear	14.1 (5.9)	254 (106)
Squamous cell carcinoma of the nasal turbinates or hard palate in male rats (Kociba)	Cubic	41.4 (1.2)	746 (22)
Squamous cell carcinoma of the lung in female rats (Kociba)	Cubic	40.4 (2.7)	730 (48)
Squamous cell carcinoma of the nasal turbinates or hard palate in female rats (Kociba)	Linear	5.0 (2.0)	90 (36)
Thyroid follicular cell adenoma in male rats (NTP)	Linear	4.0 (2.1)	144 (76)
Thyroid follicular cell adenoma in female rats (NTP)	Cubic	33.0 (3.1)	1,190 (112)
Liver adenomas and carcinomas in female rats (NTP)	Quadratic	13.0 (1.7)	469 (61)
Liver adenomas and carcinomas in male mice (NTP)	Linear	1.3 (0.86)	20.6 (13.6)
Liver adenomas and carcinomas in female mice (NTP)	Linear	15.1 (7.8)	239 (124)
Thyroid follicular cell adenomas and carcinomas in female mice (NTP)	Linear	30.1 (14.0)	478 (222)
Subcutaneous tissue sarcomas in female mice (NTP)	Lin-Cubic	43.2 (14.1)	686 (224)
Leukemias and lymphomas in female mice (NTP)	Linear	10.0 (5.4)	159 (86)

Table 8-4. Noncancer endpoints used for comparing ED_{01} values

Species	Gender	Multi-dose	Single-dose		Total
			Adult	Developmental	
Mouse	Female	25	23	5	53
	Male	0	35	20	55
	Unknown	—	—	3	3
Rat	Female	62	10	0	72
	Male	21	4	32	57
Hamster	Female	0	0	0	0
	Male	0	2	0	2
Total		**108**	**74**	**60**	**242**

Table 8-5. Ratio of ED_{01}/lowest dose, categorized by study type and endpoint type*

	Multi-dose		Single-Adult		Single-Developmental	
Category	**Out of range**	**In-range**	**Out of range**	**In-range**	**Out of range**	**In-range**
Biochemical	21 (16)	7	1 (1)	15	1(1)	0
Hepatic	4 (4)	9	0	13	—	—
Immune	8 (6)	8	13 (8)	3	—	—
Endocrine	6 (4)	3	—	—	—	—
Tissue	8 (6)	34	7 (4)	9	31 (17)	21
Toxicity	—	—	0	13	6 (0)	1
Subtotals	**47 (37)**	**61**	**21 (13)**	**53**	**38 (18)**	**22**
TOTALS	**108**		**74**		**60**	

* These data do not include analyses where a poor fit of the model to the data was obtained. "Out of range" indicates studies where the ED_{01} estimate was lower than the lowest dose used in the study. "In-range" indicates the estimate was within the experimental dose range used in the study from which the estimate was derived. Number of endpoints where the estimate was less than 1 order of magnitude lower than the lowest dose used are shown in parentheses.

Table 8-6. Estimated shape parameters, categorized by study type and endpoint type

	Multi-dose		Single-Adult		Single-Development	
Category	**Linear***	**Non-linear**	**Linear**	**Non-linear**	**Linear**	**Non-linear**
Biochemical	15	13	6	10	0	1
Hepatic	3	10	4	9	—	—
Immune	3	13	10	6	—	—
Endocrine	5	4	—	—	—	—
Tissue	21	21	10	6	14	38
Toxicity	—	—	0	13	4	3
Subtotals	**47**	**61**	**30**	**44**	**18**	**42**
TOTALS	**108**		**74**		**60**	

* "Linear" shape parameters are those where the Hill model coefficient n<1.5
These data do not include analyses where a poor fit of the model to the data was obtained.

Table 8-7. Categorization of specific endpoints

Category	Endpoint	
Biochemical	CYP 1A1 mRNA	Liver benzopyrene hydroxylase (CYP1A1 activity)
	CYP1A1 (Protein)	Liver cytochrome P-450 (Total)
	CYP1A1 EROD in liver, lung, and skin	Renal retinol concentration
	CYP1A2 (Protein)	Renal RPH activity
	CYP1A2 ACOH	Serum testosterone
	CYP1A2 mRNA	Superoxide anion production by PLC
	CYP1A2 MROD	T4UGT
	CYP1B1 mRNA	Total Ah Receptor binding
	EGF dissociation (Kd)	UGT mRNA
	EGFR autophosphorylation	UGT1A1
	EGFR maximum binding	
Hepatic	Serum 5'-nucleotidase	Serum Not Esterified chloesterol
	Serum alkaline phosphatase	Serum S. Dehydrogenase
	Serum ALT	Serum SGPT
	Serum BUN	Serum TBA
	Serum bilirubin (total, indirect, direct)	Serum total cholesterol
	Serum esterified cholesterol	Serum triglycerides
	Serum glucose	
Immune	CD4+/CD8+	Immune footpad swelling (following SRBC)
	CD8+/CD4-	Immune increment in ear thickness (following oxazalone)
	CD8-/CD4-	PFC/106 splenocytes
	CD4+/CD8-	PFC/spleen(x10-4)
	Cells/spleen(x10-6)	Total thymic cells/mouse
	Immune titer	

Table 8-7. Categorization of specific endpoints (continued)

Endocrine	Hepatic retinol	Plasma retinol	Hepatic retinyl-palmitate
	Thyroid-stimulating hormone	Thyroxine Free T4	
	Thyroxine	Thyroxine Total T4	
Tissue	Age at puberty	Epididymal sperm count	Relative kidney weight
	Body weight	Epididymidis weight	Relative liver weight
	Brain weight	Eye opening	Relative spleen weight
	Caput/corpus epid. sperm numbers	Eye opening in F/M	Relative thymus weight
	Cauda epid. sperm numbers	Glans penis weight	Seminal vesicle weight
	Cauda epididymal weight	Heart weight	Spleen atrophy
	Coagulating glands	Incisor eruption	Spleen cellularity
	Daily sperm production	Kidney weight	Testes weight
	Dorsal prostate weight	Liver weight	Thymus atrophy
	DSP/g D day 120	Ovarian weight	Thymus weight
	Endometrial lesion diameter	Ovulation (ova/rat)	Uterine horn weight
	Endometrial lesion weight	Paired epididymal weight	Uterus weight
		Pituitary gland weight	Ventral prostate weight
Toxicity	Cleft palate	Liver BDH	Sperm morphology
	Fertility index	Liver fatty change	Stomach edema
	Gestation period	Liver HCC	Testes MNGC
	Hydronephrosis	Liver HCK	Testes SFEN
	Litter size	Number of copulatory plugs	Testis descent
	Live birth index (%)	Pinna detachment	Total testis sperm numbers

Table 8-8. Steady-state ED_{01} values calculated using mechanism-based dose-response models of dioxin-regulated responses

	Response value			
Response	**Control (0 μg/kg/day)**	**Maximum (10 μg/kg/day)**	**ED_{01} (ng/kg/day)**	**Body burden $_{01}$ (ng/kg)[a]**
CYP1A1 (nmol/g)[b]	0.0216	6.09	0.0047	0.17
CYP1A2 (nmol/g)[b]	0.558	7.17	0.34	12.3
CYP1A2 (% liver induced)[c]			1.4	50.5
Internalized-EGFR (pmol/g)[b]	0	2.09	0.28	10.1
T_4 (nM)[b]	29.0	3.96	0.27	9.7
UGT RNA pmol/g	1.13	14.1	0.85	30.7
UDPGT (nmol/g)[b]	0.118	0.416	2.9	104.6
TSH pM[b]	77.8	179	1.3	46.9
Liver cancer[d]	0.35	1.00	0.15	2.7

[a]Steady-state body burdens were calculated from the formula in Section 8.2.3. assuming 100% absorption, except for the liver cancer model, which used 50% absorption.
[b]Values obtained using the extended thyroid hormone model.
[c]Values from the zonal induction model.
[d]Mechanism-based cancer model.

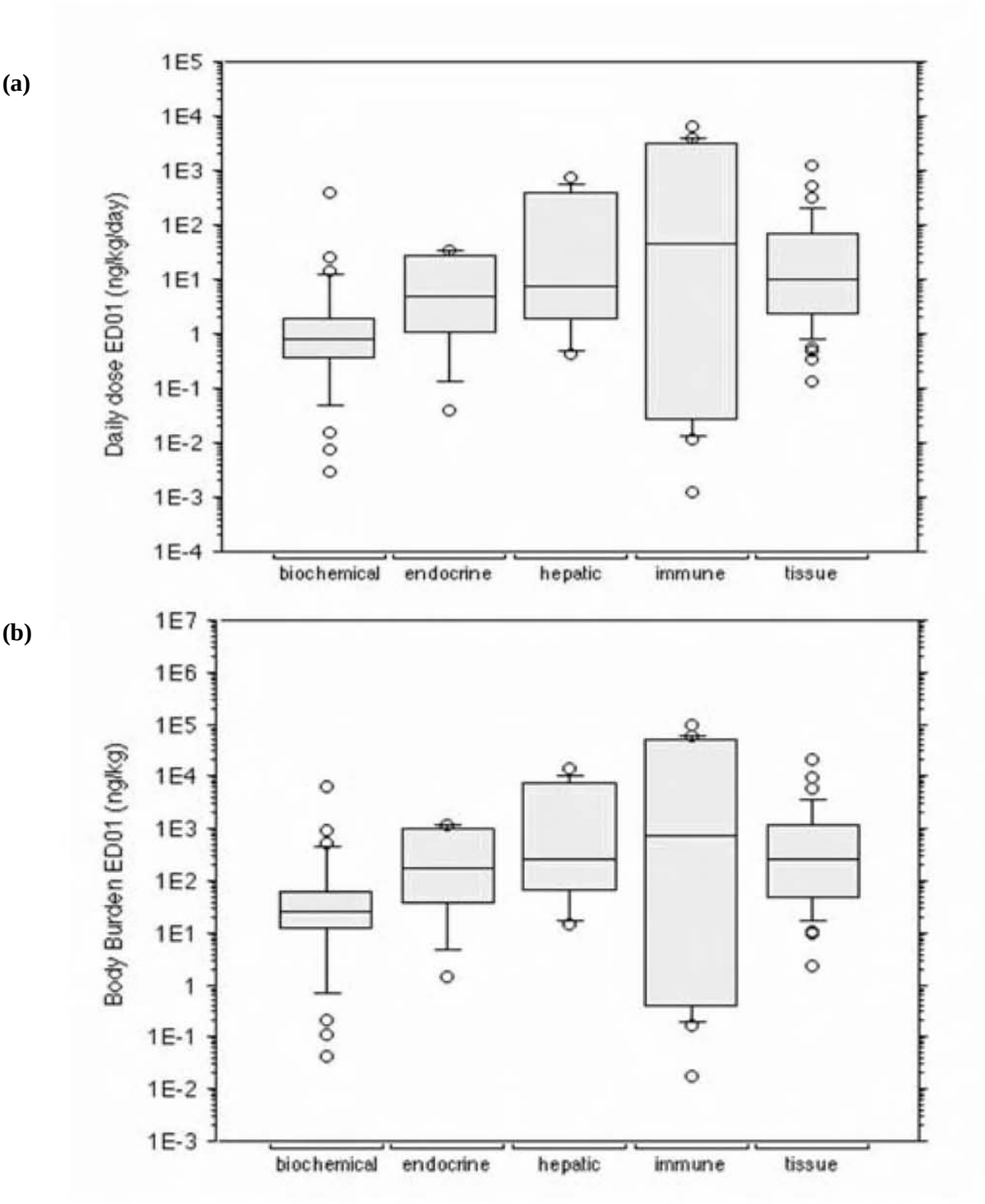
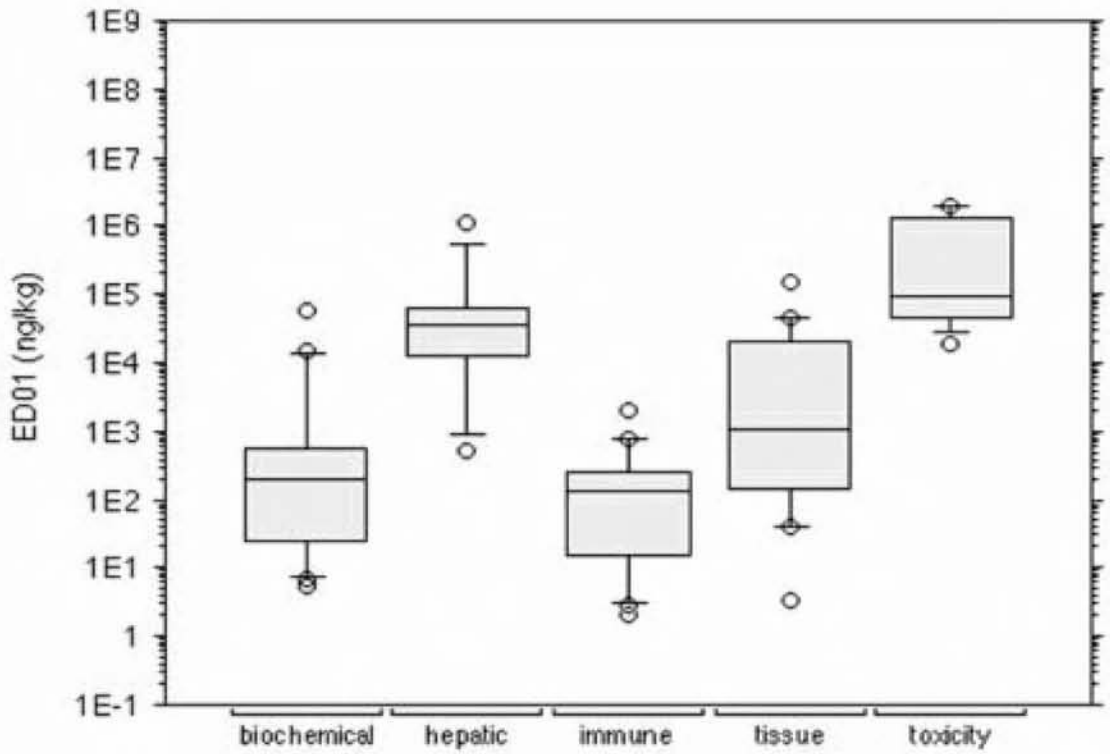


Figure 8-1. Distribution of ED_{01} and BB_{01} values in multidose studies by endpoint.
(a) ED_{01} values. **(b)** Body burden values at the ED_{01}. The distribution of individual values is presented as box plots. The boxed region contains values within the 25th to the 75th percentiles of the sample distribution, with the median value (50th percentile) shown as a line within the boxed region. The error bars represent values within the 10th to the 90th percentiles. Values above the 90th percentile and below the 10th percentile are shown as individual data points. Values are categorized according to Table 8-7.

(a)



(b)

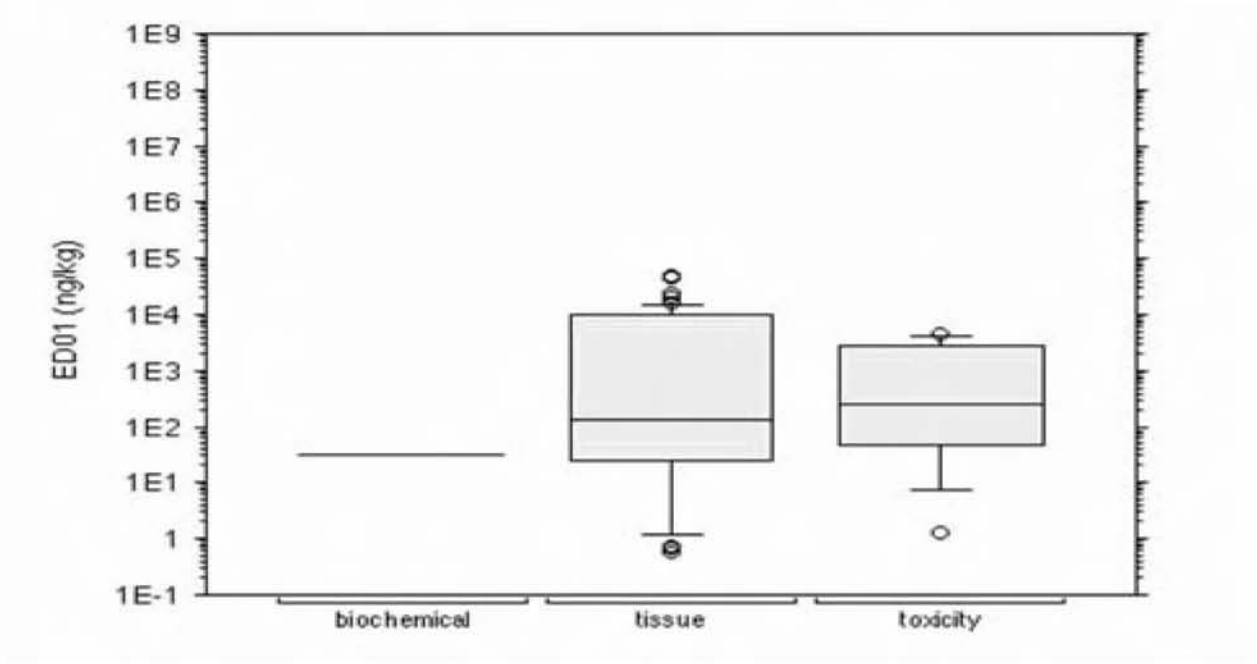


Figure 8-2. Distribution of ED_{01} values in single-dose studies by endpoint.
(a) Adult endpoints. **(b)** Developmental endpoints. The distribution of individual values is presented as box plots. The boxed region contains values within the 25th to the 75th percentiles of the sample distribution, with the median value (50th percentile) shown as a line within the boxed region. The error bars represent values within the 10th to the 90th percentiles. Values above the 90th percentile and below the 10th percentile are shown as individual data points. Values are categorized according to Table 8-7.

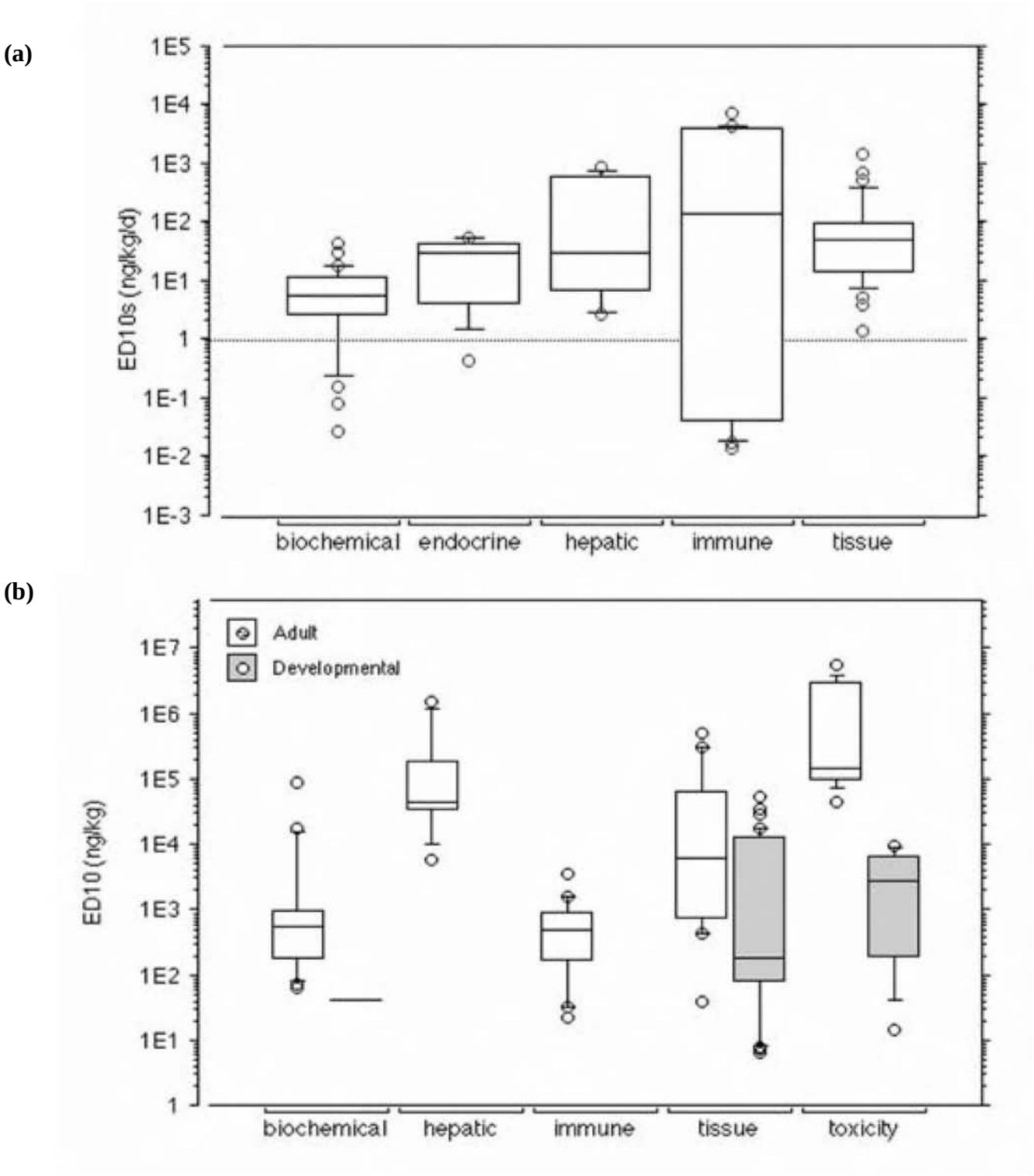


Figure 8-3. Distribution of ED_{10}s in multi-dose studies and single-dose studies by endpoint.
(a) Multi-dose studies. **(b)** Single-dose studies. The distribution of individual values is presented as box plots. The boxed region contains values within the 25th to the 75th percentiles of the sample distribution, with the median value (50th percentile) shown as a line within the boxed region. The error bars represent values within the 10th to the 90th percentiles. Values above the 90th percentile and below the 10th percentile are shown as individual data points. Values are categorized according to Table 8-7.

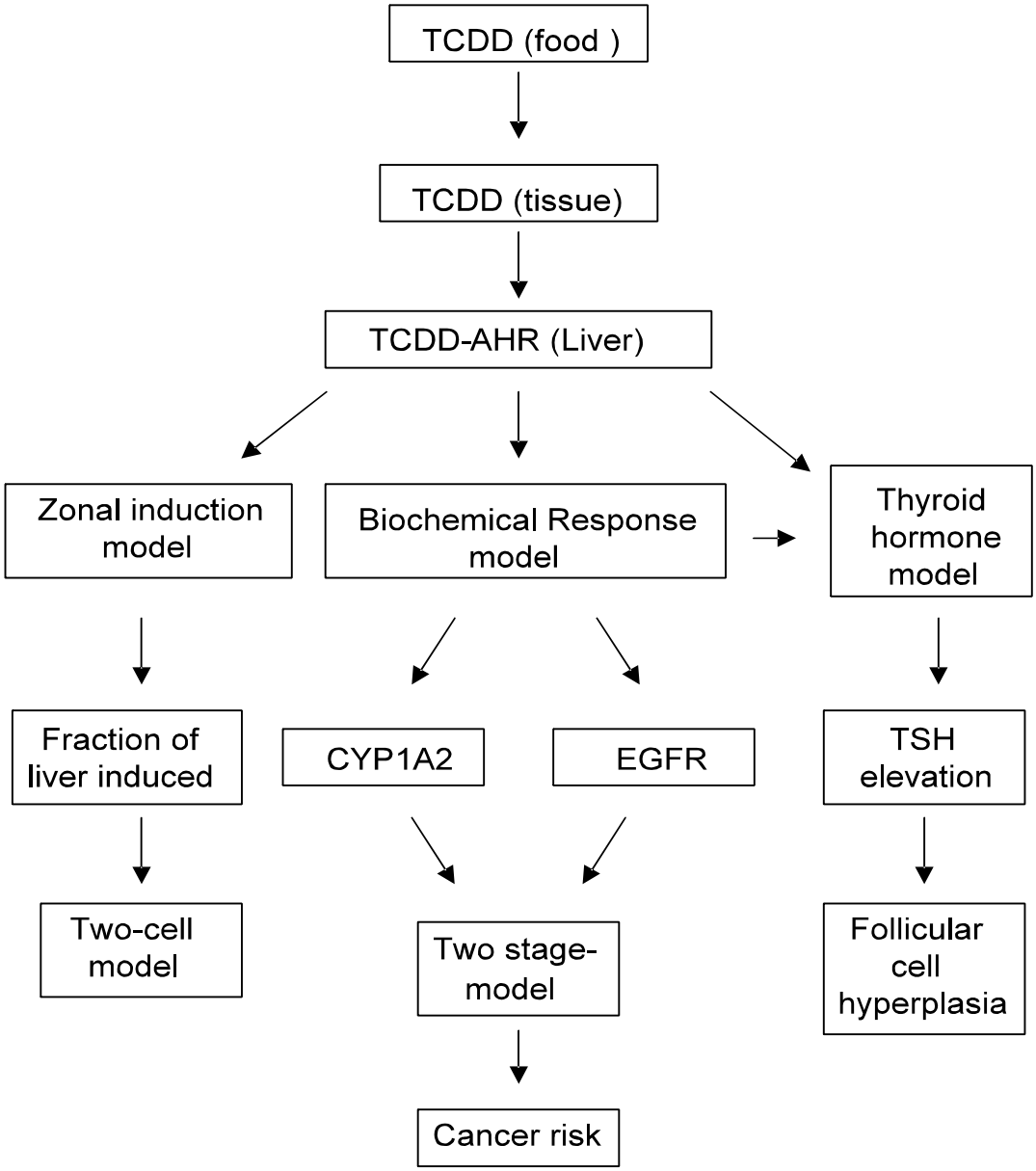


Figure 8-4. Schematic representation of the linkage of current PBPK models and biochemical/tissue response models for TCDD action.

Appendix I: Multiple-dose studies

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
Kociba et al. (1976), male Sprague-Dawley rats	13 weeks, 5x/wk, 1 ng/kg	Body weight	18.0	9.1E+01	1.6E+03	9.1E+01	1.0E+02	1.9E+03	1.0E+02	M
		Brain weight	5.7	5.4E+01	9.8E+02	5.4E+01	8.3E+01	1.5E+03	8.3E+01	M
		Rel brain weight	4.9	3.2E+02	5.9E+03	3.2E+02	5.2E+02	9.4E+03	5.2E+02	M
		Heart weight	6.4	6.8E+01	1.2E+03	6.8E+01	9.9E+01	1.8E+03	9.9E+01	M
		Kidney weight	7.4	6.2E+01	1.1E+03	6.2E+01	8.5E+01	1.5E+03	8.5E+01	M
		Liver weight	1.0	1.2E-01	2.3E+04	1.2E-01	1.4E+00	2.6E+01	1.4E+00	G
		Rel liver weight	1.0	1.1E+00	1.9E+01	1.1E+00	1.2E+01	2.1E+02	1.2E+01	G
		Serum alkaline phosphatase	6.2	3.8E+02	6.8E+03	3.8E+02	5.5E+02	9.9E+03	5.5E+02	M
		Serum BUN	6.9	5.1E+02	9.2	5.1E+02	7.1E+02	1.3E+04	7.1E+02	M
		Serum direct bilirubin	NA[i]	NA	NA	NA	NA	NA	NA	NF[j]
		Serum indirect bilirubin	NA	NA	NA	NA	NA	NA	NA	NF
		Serum total bilirubin	7.0	4.8E+02	8.7E+03	4.8E+02	6.7E+02	1.2E+04	6.7E+02	G
		Spleen weight	6.4	5.4E+01	9.8E+02	5.4E+01	7.9E+01	1.4E+03	7.9E+01	M
		Rel spleen weight	8.6	5.3E+02	9.5E+03	5.3E+02	6.9E+02	1.2E+04	6.9E+02	M

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		Rel testes weight	7.1	7.3E+01	1.3E+03	7.3E+01	1.0E+02	1.9E+03	1.0E+02	M
		Thymus weight	1.0	3.7E+00	6.7E+01	3.7E+00	4.0E+01	7.3E+02	4.0E+01	M
		Rel thymus weight	1.0	2.6E+00	4.8E+01	2.6E+00	3.0E+01	5.4E+02	3.0E+01	M
Kociba et al. (1976), female Sprague-Dawley rats	13 weeks, 5x/wk, 1 ng/kg	Body weight	1.0	4.8E+00	8.6E+01	4.8E+00	4.7E+01	8.5E+02	4.7E+01	G
		Brain weight	1.0	5.8E+00	1.1E+02	5.8E+00	6.5E+01	1.2E+03	6.5E+01	M
		Rel brain weight	5.8	6.8E+01	1.2E+03	6.8E+01	1.1E+02	1.9E+03	1.1E+02	M
		Heart weight	5.5	5.2E+01	9.4E+02	5.2E+01	8.1E+01	1.5E+03	8.1E+01	M
		Kidney weight	7.3	5.1E+02	9.8E+03	5.1E+02	7.0E+02	1.3E+04	7.0E+02	M
		Liver weight	7.1	6.0E+00	1.1E+02	6.0E+00	8.4E+00	1.5E+02	8.4E+00	M
		Rel liver weight	1.1	5.4E-01	9.8E+00	5.4E-01	5.2E+00	9.4E+01	5.2E+00	G
		Serum alkaline phosphatase	7.7	7.3E+00	1.3E+02	7.3E+00	9.9E+00	1.8E+02	9.9E+00	M
		Serum direct bilirubin	1.0	6.8E+00	1.2E+02	6.8E+00	7.5E+01	1.3E+03	7.5E+01	M
		Serum indirect bilirubin	NA	NA	NA	NA	NA	NA	NA	NF
		Serum total bilirubin	18.0	7.7E+02	1.4E+04	7.7E+02	8.8E+02	1.6E+04	8.8E+02	M

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		Serum SGPT	14.1	2.3E+02	4.2E+03	2.3E+02	2.8E+02	5.0E+03	2.8E+02	P
		Thymus weight	1.0	1.3E+00	2.3E+01	1.3E+00	1.4E+01	2.5E+02	1.4E+01	G
		Rel thymus weight	1.0	1.0E+00	1.9E+01	1.0E+00	1.1E+01	2.0E+02	1.1E+01	G
Clark et al. (1981), male C57Bl/6 mice	4 weeks, 1x/wk, 1 week after last dose, 400 ng/kg	Immune footpad swelling (following SRBC)	7.0	2.6E+03	3.8E+04	5.7E+01	2.8E+04	4.1E+05	6.1E+02	P
		Immune increment in ear thickness (following oxazalone)	18.0	1.6E+02	2.3E+03	3.4E+00	1.6E+03	2.3E+04	3.4E+01	P
Tritscher et al. (1992), female Sprague-Dawley rats	31 weeks, 1x/2 weeks, 3.5 ng/kg/day	CYP1A1 (Protein) (DEN)	1.2	4.1E-01	1.5E+01	1.2E-01	3.0E+00	1.1E+02	8.6E-01	G
		CYP1A1 (Protein) (saline)	1.0	3.5E-01	1.3E+01	10.0E-02	3.8E+00	1.4E+02	1.1E+00	G
		CYP1A2 (Protein) (DEN)	1.0	5.1E-01	1.9E+01	1.5E-01	5.6E+00	2.0E+02	1.6E+00	G
		CYP1A2 (Protein) (saline)	1.0	3.6E-01	1.3E+01	1.0E-01	3.9E+00	1.4E+02	1.1E+00	G

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
Fox et al. (1993), female Sprague-Dawley rats	7 days, 5 ng/kg (initial dose), 0.9 ng/kg/4 days until 0.03 ng/g steady-state achieved	Body weight	15.2	1.2E+03	2.2E+04	1.4E+03	1.4E+03	2.5E+04	1.7E+03	M
		Body weight change	2.5	7.9E+01	1.4E+03	9.4E+01	2.0E+02	3.6E+03	2.4E+02	M
		Liver weight	11.2	3.3E+01	6.0E+02	3.9E+01	4.1E+01	7.3E+02	4.8E+01	M
		Liver weight:body weight ratio	1.0	9.6E-01	1.7E+01	1.1E+00	9.8E+00	1.8E+02	1.2E+01	G
Fox et al. (1993), female Sprague-Dawley rats	14 days, 5 ng/kg (initial dose), 0.9 ng/kg/4 days until 0.03 ng/g steady-state achieved	Body weight	1.0	2.0E+00	3.6E+01	3.7E+00	2.1E+01	3.8E+02	3.9E+01	G
		Body weight change	2.7	5.5E+01	1.0E+03	1.0E+02	1.4E+02	2.4E+03	2.5E+02	G
		Liver weight	1.0	1.2E+00	2.2E+01	2.2E+00	1.3E+01	2.4E+02	2.4E+01	G
		Liver weight:body weight ratio	1.0	1.9E+01	3.4E+02	3.5E+01	1.9E+02	3.4E+03	3.5E+02	M

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
Fox et al. (1993), male Sprague-Dawley rats	7 days, 5 ng/kg (initial dose), 0.9 ng/kg/4 days until 0.03 ng/g steady-state achieved	Body weight	5.3	9.2E-06	1.7E-04	1.1E-05	1.5E-05	2.6E-04	1.7E-05	P
		Body weight change	2.4	1.3E+02	2.3E+03	1.5E+02	3.4E+02	6.2E+03	4.1E+02	M
		Liver weight	1.0	2.8E+00	5.0E+01	3.3E+00	3.1E+01	5.5E+02	3.6E+01	G
		Liver weight:body weight ratio	3.1	7.7E+01	1.4E+03	9.1E+01	1.7E+02	3.0E+03	2.0E+02	G
Fox et al. (1993), male Sprague-Dawley rats	14 days, 5 ng/kg (initial dose), 0.9 ng/kg/4 days until 0.03 ng/g steady-state achieved	Body weight	18	1.2E-05	2.2E-04	2.3E-05	1.4E-05	2.6E-04	2.6E-05	P
		Body weight change	18	1.1E+03	2.0E+04	2.0E+03	1.3E+03	2.3E+04	2.3E+03	P
		Liver weight	6.2	6.3E+00	1.1E+02	1.1E+01	9.2E+00	1.7E+02	1.7E+01	M
		Liver weight:body weight ratio	2.5	3.4E+01	6.1E+02	6.2E+01	8.9E+01	1.6E+03	1.6E+02	G
Maronpot et al. (1993), female Sprague-Dawley rats	31 weeks, 1x/2weeks, 3.5 ng/kg/day (DEN-initiated)	Serum 5'-nucleotidase	1.9	8.3E-01	3.0E+01	2.4E-01	3.0E+00	1.1E+02	8.5E-01	G

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		Serum alkaline phosphatase	2.4	7.6E+00	2.7E+02	2.2E+00	2.0E+01	7.4E+02	5.8E+00	M
		Serum s. dehydrogenase	1.0	5.1E-01	1.8E+01	1.5E-01	5.6E+00	2.0E+02	1.6E+00	G
		Serum total cholesterol	1.3	4.2E-01	1.5E+01	1.2E-01	2.6E+00	9.3E+01	7.4E-01	G
		Serum triglycerides	18.0	2.8E+01	1.0E+03	8.0E+00	3.2E+01	1.2E+03	9.2E+00	M
Maronpot et al. (1993), female Sprague-Dawley rats	31 weeks, 1x/2 weeks, 3.5 ng/kg/day (SALINE)	Serum 5'-nucleotidase	18.0	2.6E+01	9.2E+02	7.3E+00	2.9E+01	1.1E+03	8.3E+00	G
		Serum total cholesterol	2.0	2.3E+00	8.3E+01	6.6E-01	7.4E+00	2.7E+02	2.1E+00	G
		Serum triglycerides	18.0	9.1E+01	3.3E+03	8.0E+00	1.1E+02	3.8E+03	3.0E+01	P
Sewall et al. (1993), female Sprague-Dawley rats	31 weeks, 1x/2 weeks, 3.5 ng/kg/day (DEN-initiated and saline-treated)	EGF dissociation (K_d) (DEN)	1.0	8.1E-01	2.9E+01	2.3E-01	8.9E+00	3.2E+02	2.6E+00	M
		EGF dissociation (K_d) (saline)	18.0	1.4E+01	5.0E+02	4.0E+00	1.6E+01	5.9E+02	4.7E+00	M

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		EGFR autophospho-rylation	1.0	4.9E-01	1.8E+01	1.4E-01	5.1E+00	1.8E+02	1.5E+00	G
		EGFR Maximum binding (DEN)	1.6	1.7E+00	6.1E+01	4.8E-01	7.7E+00	2.8E+02	2.2E+00	G
		EGFR Maximum binding (saline	1.5	3.8E-01	1.4E+01	1.1E-01	1.9E+00	6.8E+01	5.4E-01	G
DeVito et al. (1994), female B6C3F1 mice	13 weeks, 5x/week, 1.5 ng/kg/day	CYP1A1 EROD	1.6	3.2E+00	5.1E+01	2.1E+00	1.5E+01	2.3E+02	9.8E+00	G
		CYP1A1 EROD lung	1.3	6.1E-01	9.7E+00	4.1E-01	3.7E+00	5.8E+01	2.5E+00	G
		CYP1A1 EROD skin	NA	NA	NA	NA	NA	NA	NA	NF
		CYP1A2 ACOH	1.0	1.2E-01	1.9E+00	8.2E-02	1.3E+00	2.1E+01	9.0E-01	G
Schrenck et al. (1994), female Wistar rat	13 weeks, 1x/2 weeks, 2 ng/kg	Body weight	10.7	1.3E+01	4.2E+02	6.6E+00	1.7E+01	5.3E+02	8.3E+00	G
		CYP1A1 EROD	1.2	8.2E-01	2.6E+01	4.1E-01	5.6E+00	1.8E+02	2.8E+00	G
		Relative liver weight	1.0	3.5E-01	1.1E+01	1.8E-01	3.9E+00	1.2E+02	1.9E+00	G

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
Sewall et al. (1995), female Sprague-Dawley rats	31 weeks, 1x/2 weeks, 3.5 ng/kg/day, (DEN-initiated)	CYP 1A1 mRNA	18.0	2.6E+01	9.4E+02	7.4E+00	3.0E+01	1.1E+03	8.5E+00	M
		Thyroid-stimu-lating hormone	12.1	2.6E+01	9.3E+02	7.4E+00	3.1E+01	1.1E+03	9.0E+00	M
		Thyroxine	1.9	1.3E+00	4.8E+01	3.8E-01	4.7E+00	1.7E+02	1.3E+00	G
		UGT mRNA	16.0	3.7E-01	1.3E+01	1.1E-01	4.3E-01	1.6E+01	1.2E-01	M
VanBirgelen et al. (1995), female Sprague-Dawley rats	13 weeks, 1x/day, 14 ng/kg/d	CYP1A1 EROD	1.3	1.0E+00	3.8E+01	7.5E-02	6.9E+00	2.5E+02	4.9E-01	G
		T4UGT	1.0	1.6E+00	5.8E+01	1.1E-01	1.8E+01	6.3E+02	1.3E+00	G
		Thyroxine ft4	1.0	4.9E+00	1.8E+02	3.5E-01	5.4E+01	1.9E+03	3.8E+00	M
		Thyroxine tt4	16.6	3.3E+01	1.2E+03	2.4E+00	3.8E+01	1.4E+03	2.7E+00	M
		UGT1A1	1.7	1.5E+00	5.3E+01	1.0E-01	6.0E+00	2.2E+02	4.3E-01	M
VanBirgelen et al. (1995b), female Sprague-Dawleyrats	13 weeks, 1x/day, 14ng/kg/d	Body weight	1.0	4.3E+00	1.6E+02	3.1E-01	4.7E+01	1.7E+03	3.4E+00	G
		CYP1A1 EROD	1.0	6.1E-01	2.2E+01	4.3E-02	6.7E+00	2.4E+02	4.8E-01	G
		CYP1A2 ACOH	2.1	2.1E+00	7.4E+01	1.5E-01	6.5E+00	2.3E+02	4.6E-01	M

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		Hepatic retinol	1.0	2.8E-01	1.0E+01	2.0E-02	3.1E+00	1.1E+02	2.2E-01	G
		Hepatic retinyl-palmitate	1.0	4.0E-02	1.5E+00	2.9E-03	4.4E-01	1.6E+01	3.2E-02	G
		Liver weight	18.0	2.2E+02	8.0E+03	1.6E+01	2.5E+02	9.1E+03	1.8E+01	P
		Liver weight:body weight ratio	1.0	4.9E+00	1.8E+02	3.5E-01	5.4E+01	2.0E+03	3.9E+00	G
		Plasma retinol	1.2	2.3E+00	8.2E+01	1.6E-01	1.7E+01	6.0E+02	1.2E+00	G
		Relative kidney weight	1.0	4.8E-01	1.7E+01	3.4E-02	5.3E+00	1.9E+02	3.8E-01	G
		Relative spleen weight	0.9[f]	4.9E+00	1.8E+02	3.5E-01	7.4E+01	2.7E+03	5.3E+00	G
		Relative thymus weight	1.0	3.0E+00	1.1E+02	2.1E-01	3.3E+01	1.2E+03	2.3E+00	M
		Thymus weight	1.0	2.5E+00	8.9E+01	1.8E-01	2.7E+01	9.7E+02	1.9E+00	M
		Thyroxine ft4	1.0	4.9E+00	1.8E+02	3.5E-01	5.4E+01	1.9E+03	3.8E+00	G
		Thyroxine tt4	16.6	3.3E+01	1.2E+03	2.4E+00	3.8E+01	1.4E+03	2.7E+00	M
Rhile et al. (1996), female DBA/2 mice	11 days, 1x/day, 100 ng/kg	Total thymic cells/mouse	8.5	6.5E+02	1.0E+04	6.5E+00	8.6E+02	1.4E+04	8.6E+00	M
		CD8+ cells	NA	NA	NA	NA	NA	NA	NA	NF
		CD8+/CD4+	18.0	6.4E+03	1.5E+05	6.4E+01	7.2E+03	1.1E+05	7.2E+01	M
		CD8-/CD4-	NA	NA	NA	NA	NA	NA	NA	NF

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		CD4+	17.5	1.7E+02	2.7E+03	1.7E+00	1.9E+02	3.0E+03	1.9E+00	M
Rhile et al. (1996), female C57 BL/6 mice	11 days, 1x/day, 100 ng/kg	Total thymic cells/mouse	15.0	7.5E+01	1.2E+03	7.5E-01	8.9E+01	1.4E+03	8.9E-01	M
		CD8+ cells	13.5	3.4E+03	5.4E+04	3.4E+01	4.1E+03	6.5E+04	4.1E+01	M
		CD8+/CD4+	11.2	3.2E+03	4.9E+04	3.1E+01	3.8E+03	6.1E+04	3.8E+01	G
		CD8-/CD4-	1.0	9.9E-01	1.6E+01	9.9E-03	1.1E+01	1.7E+02	1.1E-01	G
Rhile et al. (1996), female C57BL/6 lpr/lpr mice	11 days, 1x/day, 100 ng/kg	Total thymic cells/mouse	1.0	1.6E+01	2.5E+02	1.6E-01	1.8E+02	2.8E+03	1.8E+00	G
		CD8+ cells	18.0	3.8E+03	6.1E+04	3.8E+01	4.3E+03	6.9E+04	4.3E+01	M
		CD8+/CD4+	18.0	2.8E+04	4.5E+05	2.9E+02	3.3E+04	5.2E+05	3.3E+02	P
		CD8-/CD4-	15.3	1.2E+04	1.9E+05	1.2E+02	1.4E+04	2.3E+05	1.4E+02	P
		CD4+	18.0	3.6E+04	5.7E+05	3.6E+01	4.1E+03	6.5E+04	4.1E+01	M
Vogel et al. (1997), female C57BL/6 mice	23 days, 1 ng/kg (initial dose), 0.2 ng/kg/week (3x total)	Immune CD4+/CD8- (23 d)	6.1	2.9E-02	4.2E-01	4.2E-01	4.3E-02	6.3E-01	6.2E-01	G
		Immune CD4-/CD8- (23 d)	1.0	1.3E-03	1.8E-02	1.8E-02	1.4E-02	2.0E-01	2.0E-01	M
		Immune CD4-/CD8+ (23 d)	6.1	2.5E-02	3.7E-01	3.6E-01	3.8E-02	5.5E-01	5.4E-01	G

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
		ImmuneCD4+/ CD8+ (23 d)	5.5	2.7E-02	3.9E-01	3.8E-01	4.2E-02	6.0E-01	5.9E-01	G
Vogel et al. (1997), female C57BL/6 mice	79 days, 1 ng/kg (initial dose), 0.2 ng/kg/week, (7x total)	Immune CD4+/CD8- (79 d)	13.4	6.2E-02	8.9E-01	2.1E+00	7.4E-02	1.1E+00	2.5E+00	P
		Immune CD4-/CD8- (79 d)	18.0	7.9E-02	1.1E+00	2.6E+00	9.0E-02	1.3E+00	3.0E+00	G
		ImmuneCD4-/CD8+ (79 d)	6.6	1.2E-02	1.7E-01	4.0E-01	1.7E-02	2.5E-01	5.7E-01	M
Vogel et al. (1997), female C57BL/6 mice	135 days, 1 ng/kg (initial dose), 0.2 ng/kg/week until 0.034 ng/kg steady-state reached	CYP1A1 EROD (135 d)	1.0	7.4E-03	1.1E-01	2.2E-01	8.0E-02	1.2E+00	2.4E+00	G
		CYP1A1 mRNA (135 d)	8.1	1.7E+00	2.5E+01	5.0E+01	2.3E+00	3.3E+01	6.7E+01	G
		CYP1A2 mRNA (135 d)	1.1	3.0E-03	4.3E-02	8.7E-02	2.7E-02	3.9E-01	7.9E-01	G
		CYP1A2 MROD (135 d)	1.0	1.5E-02	2.2E-01	4.6E-01	1.6E-01	2.4E+00	4.8E+00	G

Appendix I: Multiple-dose studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Body burden ED_{01}(ng/kg)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Body burden ED_{10} (ng/kg)	Relative ED_{10}[c]	Quality of fit[d]
Johnson et al. (1997), female B6C3F1 mice	18 weeks, 1x/3 wks (5x total), 3 weeks after last, 1,000 ng/kg	CYP1A1 EROD	2.8	1.9E+01	6.2E-03	8.2E+00	4.2E+01	6.6E+02	8.8E-01	G
		Endometrial lesion diameter	NA	NA	NA	NA	NA	NA	NA	NF
		Endometrial lesion weight	NA	NA	NA	NA	NA	NA	NA	NF
		Liver weight	1.1	7.7E+00	1.2E+02	1.6E-01	6.2E+01	9.8E+02	1.3E+00	G
		Thymus weight	NA	NA	NA	7.3E+00	NA	NA	NA	NF
		Ovarian weight	15.2	3.5E+02	5.5E+03	NA	4.1E+02	6.4E+03	8.5E+00	P
Walker et al. (1999), female Sprague-Dawley Rats	31 weeks, 1x/2 weeks, 3.5 ng/kg/day, (DEN-initiated)	CYP1A1 mRNA	2.0	1.6E+00	5.9E+01	4.7E-01	5.6E+00	2.0E+02	1.6E+00	G
		CYP1A2 mRNA	3.0	7.6E+00	2.7E+02	2.2E+00	1.7E+01	6.1E+02	4.8E+00	G
		CYP1B1 mRNA	3.1	7.0E+00	2.5E+02	2.0E+00	1.5E+01	5.4E+02	4.3E+00	G

[a]Dose regimen is described by study duration, exposure frequency, and lowest dose used in the study.
[b]Unless noted otherwise, the Hill model was used to fit these data.
[c]Relative ED_X effect is the ratio of daily ED_X to the lowest daily doselevel used in the study from the study.
[d]Qualitative assessment of fit: G=good (model curve goes through/near all data point mean); M=marginal (model within one std. deviation of mean); P=poor (model not within one std. deviation of means).
[e]NR- In some cases, BMDS (U.S. EPA, 1999) fails to locate a lower confidence bound on the 1% effective dose.
[f]Power model was used for these data.
[h]NR- Quality of fit was not assessed for this endpoint.

Appendix I: Multiple-dose studies (continued)

[i]NA-Models in BMDS (U.S. EPA, 1999) not applicable to these data.
[j]NF - Quality of fit not assessed for this endpoint.

Appendix II: Single-dose adult studies

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
Kitchin & Woods (1979), female Sprague-Dawley rats	3 days, 0.6 ng/kg	Liver cytochrome P-450 (total)	1.0	1.5E+01	2.6E+01	1.7E+02	2.8E+02	G
		Liver benzopyrene hydroxylase (CYP1A1 activity)	17.7	1.4E+03	2.4E+03	1.6E+03	2.7E+03	P
Olson et al. (1980), male Golden Syrian hamsters	50 days, 5,000 ng/kg	Thymus weight	1.1	3.7E+03	7.3E-01	3.5E+04	6.9E+00	G
		Spleen weight	3.5	1.5E+05	3.1E+01	3.0E+05	6.1E+01	M
Vecchi et al. (1983), female B6 mice	12 days, 1,200 ng/kg	Body weight	12.0	2.0E+04	1.6E+01	2.4E+04	2.0E+01	G
		Thymus weight	1.4	1.5E+02	1.3E-02	8.3E+02	6.9E-01	G
		PFC/1E+06 splenocytes	1.0	2.7E+00	2.3E-04	1.3E+02	1.1E-01	G
		PFC/spleen	1.0	3.9E+00	3.3E-04	2.1E+02	1.7E-01	G
Vecchi et al. (1983), female C3 mice	12 days, 1,200 ng/kg	Body weight	11.1	4.4E+03	3.6E-01	5.4E+03	4.5E+00	P
		Thymus weight	1.0	3.9E+01	3.3E-03	4.3E+02	3.6E-01	G
Vecchi et al. (1983), female D2 mice	12 days, 1,200 ng/kg	Body weight	17.8	3.8E+05	3.1E+02	4.3E+05	3.6E+02	P
		Thymus weight	1.0	3.5E+00	2.9E-03	3.8E+01	3.2E-02	M
		PFC/1E+06 splenocytes	1.0	5.2E+01	4.3E-02	5.7E+02	4.7E-01	G
		PFC/spleen	1.3	1.3E+02	1.1E-01	8.5E+02	7.1E-01	G

Appendix II: Single-dose adult studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
Vecchi et al. (1983), female B6D2F1 mice	12 days, 1,200 ng/kg	Thymus weight	1.0	6.1E+01	5.1E-02	6.6E+02	5.5E-01	G
		PFC/1E+06 splenocytes	1.0	1.4E+01	1.2E-03	1.6E+03	1.3E+00	G
		PFC/spleen	1.0	1.4E+01	1.2E-03	1.5E+03	1.2E+00	G
Abraham et al, (1988), female Wistar rats	7 days, 1 ng/kg	Liver EROD (CYP1A1 activity)	1.1	1.6E+01	1.6E+01	7.3E+01	7.3E+01	G
		Liver cytochrome P450 (total)	1.0	6.7E+00	6.7E+00	1.4E+02	1.4E+02	G
Davis and Safe (1988), male 657BL/6J mice	9 days, 1 nmol/kg	Spleen cellularity	18.0	4.5E+02	1.4E+00	5.2E+02	1.6E+00	M
		PFCs/spleen	4.2	2.0E+02	6.3E-01	3.6E+02	1.1E+00	G
		PFCs/1E+06 viable cells	4.0	2.1E+02	6.5E-01	3.8E+02	1.2E+00	G
Birnbaum et al. (1990), male C57BL/6J (Ahb/b) mice	35 days, 50 ng	Serum TBA	18.0	4.6E+04	9.1E+02	5.2E+04	1.0E+03	M
		Serum SDH	2.8	1.7E+04	3.4E+02	3.9E+04	7.8E+02	M
		Serum ALT	2.4	1.6E+04	3.2E+02	4.3E+04	8.6E+02	M
		Serum 5'-NUC	18.0	8.8E+04	1.8E+03	1.0E+05	2.0E+03	M
		Serum glucose	18.0	5.3E+04	1.1E+03	6.0E+04	1.2E+03	M
Birnbaum et al. (1990), male C57BL/6J (Ahb/b) mice	35 days, 50 ng	Serum total cholesterol	18.0	3.5E+04	6.9E+02	4.0E+04	7.9E+02	M
		Serum NEChol	4.7	7.6E-04	1.5E-05	1.3E-03	2.5E-05	P

Appendix II: Single-dose adult studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
		Serum Echol	18.0	3.5E+04	7.1E+02	4.0E+04	8.1E+02	M
		Liver Hepatocellular cytomegaly	7.2[g]	8.5E+04	1.7E+03	1.2E+05	2.3E+03	G
		Liver Hepatocellular karyomegaly	5.8[g]	3.0E+04	6.0E+02	4.5E+04	8.9E+02	G
		Fatty liver change	7.9[g]	5.8E+04	1.2E+03	7.8E+04	1.6E+03	G
		Liver bile duct hyperplasia	2.6[g]	4.8E+04	9.6E+02	1.2E+05	2.4E+03	G
		Thymic atrophy	2.0[g]	2.3E+04	4.6E+02	7.6E+04	1.5E+03	G
		Splenic atrophy	1.9[g]	1.6E+04	3.3E+02	5.5E+04	1.1E+03	G
		Testes: multinucleated spermatid giant cells	2.3[g]	3.7E+04	7.4E+02	1.0E+05	2.1E+03	G
		Testes: seminiferous tubule epithelium necrosis	6.9[g]	1.0E+05	2.0E+03	1.4E+05	2.9E+03	G
		Gland. stomach edema	1.5[g]	1.8E+04	3.7E+02	8.6E+04	1.7E+03	G
Birnbaum et al. (1990), male C57BL/6J (Ahd/d) mice	35 days, 400 ng	Serum TBA	2.3	4.0E+05	9.9E+02	1.1E+06	2.7E+03	M
		Serum SDH	7.1	1.1E+06	2.1E+04	1.5E+06	3.8E+03	M
		Serum ALT	1.0	4.2E+04	1.0E+02	4.2E+05	1.0E+03	M
		Serum 5'-NUC	18.0	3.2E+05	8.1E+02	3.7E+05	9.2E+02	P
		Serum glucose	18.0	6.1E+05	1.5E+03	6.9E+05	1.7E+03	P

Appendix II: Single-dose adult studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
		Serum triglycerides	18.0	1.8E+06	4.6E+03	2.1E+06	5.3E+03	P
		Serum total cholesterol	1.0	5.1E+02	1.3E+00	5.6E+03	1.4E+01	G
		Serum NEChol	1.0	1.0E+03	2.5E+00	1.1E+04	2.8E+01	G
		Serum Echol	1.0	1.7E+03	4.2E+00	1.8E+04	4.6E+01	G
		Liver Hepatocellular cytomegaly	4.2[g]	1.5E+06	3.8E+03	2.7E+06	6.7E+03	M
		Liver Hepatocellular karyomegaly	3.1[g]	9.2E+04	2.3E+02	1.9E+05	4.9E+02	M
		Fatty Liver change	2.6[g]	6.9E+05	1.7E+03	1.7E+06	4.3E+03	M
		Liver BDH	1.6[g]	1.3E+06	3.2E+03	5.4E+06	1.3E+04	M
		Thymic atrophy	1.0[g]	4.7E+04	1.2E+02	4.9E+05	1.2E+03	M
		Splenic atrophy	1.0[g]	2.3E+04	5.8E+01	2.4E+05	6.1E+02	M
		Testes: seminiferous tubule epithelium necrosis	4.2[g]	1.9E+06	4.9E+03	3.4E+06	8.5E+03	G
		Gland. stomach edema	4.2[g]	1.9E+06	4.9E+03	3.4E+06	8.5E+03	G
Jurek et al. (1990), male Sprague-Dawley rats	12 days, 1 nmol/kg	Body weight	1.0	9.2E+02	2.9E+00	1.0E+04	3.1E+01	M
		Liver weight:body weight ratio	8.2	1.1E+06	3.5E+03	1.4E+03	4.2E+00	P
		Kidney weight:body weight ratio	2.7	3.4E-03	1.1E-05	8.3E-03	2.6E-05	P

Appendix II: Single-dose adult studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
		Renal retinol concentration	12.3	2.0E+03	6.3E+00	2.5E+03	7.6E+00	M
		Renal RPH activity	18.0	1.5E+04	4.5E+01	1.7E+04	5.2E+01	M
Alsharif et al. (1994), female Sprague-Dawley rats	1 day, 5 ng/kg	Superoxide anion production by PLC	5.4	5.7E+04	1.1E+04	8.9E+04	1.8E+04	G
Narasimhan et al. (1994), female B6C3F1 mice	24 hrs., 5 ng/kg	Liver EROD (CYP1A1 activity)	1.1	8.4E+01	1.7E+01	7.2E+02	1.4E+02	G
		Liver CYP1A1 (mRNA)	1	5.6E+00	1.1E+00	6.2E+01	1.2E+01	G
		Liver CYP1A2 (mRNA)	3.2	1.7E+02	3.4E+01	3.7E+02	7.3E+01	G
		Spleen PFC/1E+06cells	1.0	2.0E+00	4.1E-01	2.2E+01	4.5E+00	G
	4 days, 5 ng/kg	Total AhR binding	3.8	3.5E+02	7.0E+01	6.5E+02	1.3E+02	G
Harper et al. (1994), male C57BL/6 mice	8 days, 0.6 mg/kg	Immune titer	4.8	3.0E+02	5.0E-01	5.0E+02	8.3E-01	G
		PFC/1E+06 cells	6.1	3.3E+02	5.5E-01	4.9E+02	8.1E-01	M
Smialowicz et al. (1994), male F344 rats	1x followed by immunization with SRBC 7 days later, 100 ng/kg	PFC/1E+06 cells	18.0	1.6E+04	1.6E+02	1.8E+04	1.8E+02	P
		PFC/spleen($\times 10^{-4}$)	18.0	2.3E+04	2.3E+02	2.6E+04	2.6E+02	P
		Cells/spleen($\times 10^{-6}$)	18.0	7.3E+03	7.3E+01	8.3E+03	8.3E+01	P
		Titer(log2)	1.4	1.2E+02	1.2E+00	6.9E+02	6.9E+00	G

Appendix II: Single-dose adult studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
Smialowicz et al. (1994), female F344 rats	1x followed by immunization with SRBC 7 days later, 100 ng/kg	PFC/1E+06 cells	1.0	3.4E+02	3.4E+00	3.4E+03	3.4E+01	P
		PFC/spleen($\times 10^{-4}$)	1.0	3.6E+02	3.6E+00	3.6E+03	3.6E+01	P
Smialowicz et al. (1994), female B6C3F1 mice	1x followed by immunization with SRBC 7 days later, 300 ng/kg	PFC/1E+06 cells	1.0	2.9E+00	9.6E-03	3.2E+01	1.1E-01	M
		PFC/spleen($\times 10^{-4}$)	1.1	4.4E+00	1.5E-02	4.0E+01	1.3E-01	G
Vanden Heuvel et al. (1994a), female Sprague-Dawley rats	4 days, 0.1 ng/kg	CYP1A1 mRNA	3.6	3.9E+02	3.9E+03	7.7E+02	7.7E+03	G
		UGT mRNA	1.4	3.5E+01	3.5E+02	1.9E+02	1.9E+03	G
Diliberto et al. (1995), female B6C3F1 mice	S, 7, 14, 21, 35 days, 100 ng/kg	Liver EROD (CYP1A1): 7 days	1.0	2.7E+01	2.7E-01	3.0E+02	3.0E+00	P
		Liver EROD (CYP1A1): 14 days	3.5	2.8E+02	2.8E+00	5.5E+02	5.5E+00	G
		Liver EROD (CYP1A1): 21 days	2.8	2.4E+02	2.4E+00	5.7E+02	5.7E+00	G
		Liver EROD (CYP1A1): 35 days	6.5	7.4E+02	7.4E+00	1.1E+03	1.1E+01	M
Li et al. (1995), female Sprague-Dawley rats	4 days, 300 ng/kg	Body weight	3.7	1.2E+03	3.9E+00	2.2E+03	7.4E+00	G
		Ovarian weight	1.0	1.7E+02	5.7E-01	1.9E+03	6.2E+00	G

Appendix II: Single-dose adult studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	Daily ED_{01} (ng/kg/day)	Relative ED_{01}[c]	Daily ED_{10} (ng/kg/day)	Relative ED_{10}[c]	Quality of fit[d]
		Ovulation (ova/rat)	1.4	1.5E+02	4.9E-01	8.7E+02	2.9E+00	G
VanBirgelen et al. (1996), female B6C3F1 mice	S, 7 days, 100 ng/kg	CYP1A1 EROD	1.8	7.1E+01	7.1E-01	2.7E+02	2.7E+00	G

[a]Dose regimen is described by study duration (total days after single administration) and lowest dose used in the study.
[b]Unless noted otherwise, the Hill model was used to fit these data.
[c]Relative ED_X is the ratio of the ED_X to the lowest dose tested in the study.
[d]Qualitative assessment of fit: G=good (model curve goes through/near all data point means); M=marginal (model within one std. deviation of means); P=poor (model not within one std. deviation of means).
[e]NR- In some cases, BMDS (U.S. EPA, 1999) fails to locate a lower confidence bound on the 1% effective dose.
[f]Power model used to fit these data.
[g]Weibull model used to fit these data.
[h]NA - Models in BMDS (U.S. EPA, 1999) not applicable to these data.
[i]NF- Quality of fit not assessed for this endpoint.

Appendix III: Single-dose developmental studies

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	ED_{01} (ng/kg/day)	Relative ED_{01}c	ED_{10} (ng/kg/day)	Relative ED_{10}[C]	Quality of fit[d]
Birnbaum et al. (1989), C57BL/6N mice	GD 10 or 12, 8 or 6 days (sacrificed on GD 18), 6,000 ng/kg	Cleft palate GD-10[e]	3.5	3.3E+03	3.3E+00	6.4E+03	1.1E+00	G
		Cleft palate GD-12[e]	6.4	4.4E+03	4.4E+00	6.3E+03	1.1E+00	G
		Hydronephrosis GD-10[e]	1.0	3.2E+01	3.2E-02	3.3E+02	5.5E-02	M
		Hydronephrosis GD-12[e]	2.3	2.1E+02	2.1E-01	5.7E+02	9.5E-02	P
Mably et al. (1992b,c), pregnant female, male offspring, Holtzman Sprague-Dawley rats	GD 15, postnatal day (PND) 49, 63, or 120, 64 ng/kg	Sperm morph. – day 120	4.4	8.7E+01	1.4E+00	1.5E+02	2.3E+00	G
		Fertility index	NA[g]	NA	NA	NA	NA	NF[h]
		Cauda sperm count day 63	1.0	6.6E-01	1.0E-02	7.2E+00	1.1E-01	G
		Cauda sperm count - day 120	1.0	7.6E-01	1.2E-02	8.3E+00	1.3E-01	G
		Cauda sperm count/g - day 120	1.7	3.7E+00	5.8E-02	1.5E+01	2.3E-01	G
		DSP/g - day 63	1.0	5.6E-01	8.8E-03	6.2E+00	9.7E-02	G
		DSP/g - day 120	1.4	1.4E+00	2.2E-02	7.9E+00	1.2E-01	G
		DSP/g – day 49	1.7	6.6E+00	1.0E-01	2.8E+01	4.4E-01	G
		Reproductive outcomes of females:						
		Litter size	18.0	7.9E+01	1.2E+00	9.1E+01	1.4E+00	P
		Live birth index (%)	NA	NA	NA	NA	NA	NF

Appendix III. Single-dose developmental studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	ED_{01} (ng/kg/day)	Relative ED_{01}c	ED_{10} (ng/kg/day)	Relative ED_{10}[C]	Quality of fit[d]
		Age of indices of dev. in pups:						
		Pinna detachment	17.0	7.7E+02	1.2E+01	8.8E+02	1.4E+01	P
		Incisor eruption	1.0	1.3E+01	2.0E-01	1.3E+02	2.1E+00	G
		Eye opening	1.0	7.0E+00	1.1E-01	7.4E+01	1.2E+00	G
		Testis descent	1.0	1.3E+00	2.1E-02	1.4E+01	2.3E-01	G
Theobald et al. (1997), pregnant female, male and female offspring ICR mice	GD 14, PND 44, 15,000 ng/kg	Testes weight	1.0	7.4E+02	6.5E+00	6.9E+03	4.6E-01	M
		Epididymidis wt.	18.0	4.8E+04	3.2E+00	5.4E+04	3.6E+00	M
		Dorsal prostate wt.	1.0	3.0E+02	2.0E-02	3.3E+03	2.2E-01	P
		Ventral prostate wt.	2.9	1.2E-04	8.0E-09	2.8E-04	1.9E-08	M
		Coagulating glands	1.7	3.3E+03	2.2E-01	1.3E+04	8.7E-01	G
		Seminal vesicles	18.0	4.5E+04	3.0E+00	5.2E+04	3.4E+00	M
		Ovary weight	18.0	2.4E+04	1.6E+00	2.8E+04	1.8E+00	M
		Uterus weight	4.5	9.8E+03	6.5E-01	1.7E+04	1.1E+00	G
Theobald et al. (1997), pregnant female, male and female offspring ICR mice	GD 14, PND 65, 15,000 ng/kg	Testes weight	18.0	1.1E+04	7.5E-01	1.3E+04	8.5E-01	M
		Epididymidis wt.	3.1	1.4E-04	9.5E-09	9.4E-04	6.2E-08	P
		Ventral prostate wt.	18.0	1.1E+04	NR	1.3E+04	8.6E-01	M

Appendix III. Single-dose developmental studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	ED_{01} (ng/kg/day)	Relative ED_{01}c	ED_{10} (ng/kg/day)	Relative ED_{10}[C]	Quality of fit[d]
		Coagulating glands	18.0	1.1E+04	7.5E-01	1.3E+04	8.6E-01	M
		Seminal vesicles	1.0	1.2E+03	7.5E-01	1.2E+04	7.8E-01	M
		Sperm production: ESN	13.4	1.0E+04	7.8E-02	1.2E+04	8.2E-01	M
		Sperm production: DSP	18.0	1.5E+04	6.8E-01	1.7E+04	1.1E+00	M
		Pituitary gland wt. (males) (PND 65)	11.5	3.0E+05	9.8E-01	3.7E+05	2.5E+01	P
Theobald et al. (1997), pregnant female, male and female offspring ICR mice	GD 14,PND 114/128, 15,000 ng/kg	Epididymidis wt.	NA	NA	2.0E+01	NA	NA	NF
		Dorsal prostate wt.	1.0	5.0E+02	NA	5.3E+03	3.6E-01	P
		Ventral prostate wt.	18.0	1.1E+04	3.4E-02	1.3E+04	8.4E-01	M
		Coagulating glands	18.0	1.1E+04	7.3E-01	1.3E+04	8.6E-01	M
		Seminal vesicles	NA	NA	7.6E-01	NA	NA	NF
		Sperm production: ESN (PND 114/128)	NA	NA	NA	NA	NA	NF
		Female rep: ovary wt. (PND 114)	18.0	1.6E+04	NA	1.8E+04	1.2E+00	M
		Female rep: uterus wt. (PND 114)	4.5	2.1E+04	1.0E+00	3.5E+04	2.4E+00	G
Theobald et al. (1997), pregnant female, male and female offspring ICR mice	GD 14,PND 114/128, 15,000 ng/kg	Pituitary gland wt. (males) (PND 128)	NA	NA	1.4E+00	NA	NA	NF

Appendix III. Single-dose developmental studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	ED_{01} (ng/kg/day)	Relative ED_{01}c	ED_{10} (ng/kg/day)	Relative ED_{10}[C]	Quality of fit[d]
		Pituitary wt. (females) (PND 128)	18.0	1.1E+04	NA	1.2E+04	8.2E-01	M
		Hydronephrosis (females)	1.1[e]	1.2E+03	7.2E-01	9.4E+03	6.3E-01	M
		Eye opening (females)	1.0	3.8E+01	8.0E-02	4.2E+02	2.8E-02	M
		Thymus weight (females)	1.0	3.2E+02	2.5E-03	3.5E+03	2.3E-01	M
		Hydronephrosis (males)	1.0[e]	2.6E+02	2.1E-02	2.7E+03	1.8E-01	M
		Eye opening (males)	1.0	7.6E+01	1.7E-02	8.4E+02	5.6E-02	G
		Thymus weight (males)	3.4	1.6E-04	5.1E-03	3.2E-04	2.1E-08	P
Gray et al. (1997), Long Evans Hooded rat male offspring	GD 15, PND 49,50 ng/kg	Body weight (day 49)	9.6	1.4E+02	1.0E-08	1.8E+02	3.5E+00	G
		Testes weight (49)	1.1	1.0E+01	2.7E+00	8.4E+01	1.7E+00	G
		Paired epididymal weight (49)	13.9	1.4E+02	2.1E-01	1.7E+02	3.4E+00	M
		Cauda epididymus (49)	18.0	7.9E+01	2.9E+00	9.0E+01	1.8E+00	G
		Epididymal sperm count (49)	1.0	1.5E-01	1.6E+00	1.7E+00	3.4E-02	P
		Ventral prostate weight (49)	12.4	1.4E+02	3.0E-03	1.6E+02	3.3E+00	G
		Seminal vesicle weight (49)	17.9	1.5E+02	2.7E+00	1.7E+02	3.5E+00	M

Appendix III. Single-dose developmental studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	ED_{01} (ng/kg/day)	Relative ED_{01}c	ED_{10} (ng/kg/day)	Relative ED_{10}[C]	Quality of fit[d]
		Daily sperm production (49)	14.1	5.9E+02	3.0E+00	6.9E+02	1.4E+01	M
		Age at puberty (49)	2.8	4.0E+01	1.2E+01	9.4E+01	1.9E+00	P
		Body weight at puberty (49)	13.6	1.4E+02	1.3E+03	1.6E+02	3.2E+00	M
		Pituitary (49)	8.9	9.6E+01	7.9E-01	1.3E+02	2.5E+00	M
Gray et al. (1997), Long Evans Hooded rat male offspring	GD 15, PND 63,50 ng/kg	Body weight (63)	17.5	1.6E+02	2.7E+00	1.8E+02	3.6E+00	P
		Testes weight (63)	10.8	1.3E+02	1.9E+00	1.6E+02	3.2E+00	G
		Paired epididymal weight (63)	14.2	1.4E+02	3.2E+00	1.6E+02	3.3E+00	P
		Cauda epididymus (63)	12.1	1.3E+02	2.6E+00	1.6E+02	3.1E+00	G
		Epididymal sperm count (63)	11.2	1.4E+02	2.8E+00	1.7E+02	3.5E+00	G
		Ventral prostate weight (63)	14.0	1.4E+02	2.6E+00	1.7E+02	3.4E+00	P
		Seminal vesicle weight (63)	11.3	1.6E+02	2.8E+00	2.0E+02	4.0E+00	G
		Daily sperm production (63)	13.6	5.4E+02	2.8E+00	6.4E+02	1.3E+01	M
		Serum testosterone (63)	10.3	3.3E+01	3.2E+00	4.1E+01	8.2E-01	M
		Pituitary (63)	8.7	3.7E+01	1.1E+01	4.9E+01	9.7E-01	M

Appendix III. Single-dose developmental studies (continued)

Study description	Dose regimen[a]	Endpoint[b]	Shape parameter	ED_{01} (ng/kg/day)	Relative ED_{01}c	ED_{10} (ng/kg/day)	Relative ED_{10}[C]	Quality of fit[d]
Gray et al. (1997), Long Evans Hooded rat male offspring	GD 15, offspring examined 15 months, 50 ng/kg	Body weight	13.0	1.6E+02	6.5E-01	1.9E+02	3.8E+00	M
		Seminal vesicle weight	18.0	7.8E+01	7.4E-01	8.9E+01	1.8E+00	G
		Glans penis weight	1.4	3.8E+00	3.1E+00	2.2E+01	4.5E-01	G
		Paired epididymal weight	18.0	7.3E+01	5.5E+02	8.4E+01	1.7E+00	P
		Cauda epididymal weight	10.7	3.3E+01	1.6E+00	4.1E+01	8.2E-01	P
		Epididymal sperm numbers	4.3	3.8E+01	7.6E-02	6.6E+01	1.3E+00	G
		Caput/corpus epid. sperm numbers	15.5	1.2E+02	1.5E+00	1.4E+02	2.9E+00	P
		Cauda epid. sperm numbers	2.9	1.4E+01	6.5E-01	3.1E+01	6.3E-01	G
		Number of copulatory plugs	2.4	1.1E-06	7.5E-01	3.2E-06	6.3E-08	P
		Total testis sperm numbers	12.3	1.6E+02	2.5E+00	2.0E+02	4.0E+00	P
		Pituitary weight	18.0	7.7E+01	2.7E-01	8.8E+01	1.8E+00	P

[a] Dose regimen is described by specific time of single administration, duration or offspring examination day, and lowest dose used in the study.
[b] Unless noted otherwise, the Hill model was used to fit these data.
[c] Relative ED_X is the ratio of the ED_X to the lowest dose tested in the study
[d] Qualitative assessment of fit: G=good (model curve goes through/near all data point mean); M=marginal (model within one std. deviation of means); P= poor (model not within one std. deviation of means).
[e] The Weibull model was fit to these data.

Appendix III. Single-dose developmental studies (continued)

[f] NR-In some cases, the BMDS (U.S. EPA, 1999) fails to locate a lower confidence bound on the 1% effective dose.
[g] NA-Models in BMDS (U.S. EPA, 1999) not applicable to these data.
[h] NF-Quality of fit was not assessed for this endpoint.

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Chapter 9. Toxic Equivalency Factors (TEF) for Dioxin and Related Compounds

Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

Part II: Health Assessment for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds

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9. TOXIC EQUIVALENCY FACTORS (TEF) FOR DIOXIN AND RELATED COMPOUNDS

9.1. INTRODUCTION

Previous risk assessments of dioxin and dioxin-like compounds from around the world have employed the Toxic Equivalency Factor (TEF) methodology. This method is also used throughout EPA's dioxin reassessment. This chapter has been added to the EPA's dioxin reassessment effort to address questions raised by the Agency's Science Advisory Board (SAB) in 1995. In its Report to the Administrator (U.S. EPA, 1995), the Committee said it "supports EPA's use of Toxic Equivalencies for exposure analysis..." However, the SAB suggested that, as the toxic equivalent (TEQ) approach was a critical component of risk assessment for dioxin and related compounds, the Agency should be explicit in its description of the history and application of the process and go beyond reliance on the Agency's published reference documents on the subject (U.S. EPA, 1987; 1989; 1991) to discuss issues raised in review and comment on this approach. Significant additional literature is now available on the subject, and this chapter provides the reader with a summary which is up-to-date through 2000. Future research will be needed to address uncertainties inherent in the current approach. The World Health Organization (WHO) has suggested that the TEQ scheme be reevaluated every 5 years and that TEFs and their application to risk assessment be re-analyzed to account for emerging scientific information (van den Berg et al., 1998).

9.2. HISTORICAL CONTEXT OF TEFs

A wide variety of polyhalogenated aromatic hydrocarbon (PHAH) compounds can be detected as complex mixtures in both abiotic and biotic samples. Because of PHAHs' known global environmental distribution and their toxicity to experimental animals (DeVito et al., 1995; DeVito and Birnbaum, 1995; Grassman et al., 1998)(see Part II, Chapters 3-6), to wildlife (Giesy and Kannan, 1998; Ross, 2000), and to humans (IARC, 1997) (see also Part II, Chapter 7), hazard characterization and risk assessment activities have tended to focus on a subset of polychlorinated dibenzo-*p*-dioxin (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs)(Figure 9-1). The subset of compounds, shown in Figure 9-1, are known as "dioxin-like" and have been assigned TEF values by WHO. In this chapter, the development of TEFs for these and other PHAHs is discussed.

9.2.1. TEFs for PCDDs and PCDFs

In 1983, the Ontario Ministry of the Environment produced a Scientific Criteria Document for PCDDs and PCDFs which concluded, based on a review of available scientific information,

that dioxin and dibenzofurans were structurally similar compounds that shared a common cellular mechanism of action (activation of the aryl hydrocarbon receptor or AhR) and induced comparable biological and toxic responses, and that the development of environmental standards for human health concerns should be based on a "toxic equivalency" approach with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as the prototype (OME, 1984). The final recommendation divided all PCDD/PCDF congeners into their respective homologue groups and assigned to each group a toxicity factor relative to TCDD (Table 9-1). These numerical factors could then be applied to transform various concentrations of PCDDs and PCDFs into equivalent concentrations of 2,3,7,8-TCDD. Shortly thereafter, the first use of a TEF-like method was described by Eadon et al. (1986) as a means to estimate potential health risks associated with a PCB transformer fire in Binghamton, NY.

Following up on an initial risk assessment methodology designed to address the emission of dioxins and furans from waste incinerators, EPA also concluded that TEFs were the best available interim scientific policy for dealing with complex mixtures of these contaminants. With the mandate to develop active research programs that would address the limitations inherent to this risk management technique, the Agency recommended TEFs for specific congeners, rather than isomeric groups (Table 9-2; U.S. EPA, 1987). In an analogous fashion to OME's approach, concentrations of PCDDs and PCDFs would be analytically determined, the concentration of each congener would be multiplied by its respective TEF value, and all the products would be summed to give a single 2,3,7,8-TCDD equivalent. This approach has been described mathematically as:

$$\text{Total Toxic Equivalency (TEQ)} = \sum_{n=1}^{k} C_n * TEF_n$$

C_n equals the concentration of the individual congener in the complex mixture under analysis. TEFs were determined by inspection of the available congener-specific data and an assignment of an "order of magnitude" estimate of relative toxicity when compared to 2,3,7,8-TCDD. In vitro AhR binding and in vitro and in vivo toxicity studies were considered in setting individual TEFs. Scientific judgment and expert opinion formed the basis for these TEF values. External review of the toxicity and pharmacokinetic data utilized by EPA in setting these TEFs supported the basic approach as a "reasonable estimate" of the relative toxicity of PCDDs and PCDFs (Olson et al., 1989).

A 3-year study conducted by the North Atlantic Treaty Organization Committee on the Challenges of Modern Society (NATO/CCMS) also concluded that the TEF approach was the best available interim measure for PCDD/PCDF risk assessment. On the basis of examination of the available data dealing with exposure, hazard assessment, and analytical methodologies

related to dioxin and furans, an International Toxicity Equivalency Factor (I-TEF) scheme was presented (Table 9-2; NATO/CCMS, 1988). This review also concluded that "data strongly support the role of the AhR in mediating the biologic and toxic responses elicited by 2,3,7,8-TCDD and related PCDDs and PCDFs and provide the scientific basis for the development of TEFs for this class of compounds." Various refinements to previous efforts included selection of TEF values based more on in vivo toxicities, assigning TEF values to octachlorodibenzo-*p*-dioxin and octachlorodibenzofuran, and removing any TEF values for all non-2,3,7,8-substituted congeners. Although it was indicated that, theoretically, it may be possible to detect nearly all of the 210 PCDD/DF isomers in the environment, seventeen 2,3,7,8-substituted congeners were known to be preferentially retained and bioaccumulated. For example, when fish or a variety of rodent species were exposed to a complex mixture of PCDDs/PCDFs from incinerator fly ash, the 2,3,7,8-substituted congeners, which were minor components of the original mixture, predominated in the analysis of their tissues (Kuehl et al., 1986; van den Berg et al., 1994). In addition, when humans were exposed to a complex mixture of more than 40 different PCDF congeners during the Oriental rice oil poisoning episodes, only the 2,3,7,8-substituted congeners were detected in subsequent blood and adipose tissue analysis (Ryan et al., 1990). EPA, which had participated in the NATO/CCMS exercise, officially adopted the revised I-TEFs in 1989, with the caveat that this risk assessment approach remains interim and continued revisions should be made (U.S. EPA, 1989; Kutz et al., 1990). The use of the TEF model for risk assessment and risk management purposes has been formally adopted by a number of countries (Canada, Germany, Italy, the Netherlands, Sweden, the United Kingdom, U.S.A.) (Yrjänheiki, 1992), and as guidance by international organizations such as the International Programme on Chemical Safety, WHO.

9.2.2. TEFs for PCBs

During the period of TEF development for PCDDs/PCDFs, a considerable body of experimental evidence was also being generated regarding the structure-activity relationships between the different polychlorinated biphenyl homologue classes (Safe, 1990, 1994). Following the synthesis of analytical standards for all 209 theoretical PCB congeners by 1984, subsequent analysis of a variety of commercial samples was able to identify all but 26 (Jones, 1988). However, once released into the environment, PCBs are subject to a variety of photolysis and biodegradation processes, to the extent that only 50-75 congeners are routinely detected in higher trophic level species (van den Berg et al., 1995). Initial structure-activity relationship studies revealed that those congeners substituted in only the meta and para positions were approximate isostereomers of TCDD. Subsequent toxicological studies confirmed that these non-ortho-substituted, "coplanar" PCBs (e.g., PCB 77, 81, 126, 169) did induce a variety of in vitro and in

vivo effects similar to TCDD (Leece et al., 1985). Maximum TCDD-like activity is obtained for PCBs when there are no ortho, two or more meta, and both para positions occupied (Figure 9-1). Introduction of a single ortho substituent to the biphenyl (mono-ortho "coplanars") results in a diminishing, but not elimination, of TCDD-like activity and toxicological responses resembling commercial mixtures of PCBs. The addition of a single ortho substituent also increases the non-dioxin-like activity of the compound. Several congeners from this group are prevalent in both commercial PCBs and a wide variety of environmental samples. Some of the more persistent mono-ortho substituted PCBs (PCBs 105, 118, 156) can be found in human serum and adipose samples at levels up to three orders of magnitude higher than the "coplanar" PCBs, PCDDs and PCDFs (Patterson et al., 1994). In limited studies a third group of PCB congeners, the di-ortho "non-coplanars," has exhibited only minor amounts of dioxin-like activity (if any), usually 4-6 orders of magnitude less potent than TCDD (Safe, 1990). Recent studies have demonstrated that some of the earlier methods of preparation of these di-ortho non-coplanar PCBs had trace contaminants of PCDFs, which may account for the weak dioxin-like activity of these compounds (van der Kolk et al., 1992). In 1991, EPA convened a workshop to consider TEFs for PCBs (Barnes et al., 1991). The consensus was that a small subset of the PCBs displayed dioxin-like activity and met the criteria for inclusion in the TEF methodology. Such proposals for the TEF methodology also seem to have utility in assessing risks to wildlife (van den Berg et al., 1998; Giesey and Kannan, 1998; Ross, 2000).

PCBs are often classified into two categories: "dioxin-like" and "non-dioxin-like." The dioxin-like PCBs bind to the AhR and produce dioxin-like effects in experimental animals. All other PCBs then fall into the non-dioxin-like classification. Although the dioxin-like PCBs are generally more potent at inducing biological effects, they constitute only a minor portion of the mass of PCBs found in environmental and biological samples. The non-dioxin-like PCBs account for a majority of the mass of the PCBs found in environmental and biological samples. The use of the term non-dioxin-like PCBs is not necessarily useful. The PCBs not included in the TEF scheme (i.e., the non-dioxin-like PCBs) are not a single class of compounds and have multiple toxicities with separate structure-activity relationships (Barnes et al., 1991). Not enough congener-specific research has been performed to adequately characterize or classify these compounds. For example, the "neurotoxic" PCBs have been typically defined by structure-activity relationships for decreasing dopamine concentrations or alterations in intracellular calcium in cell culture (Shain et al., 1991; Kodavanti et al., 1996).

As part of the joint WHO European Centre for Environmental Health (WHO-ECEH) and the International Programme on Chemical Safety (IPCS) project to harmonize TEF schemes for dioxin-like compounds, a database was generated consisting of all available relevant toxicological data for PCBs up to the end of 1993. Of almost 1,200 peer-reviewed publications,

146 were selected and analyzed on the basis of the following criteria: at least one PCB congener was investigated; TCDD or a reference coplanar PCB (77, 126, 169) was used during the experiment or results were available from previous experiments (same author, laboratory, experimental design); and the endpoint in question was affected by both the reference compound and the PCB congener in question (i.e., dioxin-specific). TEFs were then determined from a total of 60 articles/manuscripts on the basis of the reported results for 14 different biological/toxicological parameters. Following scientific consultation by 12 experts from 8 different countries, interim TEF values were recommended for 13 dioxin-like PCBs (Table 9-2), based on four inclusion criteria: (1) the compound should show structural similarity to PCDDs and PCDFs; (2) it should bind to the Ah receptor; (3) it should induce dioxin-specific biochemical and toxic responses; and (4) it should be persistent and accumulate in the food chain (Ahlborg et al., 1994). Increased consideration was given to selection of a TEF value based on repeat-dosing in vivo experiments, when available.

There is experimental evidence to suggest that a limited number of PCB congeners classified as weak or non-AhR agonists could effect concentration-dependent nonadditive interactions with dioxin-like compounds (Safe, 1990; 1994). Both antagonistic (Safe, 1990; Morrissey et al., 1992; Smialowicz et al., 1997b) and synergistic (Safe, 1990; van Birgelen et al., 1996a,b; van Birgelen et al., 1997) interactions between TCDD and PCBs have been observed in experimental systems. The non-additive interactions of the PCBs are thought to be mediated through non-AhR pathways (Smialowicz et al., 1997). These interactions usually occur at extremely high doses of the PCBs that are not environmentally relevant, and thus the nonadditive interactions are thought not to significantly detract from the TEF methodology (van den Berg et al., 1998; Birnbaum, 1999).

9.2.3. The Most Recent Evaluation of TEFs for PCDDs, PCDFs, and PCBs

An additional recommendation from the first WHO PCB TEF consultation was that the current database should be expanded to include all relevant information on PCDDs, PCDFs, and other dioxin-like compounds that satisfied the four inclusion criteria. Prior to the second WHO-ECEH consultation in 1997, various terminologies or definitions applicable to TEFs were reviewed and standardized. Whereas previously the term TEF had been used to describe all scientific endpoints used in comparison with TCDD, it was noted that a variety of experimental parameters may not be considered “toxic,” but are considered as biological/biochemical responses, such as AhR binding and alkoxyresorufin O-dealkylase induction. The decision was that any experimental endpoint for which a numerical value of the relative potency compared to TCDD had been generated from a single laboratory examining a single endpoint would be known as a relative potency value, or REP. The term TEF would then be restricted to describe an order-

of-magnitude consensus estimate of the toxicity of a compound relative to the toxicity of TCDD that is derived using careful scientific judgment of all available data (van Leeuwen, 1997; van den Berg et al., 1998).

At the second WHO-ECEH consultation in 1997, relative potency factors were calculated based on the following methodology (van den Berg et al., 1998):

- Assigned as reported in the publication/manuscript (verified from available data).
- Calculated from the dose-response curves using linear interpolation of log doses comparing the same effect levels with correction for different control levels.
- Calculated from ratios of low or no observed effect levels (LOELs, NOELs) and effect concentration/dose 10%, 25% or 50% values ($ED/EC_{10,25,50}$).
- Calculated from ratios of tumor promotion indexes or maximal enzyme induction levels.
- Calculated from ratios of Ah receptor binding affinities (K_d).

Whereas the resulting range of in vitro/in vivo REP values for a particular congener may span 3-4 orders of magnitude, final selection of a TEF value gave greater weight to REPs from repeat-dose in vivo experiments (chronic > subchronic > subacute > acute). As with the PCB TEF consultation, dioxin-specific endpoints were also given higher priority. A rounding-off procedure (nearest 1 or 5) was also employed for final TEF selection (Table 9-2). It should be noted that the TEF was rounded up or down depending on the compound, the data, and scientific judgment.

Notable amendments to the previous NATO/WHO TEF schemes include:

- On the basis of new REPs from in vivo tumor promotion and enzyme induction, a TEF of 1.0 was recommended for 1,2,3,7,8-PeCDD.
- Originally the TEF for OCDD was based on body burdens of the compound following subchronic exposures; a TEF based on administered dose is reduced to 0.0001.
- New in vivo enzyme induction potency and structural similarity with OCDD support the TEF change to 0.0001 for OCDF.
- REPs from an in vivo subchronic toxicity study (enzyme induction, hepatic retinol decreases) support reducing the TEF to 0.0001 for PCB 77.
- A TEF value of 0.0001 was assigned for PCB 81. Even though PCB 81 was not assigned a TEF value at the 1993 WHO consultation because of lack of human residue and experimental data, more recent data demonstrate similar qualitative structural activity results compared to PCB 77.

- Because of the lack of in vivo enzyme induction (CYP 1A1/A2) and reproductive toxicity with structurally similar congeners (PCB 47 and PCB 153), the previous interim TEF values for the di-ortho-substituted PCBs 170 and 180 were withdrawn.

Although a number of uncertainties associated with the TEF concept have been identified (nonadditive interactions with non-dioxin-like PCBs, natural ligands for the Ah receptor, questionable low-dose linearity of REP responses), the 1997 WHO expert meeting decided that an additive TEF model remained the most feasible risk assessment method for complex mixtures of dioxin-like PHAHs.

The WHO working group acknowledged that there are a number of other classes of chemicals that bind and activate the Ah receptor. The chemicals include, but are not limited to, polyhalogenated naphthalenes, diphenyl ethers, fluorenes, biphenyl methanes, quaterphenyls, and others. In addition, a number of brominated and chloro/bromo-substituted dioxin analogues of the PCDDs and PCDFs have been demonstrated to cause dioxin-like effects. The WHO working group concluded that "at present, insufficient environmental and toxicological data are available to establish a TEF value for any of the above compounds" (van den Berg et al., 1998).

The development and refinement of the TEF methodology can be thought of as an iterative process. As we accumulate more data on the biological effects of dioxin-like chemicals and a better knowledge base of their mode of action, the TEF methodology is improved. The latest evaluation of the TEF methodology for use in human health risk assessment by the WHO working group provides the most accurate assessment of the TEFs for dioxin-like chemicals. The WHO_{98} TEF values are recommended for use in human health risk assessment.

In January 1998, EPA and the U.S. Fish and Wildlife Service sponsored a meeting entitled "Workshop on the Application of 2,3,7,8-TCDD Toxicity Equivalency Factors to Fish and Wildlife." The major objective of the workshop was to address uncertainties associated with the use of the TEF methodology in ecological risk assessment. Twenty-one experts from academia, government, industry, and environmental groups participated in the workshop. The consensus of the workgroup was that while there are uncertainties in the TEF methodology, the use of this method decreases the overall uncertainty in the risk assessment process. However, quantifying the decrease in the uncertainty of a risk assessment using the TEF methodology remains ambiguous, as does the exact uncertainty in the TEF methodology itself (U.S. EPA, 2001).

This first section has outlined the process of assessing the relative potency of chemicals and the assignment of a consensus TEF value. There are still many questions on the use of the TEF method and the validity of some of the underlying assumptions. A detailed discussion and review of the data supporting the development and use of the TEF method, as well as the data relating to the issue of additivity, is included within the specific issues section that follows.

9.2.4. Illustrative Examples of the Data Used for Deriving the TEF Values

The TEF scheme includes 17 PCDDs and PCDFs and 13 PCBs. However, in human tissue samples and food products, only five of these congeners, TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, 2,3,4,7,8-PeCDF, and PCB 126, account for over 70% of the TEQ. There is considerable data on the relative potency of these compounds in both in vitro and in vivo studies. Table 9-3 provides a summary of the REPs from in vivo data available for the compounds that account for approximately 80% of the TEQs in humans (see Part I, Volume 3, Section 4.2.). This information was obtained from the WHO database used to derive TEF values for PCDDs, PCDFs, and PCBs (Van den Berg et al., 1998). The WHO database contains duplicate recordings of studies for several of the compounds. The data in Table 9-3 does not include the duplicates. In addition, the WHO database also contains studies that used a single dose level of the test chemical, and REP values were not estimated for these studies. For example, in the WHO database for PCB 126, there are 144 in vivo endpoints. Of these 144, 50 do not have REP values associated with the entry because the study used only a single dose level. In other cases, for a given endpoint from a particular study, the REP value is presented as estimated by the authors as well as by alternative analyses by members of the WHO workgroup. In total, there are 62 data sets that have dose-response relationships sufficient enough to estimate the relative potency of PCB 126. These data sets examine enzyme induction, changes in organ and body weights, immunotoxicity, developmental toxicity, thyroid hormones, renal and hepatic retinoids, and tumor promotion. The WHO database for 1,2,3,7,8-PCDD contained studies examining enzyme induction, changes in organ and body weights, hepatic porphyria, hepatic retinoids, and tumor promotion. The WHO database for 2,3,4,7,8-PCDF contained studies examining enzyme induction, changes in organ and body weights, immunotoxicity, developmental toxicity, thyroid hormones, hepatic retinoids, hepatic porphyria, and tumor promotion. The data presented in Table 9-3 for 1,2,3,6,7,8-HxCDD is from U.S. EPA (1989) because the WHO database contained no new in vivo data for this compound. There are only three in vivo studies on the effects of 1,2,3,6,7,8-HxCDD, one of which is the NTP carcinogenicity study on a mixture of 31% 1,2,3,6,7,8-HxCDD and 67% 1,2,3,7,8,9HxCDD (NTP, 1980).

The REPs for 1,2,3,7,8-PCDD in the in vivo studies vary by approximately a factor of five. A TEF value was assigned to 1,2,3,7,8-PCDD based on the REP for tumor promotion which ranged from 0.8-1.0. The REPs for 2,3,4,7,8-PCDF and PCB 126 have a greater variability, but the assigned TEF values are similar to the means of the REP values. The mean±standard deviation for all in vivo REP values for 2,3,4,7,8-PCDF is 0.4±0.7. If only subchronic studies are examined, the mean±standard deviation of the REP values is 0.2±0.13. These REP values for 2,3,4,7,8-PCDF are similar to the TEF value of 0.5. The REPs for PCB 126 range over two orders of magnitude with a mean for all in vivo responses of 0.2±0.2. The mean REP for

subchronic studies examining PCB 126 is 0.13±0.13. The TEF for PCB 126 is 0.1, which is slightly lower than the mean of the REP values. With the exception of 1,2,3,6,7,8-HxCDD, the REPs are based on several studies from different laboratories examining different endpoints.

9.2.5. Variability in the REPs Across Endpoint, Species, Dosing Regimen and Laboratories.

Using PCB 126 as an example, the variability of the REPs across endpoint, species, laboratory and dosing regimen will be described. PCB 126 has the most in vivo studies comparing the its relative potency to TCDD of all the chemicals in the WHO data base. Upon examining this data base, it is apparent that within an endpoint there is considerable variability (greater than an order of magnitude). For instance, the REPs for hepatic EROD induction in mice following a single exposure to PCB 126 are 0.005, 0.012, 0.38 and 0.55. These studies use similar dosing paradigms and time course for endpoint determinations so there is no clear reason why these values should range over two orders of magnitude. In some cases, interlaboratory variability appears to be a significant cause for variance in the estimates of the REPs. In order to examine REPs across endpoints and control for interlaboratory variability, two studies were examined. Hemming et al (1993) examined the REPs for tumor promotion, hepatic EROD induction, and alterations in liver, thymus and body weights in rats compared to TCDD. In this study, the REPs were 0.16, 0.3, 0.05, 0.07, and 0.1 for liver, thymus and body weight changes, hepatic EROD induction and tumor promotion, respectively. While the range of these REPs is 0.05-0.3, the authors only provided point estimates of the REPs and no information was provided on the variance of these values. Thus, it is impossible to determine if the REP values are statistically different from one another. The study by Hemming et al (1993) is typical of the literature estimating the REPs for dioxin-like chemicals in that no information on the variance of these estimates are available. A recent study by DeVito et al (2000), demonstrated that the REPs for PCB 126 for hepatic and dermal ethoxyresorufin-O-deethylase (EROD) activity, a marker for CYP1A1 induction, and hepatic acetanilide 4-hydroxylase (ACOH) activity, a marker for CYP1A2 induction, were equivalent. However in this study, the REP for pulmonary EROD induction was an order of magnitude lower than the other endpoints.

The example described above suggests that the source of the variability in the REP values remains uncertain. Most studies do not provide estimates of the variance of the REP values. This decreases the ability to compare REP values across endpoints, species, dosing regimens and laboratories. One of the few studies that did provide estimates of the variance around the REPs examined only a single biochemical (ethoxyresorufin-O-deethylase activity) endpoint in different tissues and it is uncertain whether the results from this study are applicable to other endpoints (DeVito et al., 2000).

9.2.6. Critical Considerations in the Application of the TEF Methodology.

There are a number of underlying assumptions used in the development of the TEF methodology and these assumptions have significant implications in the application of this method. Some of these assumptions and there implications are listed below.

- The Ah receptor mediates most if not all of the biologic and toxic effects of TCDD.
- The TEF methodology attempts to estimate the potential TCDD-like effects of a chemical. Toxic effects of a chemical induced through mechanisms other than the Ah receptor are not accounted for in this method.
- Even though not all the molecular mechanisms following Ah receptor binding are understood, the TEF methodology is still valid.
- The chemical binds to Ah receptor and is a full agonist for endpoints of concern.
- The relative potency of a chemical is equivalent for all endpoints of concern.
- The relative potency of a chemical is equivalent for all exposure scenarios.
- The relative potency of a chemical in rodents is predictive of its relative potency in humans.
- The toxicity of a mixture of dioxins is dose additive based on the relative potencies or TEFs of the individual components .
- The TEF methodology ignores the interactions of dioxins with other chemicals present.
- Naturally occurring chemicals with short half-lives and varying degrees of affinity to the Ah receptor and intrinsic activity do not interfere with the predictions of dioxin equivalents in the mixture.
- TEFs are not calculated. They are assigned based on the following criteria:
  - Greater weight is given to REPs from repeat-dose in vivo experiments (chronic > subchronic > subacute > acute).
  - Dioxin-specific or Ah receptor mediated effects were given also higher priority.
  - A rounding-off procedure (nearest 1 or 5) was also employed for final TEF selection (Table 9-2). It should be noted that the TEF was rounded up or down depending on the compound, the data, and scientific judgment.

Many of the assumptions are necessary because of a lack of data. For example, TCDD and a mixture of hexachlorinated dioxins are the only congeners which have been tested for carcinogenicity. Thus, in order to estimate the carcinogenic potency of a mixture of dioxins, it

must be assumed that the REPs for non-cancer endpoints approximate those for cancer. While these assumptions lead to uncertainties, there is a consensus that the TEF methodology decreases the overall uncertainty of a risk assessment (USEPA, 2001). More detailed discussion of these points is presented in the following section.

9.3. SPECIFIC ISSUES

9.3.1. Ah Receptor and Toxicity Factors

Issues relating to the role of the Ah receptor as the common mediator of toxicity of dioxin-like compounds and the cross-species comparability of AhR structure and function frequently arise when the TEF approach is discussed. Recent data relating to each of these issues are discussed below.

9.3.2. The Role of the AhR in the Toxicity of Dioxin-Like Compounds

The general basis for the TEF scheme is the observation that the AhR mediates most if not all of the dioxin-like biological and toxic effects induced by compounds included in the TEF scheme (Safe, 1990; Okey et al., 1994; Birnbaum, 1994; Hankinson, 1995). Binding to the receptor is necessary, but not sufficient, to generate the wide variety of toxic effects caused by dioxin-like halogenated aromatic hydrocarbons (Sewall and Lucier, 1995; De Vito and Birnbaum, 1995) (for additional review references, see Part II, Chapter 2). There are several lines of evidence that the Ah receptor is important in the toxicity of the dioxin-like compounds. A brief discussion of this evidence shall be presented in the following section. Those wishing a more detailed discussion of this issue are referred to Part II, Chapter 2.

Initial studies on the toxicity of PAHs demonstrated that the sensitivity to these compounds varied by strain of mice and segregated with the Ah locus. The Ah locus was then found to encode a receptor designated as the aryl hydrocarbon receptor or AhR. Sensitive strains of mice expressed receptors with high binding affinity for these compounds, while the resistant mice expressed a receptor that poorly bound the PAHs. One of the best ligands for this receptor was TCDD. Shortly after the discovery of the AhR, structure-activity relationship studies demonstrated a concordance between binding affinity to the Ah receptor and toxic potency in vivo in mice. Further support of the role of the AhR in the toxicity of dioxin-like compounds was demonstrated following the development of AhR knockout mice (Fernandez-Salguero et al., 1995; Schmidt et al., 1996; Mimura et al., 1997; Lahvis and Bradfield, 1998). The Ah receptor knockout mice are a strain of mice in which the Ah receptor has been genetically altered so that the receptor is not expressed or “knocked-out” in these mice. Administration of TCDD at doses more than 10 times the LD_{50} of wild-type mice has not produced any significant dioxin-like effects, either biochemical or toxicological, in the AhR knockout mice (Fernandez-Salguero et

al., 1996; Peters et al., 1999). These data as a whole demonstrate that the binding to the AhR is the initial step in the toxicity of dioxin-like compounds.

9.3.3. Species Comparison of the AhR

Although binding to the AhR initiates a cascade of molecular and cellular events leading to toxicity, the exact mechanism of action of dioxin-like compounds is not completely understood. One difficulty in determining the mechanism is our limited understanding of the normal physiological role of the AhR, which would aid in understanding of potential species differences in response to dioxin-like chemicals. The available data indicate that the AhR does play an important role in normal processes and that there are a number of similarities in the action of the AhR between species. These data strengthen our confidence in species extrapolations with these chemicals.

There are several lines of evidence suggesting that the AhR is an important factor in developmental and homoeostatic processes. The AhR is a ligand-activated transcription factor that is a member of the basic-helix-loop-helix-Per-Arnt-Sim (bHLH-PAS) superfamily. The bHLH-PAS superfamily consists of a growing list of at least 32 proteins found in diverse organisms such as *Drosophila, C. elegans*, and humans. Many of these proteins are transcription factors that require either hetero- or homodimerization for functionality. These proteins regulate circadian rhythms (per and clock) and steroid receptor signaling (SRC-1, TIF2, RAC3) and are involved in sensing oxygen tension (Hif-1, EPAS-1/HLF) (Hahn, 1998). The AhR is also a highly conserved protein that is present in all vertebrate classes examined, including modern representatives of early vertebrates such as cartilaginous and jawless fish (Hahn, 1998). In addition, an AhR homologue has been identified in *C. elegans* (Powell-Coffman et al., 1998). The classification of the AhR as part of the bHLH-PAS superfamily and its evolutionary conservation imply that this protein may play an important role in normal physiological function. It has been proposed that understanding the function of the bHLH-PAS family of proteins and the phylogenetic evolution of the AhR may lead to an understanding of the role of this protein in normal processes (Hahn, 1998).

The process of development is a complex phenomenon that involves the specific expression of numerous genes in a spatial and temporal pattern. The importance of a particular gene in developmental biology is often inferred by its spatial and temporal expression during development. The AhR is expressed in a tissue, cell, and temporal pattern during development (Abbott et al., 1995). It is highly expressed in the neural epithelium, which forms the neural crest (Abbott et al., 1995). The expression of the AhR at critical periods during development suggests that this protein has important physiological functions.

Further evidence of the role of the AhR in developmental processes is provided by the development and study of AhR knockout mice. Three strains of AhR knockout mice have been produced using a targeted disruption of the AhR locus (Fernandez-Salguero et al., 1995; Schmidt et al., 1996; Mimura et al., 1998; Lahvis and Bradfield, 1998). The AhR -/- mice develop numerous lesions with age (Fernandez-Salguero et al., 1995). Mortality begins to increase at about 20 weeks, and by 13 months almost half of the mice either die or become moribund. Cardiovascular alterations consisting of cardiomyopathy with hypertrophy and focal fibrosis, hepatic vascular hypertrophy and mild fibrosis, gastric hyperplasia, T-cell deficiency in the spleen, and dermal lesions are apparent in these mice and the incidence and severity increases with age (Fernandez-Salguero et al., 1995). Although male and female AhR -/- mice are fertile, the females have difficulty maintaining conceptus during pregnancy, surviving pregnancy and lactation, and rearing pups to weaning (Abbott et al., 1999). It should be noted that the AhR knockout mice are resistant to the toxic effects of TCDD.

Comparisons between the AhR of experimental animals (primarily rodents) and the human AhR have revealed a number of similarities in terms of ligand and DNA binding characteristics and biochemical functions. Tissue-specific patterns of expression of AhR mRNA are similar in rats, mice, and humans, with highest levels generally detected in lung, liver, placenta, and thymus (Dolwick et al., 1993; Döhr et al., 1996). Nuclear AhR complexes isolated from human and mouse hepatoma cells (Hep G2 and Hepa 1c1c7, respectively) have similar molecular weights. Although the human AhR appears more resistant to proteolytic digestion by trypsin or chymotrypsin, the major breakdown products were similar between the two species, and photolabeling analysis with TCDD suggested common features in the ligand binding portion of the receptors (Wang et al., 1992).

Limited analysis has suggested the average human AhR exhibits a lower binding affinity for various HAHs than “responsive” rodent strains. However, similar to a variety of experimental animals, human populations demonstrate a wide variability in AhR binding affinity (Micka et al., 1997). Recent determination of AhR binding affinity (K_d) toward TCDD in 86 human placenta samples showed a greater than twenty-fold range in the binding affinity, and this range encompasses binding affinities similar to those observed in sensitive and resistant mice (Okey et al., 1997). Whereas the concentration of various ligands required to activate a human AhR reporter gene construct was higher than required with rodent cell cultures, the actual rank order of binding affinities was in agreement (Rowlands and Gustafsson, 1995). Although comparisons have been made of the TCDD binding affinity to the AhR of different species, caution should be used when attempting to predict species sensitivity to TCDD and related compounds. For mice, the sensitivity to the biochemical and toxicological effects of TCDD and related compounds is associated with the relative binding affinity of TCDD to the AhR in the

different strains (Birnbaum et al., 1990; Poland and Glover, 1990). However, the relative binding affinity of TCDD to the AhR across species does not aid in the understanding of interspecies differences in the response or sensitivity to TCDD (DeVito and Birnbaum, 1995).

The human AhR also demonstrates other slight differences when compared to the AhR from experimental animal species. The molecular mass of the human AhR ligand-binding subunit appears to be greater than the AhR subunit from certain TCDD "responsive" mouse strains but similar to the receptor molecular mass for rats (Poland and Glover, 1987). Currently there has been no association established between differences in the molecular mass of the AhR and sensitivity to a particular biochemical or toxicological response across species (Okey et al., 1994). The non-liganded human AhR appears thermally more stable compared to AhR from various rodent species, whereas the reverse situation exists with the liganded human AhR (Nakai and Bunce, 1995). Transformation of the ligand-bound human AhR receptor (isolated from colon adenocarcinoma cells) to the DNA-binding state, unlike rodent hepatic AhR, is temperature dependent (Harper et al., 1992). The importance of these species differences in transformation and stability of the AhR in the species sensitivity to TCDD remain uncertain. However, in critical areas of receptor function such as ligand recognition, transformation, and interaction with genomic response elements, the human AhR is comparable to the AhR isolated from experimental animals.

Ligand-bound or transformed AhR from a variety of mammalian species, including humans, bind to a specific DNA sequence or "dioxin response element" with similar affinities (Bank et al., 1992; Swanson and Bradfield, 1993). The bHLH structure of receptor proteins such as AhR ensures appropriate contact and binding with DNA recognition sites. Amino acid sequence analysis between mouse and human AhR shows an overall sequence homology of 72.5%, whereas the bHLH domain shows 100% amino acid concordance (Fujii-Kuriyama et al., 1995). In comparison, the deduced amino acid composition of the AhR from killifish was 78%-80%, similar to the amino acid sequence of rodent and human AhR (Hahn and Karchner, 1995). These studies demonstrate a concordance between the structure of the receptor and its function across species.

The majority of scientific evidence to date supports the theory that binding to the AhR is a necessary first step prior to dioxin-like compounds eliciting a response, as discussed in Part II, Chapter 2. Current research has identified the AhR in a variety of human tissues and cells that appear to function in a similar manner to the AhR from experimental animals, including fish, birds, and mammals. When multiple endpoints are compared across several species, there exists a high degree of homogeneity in response and sensitivity to TCDD and related compounds (DeVito et al., 1995). Therefore, these data provide adequate support for the development of the TEF methodology. However, these data also reflect the true complexity of intra- and interspecies

comparisons of biochemical and toxicological properties. Continued research into the variety of additional cytoplasmic and nuclear proteins capable of interacting with the AhR signaling pathway will ultimately lead to a better understanding of the observed species and strain variability in the response to dioxin-like chemicals and may be useful in further refining TEFs.

9.3.4. Mode of Action and Implications for the TEF Methodology

Many of the toxic effects of dioxins are mediated by disruption of normal growth and differentiation processes. For example, TCDD alone is capable of producing cancer in experimental animals. However, its genotoxicity is limited. From an operational point of view, TCDD is a tumor promoter (See Part II, Chapter 6). Tumor promoters act by disrupting the natural balance between cell replication and cell death. Similarly, many of the non-cancer effects, such as immunotoxicity and developmental toxicities, are due to TCDD-induced alterations in cell growth and differentiation. While these events are initiated by the activation of the Ah receptor, the exact molecular and cellular alterations beyond receptor binding remain uncertain. One criticism of the TEF methodology is that the exact molecular mechanisms for the toxic effects of these chemicals is uncertain and thus one cannot apply this method to mixtures with certainty. The uncertainties in understanding the exact molecular mechanism of dioxin action is not unique and does not detract significantly from the utility of the TEF methodology. The exact molecular mechanisms of the biochemical and physiological effects of estrogens are also uncertain. This does not decrease our confidence that if a chemical binds to the estrogen receptor and induces uterine growth in vivo that the chemical is estrogenic and that it can be useful to describe its potency relative to estradiol. Similarly, if a chemical binds to the Ah receptor and induces dioxin-like effects, we can classify the chemical as dioxin-like and describe its relative potency to TCDD without understanding every molecular event leading to the biological effect. For many of the chemicals assigned TEF values, there are in vitro Ah receptor binding data and a number of in vivo studies estimating the REP of these chemicals for toxic and biochemical effects.

9.3.5. Ah Receptor Ligands

A wide variety of structurally diverse anthropogenic and natural chemicals are capable of interacting with the AhR. These chemicals also have a broad range of potencies at inducing dioxin-like effects in experimental systems. One of the major differences between the anthropogenic chemicals included in the TEF methodology and the natural AhR ligands is their pharmacokinetics. The anthropogenic chemicals included in the TEF methodology are persistent and bioaccumulate in wildlife and humans. In contrast, most if not all of the natural AhR ligands are rapidly metabolized and eliminated from biological systems. The following section will

examine the differences between the chemicals included in the TEF methodology and remaining AhR ligands not included in this approach.

9.3.5.1. *Industrial/Synthetic AhR Ligands*

The synthetic compounds that bind to AhR include a number of different classes of chemicals, most notably the PCDDs, PCDFs, and PCBs. Other synthetic AhR ligands include industrial chemicals (polybrominated biphenyls, polychlorinated napthalenes, chlorinated paraffins, etc.), pesticides (hexachlorobenzene), and contaminants (polybrominated dioxins, dibenzofurans, and napthalenes) associated with various manufacturing, production, combustion, and waste disposal processes. In addition, pyrolysis of organic material can produce a number of non-halogenated polycyclic aromatic hydrocarbons (PAHs) with moderate to high affinity for AhR (Poland and Knudson, 1982; Nebert, 1989; Chaloupka et al., 1993).

Not all of the anthropogenic sources of dioxin-like compounds are included in the TEF methodology. Many of these chemicals, such as hexachlorobenzene and the brominated diphenyl ethers, are only weakly dioxin-like and have significant toxicological effects that are not mediated by the AhR. For these chemicals, it is not clear that adding them to the TEF methodology would decrease the uncertainty in the risk assessment process. For other classes of chemicals, such as the chlorinated napthalenes, environmental concentrations and human exposures are largely uncertain.

The PAHs are one class of anthropogenic chemicals not included in the TEF scheme despite evidence for AhR binding. The PAHs are not included in the TEF methodology because of their short half-lives and relatively weak AhR activity. In addition, the role of the Ah receptor in the toxicity of the PAHs is uncertain. For example, both benzo[a]pyrene and chrysene induce CYP1A1 activity through an AhR-mediated mechanism (Silkworth et al., 1995). However, while the Ah receptor also plays a role in the immune suppressive effects of benzo[a]pyrene it does not appear to be involved in the immune suppression induced by chrysene (Silkworth et al., 1995). Furthermore, PAHs are DNA reactive and mutagenic and these mechanisms play a large role in both the carcinogenicity and immunotoxicity of the PAHs (Ross and Nesnow, 1999). In contrast, TCDD and other dioxin-like compounds are not DNA reactive. While there are PAHs that bind to the AhR, the role of AhR or other competing pathways in the toxicity of these compounds has not been clearly defined.

Brominated dioxins, dibenzofurans, biphenyls, and napthalenes also induce dioxin-like effects in experimental animals (Miller and Birnbaum, 1986; Zacherewski et al., 1988; Birnbaum et al., 1991; Hornung et al., 1996; DeVito et al., 1997; Weber and Greim, 1997). The brominated dioxins and dibenzofurans may be more or less potent than their chlorinated orthologues, depending on the congener (Birnbaum et al., 1991; DeVito et al., 1997). The

sources of the brominated dioxin-like compounds are not well characterized. Some of the chemicals, such as the brominated biphenyls and their contaminants the brominated naphthalenes, were synthesized and sold as commercial flame retardants. The manufacture and use of polybrominated biphenyls has been prohibited. Brominated dibenzofurans are produced as byproducts of synthesis and pyrolysis of some brominated flame retardants. There is some evidence of human exposure to brominated dioxins and dibenzofurans from extruder operators (Ott and Zober, 1996). Polybrominated, polychlorinated, and mixed bromo- and chloro- dioxins and dibenzofurans have been found in soot from textile processing plants (Sedlak et al., 1998). Although these chemicals have been found in humans, these studies are limited to a small population and exposure to the general population remains undetermined. Future examinations of the TEF methodology should include a more detailed discussion of the brominated dioxins and dibenzofurans.

9.3.5.2. *Naturally Occurring AhR Ligands*

The evolutionary conservation of AhR and its biological function following activation by dioxin-like compounds have led to the hypothesis that there must be an endogenous or physiological ligand(s) for this receptor. Presently, the endogenous ligand remains undetermined. However, efforts to discover the natural ligand have led to the discovery of a number of naturally occurring AhR ligands. A number of naturally occurring chemicals present in the diet are capable of binding to AhR and inducing some dioxin-like effects in experimental animals (Bradfield and Bjeldanes, 1984; 1987) and humans (Michnovicz and Bradlow, 1991; Sinha et al., 1994). The question of how the interaction of these chemicals relates to the toxicity of those chemicals designated as dioxin-like has become the subject of much debate.

One class of naturally occurring chemicals that activate the AhR is the indole derivatives. Indole derivatives, naturally present in a variety of cruciferous vegetables, are capable of modulating the carcinogenicity of PAHs (Wattenberg and Loub, 1978). Indole-3-carbinol (I-3-C) and 3,3'-diindolylmethane (DIM) are major secondary metabolites found in cruciferous vegetables and induce both phase I and II metabolic enzymes (CYP1A-dependent glutathione and glucuronyl transferases, oxidoreductases) in experimental animals (Bradfield and Bjeldanes, 1984, 1987), human cell lines (Bjeldanes et al., 1991; Kleman et al., 1994), and humans (Michnovich and Bradlow, 1990, 1991). Although both compounds induce CYP450 enzymes under AhR transcriptional control, they exhibit relatively low binding affinity for the Ah receptor (Gillner et al., 1985). Further investigation revealed that I-3-C is relatively unstable in the acidic environment of the digestive tract and readily forms DIM. In turn, DIM can participate in acid condensation reactions to form indolocarbazoles (ICZs) (Chen et al., 1995). ICZs are also produced by bacterial metabolism of the common dietary amino acid tryptophan. ICZs, in

particular indolo[3,2b]carbazole, exhibit high binding affinity for the rodent AhR, approximately equipotent to 2,3,7,8-tetrachlorodibenzofuran, and can induce CYP1A1 activity in cultured cells (Bjeldanes et al., 1991; Gillner et al., 1993; Chen et al., 1995). ICZ and a methylated derivative, 5,11-dimethylindolo[3,2b]carbazole (MICZ), are also capable of binding to and activating the AhR in human hepatoma cells (HepG2) (Kleman et al., 1994). With considerably lower efficacy, I-3-C and DIM can partially displace TCDD from the AhR from human breast cancer cells (T47D) (Chen et al., 1996). These results would suggest that this group of compounds may represent a class of physiologically active AhR ligands derived from natural sources, which could either mimic dioxin-like compounds in their action or act as competitors for AhR binding.

In addition to the plant-derived indoles, experimental animals consuming thermally treated meat protein as well as humans fed cooked meat can exhibit induced CYP1A2 activity (Degawa et al., 1989). High-temperature cooking (250°C, 22 minutes) of ground beef resulted in the formation of a number of heterocyclic aromatic amines (HAAs) in part-per-billion levels, which were thought to be responsible for the observed CYP1A2 induction in human volunteers (Sinha et al., 1994). Mechanistic analysis of one particular HAA, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), has shown that it is capable of both interacting with the AhR and inducing CYP1A1/A2 activity in rats (Kleman and Gustafsson, 1996). These data should be viewed cautiously because recent data indicate that CYP1A2 can be induced through non-AhR mechanisms (Ryu et al., 1996). Because there are multiple pathways to induce CYP1A2, the increase in CYP1A2 activity following exposure to complex mixtures, such as cooked meat, does not necessarily indicate the presence of dioxin-like compounds.

Other diet-derived chemicals that can interact with the AhR include oxidized essential amino acids. UV-oxidized tryptophan is capable of inducing CYP1A1 activity in mouse hepatoma cells through an AhR-dependent mechanism (Sindhu et al., 1996). Rats exposed to UV-oxidized tryptophan in vivo also exhibited induction of hepatic and pulmonary CYP1A1 activity. Both in vitro and in vivo enzyme induction were transient, with the oxidized tryptophan possibly being metabolized by CYP1A1 (Sindhu et al., 1996). Tryptanthrins, biosynthetic compounds produced from the metabolism of tryptophan and anthranilic acid by yeast commonly found in food, are agonists for the rat AhR (Schrenk et al., 1997). Various tryptanthrins also induce CYP1A1-related enzyme activity in mouse hepatoma cells with the approximate efficacy of indolo[3,2b]carbazole.

Recent studies have demonstrated that physiological chemicals can bind to the AhR. Bilirubin was recently found to transform the AhR from mouse hepatoma cells into its DNA-binding state, resulting in CYP1A1 induction. Hemin and biliverdin can also be metabolically converted to bilirubin, resulting in AhR-dependent gene activation (Sinal and Bend, 1997). Despite these results, there is no clear evidence that these are the physiological ligands for the

AhR, nor is there evidence that these compounds can modulate the activity of dioxin-like compounds or lead to dioxin-like toxic effects in humans or animals.

9.3.5.3. *Industrial vs. Natural AhR Ligands*

There are a number of structurally diverse chemicals that bind to the Ah receptor. Some of these chemicals are industrial chemicals produced intentionally (PCBs, PBBs, etc.). Others are by-products of industrial processes (PCDDs and PCDFs). There are also a number of "natural" AhR ligands that are either plant derived (i.e. I-3-C) or are synthesized endogenously, such as bilirubin. It has been postulated that the natural ligands could be the major contributors to the daily dose of TEQs, because of their higher estimated intakes (Safe, 1995). The natural ligands tend to have short half-lives and do not accumulate. The PCDDs/PCDFs and PCBs included in the TEF methodology clearly bioaccumulate. If contributions to the total TEQ are estimated on steady-state body burdens of these chemicals instead of daily intake, then TCDD and other PCDDs/PCDFs and PCBs contribute more than 90% of the total TEQ compared to the natural ligands (DeVito and Birnbaum, 1996). The difference in the results of these analyses demonstrates our uncertainty of the relative potencies, exposures and dose metrics used in the comparisons of the synthetic dioxins vs. the natural AhR ligands.

When a comparison is attempted between the perceived relative risk from natural vs. anthropogenic AhR agonists, a number of factors should be taken into consideration. The potency of AhR ligands depends on several factors, including AhR binding affinity and pharmacokinetic properties. When estimating the relative potency of a chemical compared to TCDD, the larger the difference in pharmacokinetic properties, the greater the effect that study design has on the relative potency. Initial studies comparing the potency of indolo[3,2b]carbazole to TCDD demonstrate the importance of the pharmacokinetic differences between these chemicals. In Hepa-1 cells exposed for 4 hours, the relative potency for induction of CYP1A1 mRNA of indolo[3,2b]carbazole compared to TCDD is 0.1 (Chen et al., 1995). If the relative potency is determined after 24 hours of exposure, the potency of indolo[3,2b]carbazole drops 1,000-fold to 0.0001 (Chen et al., 1995). In addition, the dioxin-like effects of low doses of indolo[3,2b]carbazole in Hepa-1 cells are transient. Similar transient effects of other dietary-derived AhR ligands have also been reported (Xu and Bresnick, 1990; Berghard et al., 1992; Riddick et al., 1994). These data demonstrate that the relative potencies of these chemicals compared to TCDD are dependent upon the pharmacokinetic properties of the chemicals and the experimental design used in the comparisons. In addition, these data also demonstrate that for rapidly metabolizable AhR ligands, the effects are transitory and not persistent like TCDD. It appears that the transient nature of the effect is due to the transient

concentrations of these chemicals in these experimental systems. These data also demonstrate our uncertainty of the relative potency of the dietary-derived AhR ligands.

The chemicals included in the TEF scheme are those that not only bind to AhR but also bioaccumulate and have long biological half-lives in humans, typically on the order of years. In contrast, the pharmacokinetics of the endogenous or natural group are not well studied, but these chemicals tend to be short-lived, with half-lives on the order of minutes to hours. Although both PAHs and the halogenated aromatics bind to AhR and induce cytochrome P450-related enzyme activities, only the latter group produces the additional dioxin-like spectrum of toxicological responses. These toxicities are thought to be due to the persistent exposures attributable to the long half-lives of these chemicals (Riddick et al., 1994).

One caution when comparing the relative exposures to dietary AhR ligands and the anthropogenic AhR ligands is that few in vivo studies have examined the relative potency of the dietary or natural AhR ligands for toxic responses. Using the criteria of the WHO workgroup for PCDDs, PCDFs, and PCBs results in only two in vivo studies of I-3-C which compared the REP to TCDD (Wilker et al., 1996; Bjeldanes et al., 1991). In an in vivo study of the developmental effects of I-3-C, in utero exposure of rats to I-3-C resulted in a number of reproduction-related abnormalities in male offspring, only some of which resemble those induced by TCDD (Wilker et al., 1996). Because of the different spectrum of effects of I-3-C compared to TCDD in these developmental studies, it is likely that mechanisms other than AhR activation are involved in these effects. I-3-C and some of its acid catalyzed oligomerization products alter androgen and estrogen metabolism (Wilson et al., 1999; Telang et al., 1997), which may contribute to the developmental effects of I-3-C. While a number of in vitro studies have demonstrated dioxin-like enzyme induction of the indole derivatives, in order to have REP values that adequately describe the in vivo potency of these chemicals, future in vivo studies examining toxic responses are required.

9.3.5.4. *Limitations in Comparing the Quantitative Interactions between Industrial/Synthetic and Natural AhR Ligands*

Although there are limited data on the in vivo biochemical and toxicological effects of these ligands, the effects of mixtures of anthropogenic and natural AhR ligands is altogether lacking. There is one study examining the interactions of I-3-C and DIM on the effects of TCDD in cell culture systems. However, it is uncertain how to extrapolate these in vitro concentrations to present human in vivo exposures. The limited data available do not adequately address the interactions between these chemicals. Future in vivo studies are required in order to better understand the potential interactions between these classes of AhR ligands.

Another limitation in comparing the natural AhR ligands to the dioxins is the multiple effects induced by the natural AhR ligands. In vivo and in vitro studies of I-3-C indicate that it induces a number of biochemical alterations that are not mediated through the AhR (Broadbent and Broadbent, 1998). The activation of these additional pathways creates difficulties in making direct comparisons with TCDD and related chemicals. Similarly, the PAHs also have non-AhR-mediated biochemical and toxicological effects that also complicate direct comparisons with TCDD and related dioxins. For example, co-exposure to TCDD and PAHs have demonstrated both synergistic and antagonistic interactions in mice depending upon the endpoint examined (Silkworth et al., 1993).

Presently, there are several limitations in our understanding of the importance of naturally occurring dioxin-like compounds vs. the dioxin-like compounds included in the TEF methodology. First is the limited data available on the dioxin-like toxicities of the natural ligands. In addition, there is a lack of data on the interactions between these classes of chemicals. Few if any mixtures of natural AhR ligands and PCDDs or PCDFs examining a toxic response have been published. Many of the natural AhR ligands have multiple mechanisms of action that presently cannot be accounted for in the TEF methodology. For example, I-3-C has anticarcinogenic properties in tumor promotion studies, and these effects may or may not be mediated through AhR mechanisms (Manson et al., 1998). The lack of data and the role of non-AhR mechanisms in the biological effects of these chemicals prohibit a definitive conclusion on the role of natural vs. anthropogenic dioxins in human health risk assessment. Though it is important to address these issues, the available data do not lend themselves to an appropriate quantitative assessment of these issues.

One of the most significant differences between the industrial Ah receptor ligands (i.e. dioxins) and the natural Ah receptor ligands is the persistence of the dioxins in biological systems. Because of their long half-lives, dioxins provide a persistent activation of the Ah receptor. In contrast, the natural ligands are rapidly metabolized and the activation of the Ah receptor is short-lived. Determining the relative potency of the natural ligands compared to TCDD is not necessarily a trivial matter. The relative potency of these chemicals is due to their ability to bind and activate the Ah receptor and the persistence of this signal. Most of the studies examining the relative potency of the natural ligands are based on in vitro or short-term in vivo studies. The estimates of the relative potencies of these chemicals is greatly exaggerated in these short-term assays because of the bioaccumulative nature of TCDD. Studies comparing the relative potency of TCDD to TCDF have demonstrated that due to the differences in the half-lives of TCDF and TCDD, short-term studies overestimate the relative potency of TCDF compared to the relative potency observed in longer-term studies (DeVito and Birnbaum, 1995). The relative potencies of the natural ligands would best be estimated following long term

exposures. These data are unavailable and thus the estimates of the relative potencies of these chemicals is unreliable.

Although Safe has suggested that exposure to natural AhR ligands is 100 times that of TCDD and other dioxin-like compounds (Safe, 1995), the impact of the natural AhR ligands remains uncertain. Epidemiological studies suggest that human exposures to TCDD and related chemicals are associated with adverse effects, such as developmental impacts and cancer. In many of these studies, the exposed populations have approximatley 100 times more TCDD exposure than background populations (see Part II, Chapter 7). If the exposure to natural AhR ligands is included in these comparisons, then the exposed populations should have approximatley double the total TEQ exposures than the background population. It seems unlikely that epidemiological studies could discriminate between such exposures. These data suggest that the estimates of the contribution of the natural AhR ligands to the total TEQ exposure are overestimated. In addition, regardless of the background human exposure to "natural" AhR ligands, the margin of exposure to TCDD and related chemicals between the background population and populations where effects are observed remains a concern.

9.4. TOTAL TEQ AND THE ADDITIVITY CONCEPT

The issue of the scientific defensibility of additivity in determining total TEQ has been raised since the onset of the use of TEFs. Arguments regarding this approach include the presence of competing agonists or antagonists in various complex mixtures from environmental sources, interactions based on non-dioxin-like activities (inhibition or synergy), and the fact that dose-response curves for various effects may not be parallel for all congeners assigned TEFs. Although comparative pharmacokinetics have also been raised as an issue, this has generally been accounted for by the heavier weight accorded to in vivo studies in the assignment of TEFs. Despite these concerns, empirical data support the use of the additivity concept, recognizing the imprecise nature of the TEFs per se. A substantial effort has been made to test the assumptions of additivity and the ability of the TEF methodology to predict the effects of mixtures of dioxin-like compounds. These efforts have focused on environmental, commercial, and laboratory-derived mixtures. In addition, endpoints examined ranged from biochemical alterations, such as enzyme induction, to toxic responses such as tumor promotion, teratogenicity, and immunotoxicity. A brief summary of some of the more important work is given and discussed in the following section.

The TEF methodology has been examined by testing mixtures of chemicals containing dioxins and sometimes other chemicals. These mixtures have either been combined and produced in the laboratory or were actual environmental samples. Researchers have also used different approaches in estimating the TCDD equivalents of the mixtures. Some researchers

have determined the REP of the components of the mixture in the same system in which the mixture was tested and have used these REPs to estimate TCDD equivalents. These studies can provide insight into the validity of the assumption of additivity of the TEF methodology. Other researchers have used consensus TEF values to estimate the TCDD equivalents of the mixture. It is not clear if these studies can be considered true tests of the additivity assumption. The consensus TEF values have been described as conservative estimates of the relative potency of a chemical in order to protect humans and wildlife. If the consensus TEF values are conservative and protective, then they should overestimate the potency of mixtures tested in an experimental system. In essence, using the consensus TEF values should generally over predict the potency of a mixture (and therefore under predict the response) when compared to the equivalent concentrations of TCDD in an experimental system. In the following discussion of the studies examining the assumption of additivity, these differences in study design and their implications for interpretation of the data must be considered.

9.4.1. Examination of Laboratory Mixtures of PCDDs and PCDFs

Bock and colleagues evaluated the TEF methodology in several systems using both individual congeners as well as laboratory-derived mixtures (Lipp et al., 1992; Schrenk et al., 1991, 1994). REPs or toxic equivalents or "TEs" (as designated by the authors) were determined for 2,3,7,8-substituted PCDDs based on enzyme induction in human HepG2 cells, rat H4IIE cells, and primary rat hepatocytes. Three laboratory-defined mixtures (M1, M2, and M3) were prepared and then examined in these same cell culture systems. TCDD contributed between 6%-8% of the TEQs for M1 and M2, but was not present in M3. In M1, 1,2,3,4,6,7,8-HpCDD contributes approximately 60% of the TEQ, and 1,2,3,7,8-PCDD and 1,2,3,4,7,8-HxCDD contribute 10% each. In M2, 1,2,3,4,6,7,8-HpCDD contributes 45%, 1,2,3,7,8-PCDD and 1,2,3,4,7,8-HxCDD contribute 15% each; and TCDD, 1,2,3,6,7,8-HxCDD, and 1,2,3,7,8,9-HxCDD contribute less than 10% to the total TEQ. The TEQs in M3 are derived predominately from 1,2,3,4,7,8-HxCDD (50%); 1,2,3,4,7,8-HxCDD (20%); and 1,2,3,6,7,8-HxCDD (18%). These mixtures also contain up to 49 chlorinated dibenzo-*p*-dioxins. The TCDD equivalents of the mixtures were determined on the basis of the assumption of additivity using the TEF methodology and the laboratory derived REPs or TEs as well as experimentally by comparing the EC_{50}s of the mixtures with that of TCDD. According to the authors, in all three systems the data demonstrated that the components of the mixture act in an additive manner (Lipp, 1991; Schrenk et al., 1991). For example, in the human HepG2 cells the EC_{50} of a mixture of 49 different PCDDs was determined experimentally at 0.034 pg TEQ/plate, compared to the calculated or predicted EC_{50} of 0.028 pg TEQ/plate. Interestingly, the TEF methodology accurately predicted

the effects of M3, a mixture containing predominately OCDD, some heptaCDDs and hexaCDDs, and no pentaCDDs or TCDD (Schrenck et al., 1991).

Bock and colleagues also tested a mixture of 49 PCDDs in a rat liver tumor promotion study. The mixture, designated as M2, was the same mixture used in the cell culture studies described above and TCDD contributed approximatley 8% of the TEQs of this mixture. In theses studies, rats received an estimated 2-200 ng TCDD/kg/d or 200-20,000 ng mixture/kg/d. The doses of the mixture were equivalent to the TCDD doses using a TE of the mixture of 0.01 based on enzyme induction in rat hepatocytes (Schrenk et al., 1991). A comparison of the relative potency of the mixture was based on liver concentrations of the chemicals followed by TEQ calculations using the I-TEFs (NATO/CCMS, 1988). According to the authors, in the low-dose region (2-20 ng TCDD/kg/d) the I-TEFs accurately predict the enzyme-inducing activity of the mixture but tend to overestimate the potency of the mixture at the higher doses (20-200 ng/kg/d). Also, according to the authors, the I-TEFs provide a rough estimate of the tumor-promoting potency of the mixture but overestimate the mixture's potency . However, the authors did not quantify or qualify the magnitude of the overestimation.

In the studies by Schrenk and colleagues, the TEQs were based on tissue dose, not administered dose. Recent studies by DeVito et al. (1997b, 2000) indicate that the REP for dioxin-like compounds can differ when determined based on administered or tissue dose. The higher chlorinated dioxins tend to accumulate in hepatic tissue to a greater extent than does TCDD, and their REPs tend to decrease when estimated based on tissue dose (DeVito et al., 1997b, 2000). Because the I-TEFs are based on an administered dose, they may not predict the response when the TEQ dose is expressed as liver concentration. If the TEQ dose in the data by Schrenk et al. (1994) is compared on an administered dose, then the dose-response relationship for increases in relative volume of preneoplastic ATPase-deficient hepatic foci (% of liver) are comparable between TCDD and the mixture, indicating that additive TEFs provided an approximation of the tumor-promoting ability of a complex mixture of PCDDs (Schrenck et al., 1994). In addition, because TCDD contributed less than 10% of the total TEQ in these mixtures, these data indicate that the assumption of additivity reasonably predicts the response of complex mixtures of dioxins.

In responsive mouse strains, induction of cleft palate and hydronephrosis by TCDD occurs at doses between 3 and 90 μg TCDD/kg (Nagao et al., 1993; Weber et al., 1985; Birnbaum et al., 1985, 1987, 1991). Several groups have examined the assumption of additivity using teratogenic effects of dioxins as an endpoint. Birnbaum and colleagues examined TEF methodology using mouse teratogenicity as an endpoint (Weber et al., 1985; Birnbaum et al., 1985, 1987, 1991). REPs were derived for 2,3,7,8-TCDF, 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDF, and 1,2,3,4,7,8-HxCDF (Weber et al., 1984, 1985; Birnbaum et al., 1987). Analysis of the dose-

response for these chemicals, based on administered dose, demonstrated parallel slopes. According to the authors, dose-response analysis of two mixtures containing either TCDD and 2,3,7,8-TCDF or 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF demonstrated strict additivity (Birnbaum et al., 1987; Weber et al., 1985).

Nagao et al. (1993) also examined the TEF methodology using teratogenicity in mice as an endpoint. Mice were exposed to a single dose of TCDD (5-90 μg/kg) or a mixture of PCDDs, or one of two different mixtures of PCDFs. The mixtures contained no detectable TCDD. The I-TEFs were used to determine the TEQ of the mixtures. According to the authors, the I-TEFs predicted the potency of the PCDD mixture, and the dose-response relationship was consistent with the assumption of additivity. The I-TEFs overestimated the potency of the PCDF mixtures by two- or fourfold. All three mixtures contained significant concentrations of non 2,3,7,8-chloro-substituted PCDDs and PCDFs in addition to the dioxin-like compounds present. In the studies by Birnbaum and colleagues (Weber et al., 1985; Birnbaum et al., 1985, 1987, 1991) and Nagao et al. (1993) examining the assumption of additivity using teratogenicity as an endpoint, the TEF methodology proves useful in estimating the effects of these mixtures.

Rozman and colleagues have examined the assumption of additivity of PCDDs in both acute and subchronic studies. In acute studies, TCDD (20-60 μg/kg), 1,2,3,7,8-PCDD (100-300 μg/kg), 1,2,3,4,7,8-HxCDD (700-1,400 μg/kg), and 1,2,3,4,6,7,8-HpCDD (3,000-8,000 μg/kg) were administered to male rats, and REP values were determined for lethality. A mixture of all four chemicals at equally potent concentrations was then prepared and dose-response studies were performed with the mixture at doses that would produce 20%, 50%, and 80% mortality. The mixture studies demonstrated strict additivity of these four chemicals for biochemical and toxicological effects (Stahl et al., 1992; Weber et al, 1992a,b). Following the acute studies, Viluksela et al. (1998a,b) prepared a mixture of these chemicals and estimated the TEQ based on the REPs from the acute studies. A loading/maintenance dose regimen was used for 90 days and the animals were followed for an additional 90 days. According to the authors, the assumption of additivity predicted the response of the mixture for lethality, wasting, hemorrhage, and anemia, as well as numerous biochemical alterations such as induction of hepatic EROD activity and decreases in hepatic phosphenolpyruvate carboxykinase and hepatic tryptophan 2,3-dioxygenase (Viluksela et al., 1997; 1998). Increases in serum tryptophan concentrations and decreases in serum thyroxine concentrations were also predicted by the TEF methodology (Viluksila et al., 1998a).

Rozman and colleagues followed up these initial studies by examining the assumption of additivity of the effects of PCDDs as endocrine disruptors (Gao et al., 1999). Ovulation is a complex physiological phenomenon that requires the coordinated interaction of numerous endocrine hormones. In a rat model, ovulation can be inhibited by TCDD at doses between 2 to

32 μg/kg (Gao et al., 1999). Dose-response analysis of TCCD, 1,2,3,7,8-PeCDD, and 1,2,3,4,7,8-HxCDD demonstrate that the slopes are parallel and the REPs are 0.2 and 0.04, respectively. According to the authors, the dose response for a mixture of these chemicals, in which the components were at equally potent concentrations, further demonstrated the response additivity of mixtures of PCDDs and the predictive ability of the TEF methodology (Gao et al., 1999).

The research on the interactions between mixtures of PCDDs and PCDFs has taken two approaches. The first is to derive REP values in the same system in which the mixtures shall be tested. These studies confirm that the assumption of additivity can predict the response of mixtures of PCDDs and PCDFs. A second approach is to use the I-TEFs to assess the potency of a mixture. These studies tend to indicate that the I-TEFs overestimate the potency of a mixture by factors of two to four. Recently, the WHO TEFs have been described as "order of magnitude" estimates of the potency of dioxin-like compounds. However, the studies using consensus TEFs demonstrate that for mixtures of PCDDs and PCDFs, the TEF methodology will predict within a half-order of magnitude or less (Schrenck et al., 1994; Nagao et al., 1993). In either case, the TEF methodology accurately predicts the responses of experimentally defined mixtures of PCDDs and PCDFs. Furthermore, several of these studies described the effects of mixtures containing either no TCDD or with TCDD contributing less than 10% of the TEQ in the presence of significant concentrations of non-2378- CDDs and CDFs. These studies strongly support the use of the TEF methodology.

9.4.2. Examination of Commercial or Laboratory-Derived Mixtures of PCDDs, PCDFs, and PCBs

Commercial mixtures of PCBs elicit a broad spectrum of biological and toxicological responses in both experimental animals and humans. Some of the observed effects resemble those induced by dioxin and furans (enzyme induction, immunotoxicity, teratogenicity, endocrine alterations, etc.). Attempts to expand the TEF approach to risk assessment of PCBs have investigated the ability of both commercial PCBs and individual congeners, selected on the basis of structure-activity relationships, to induce dioxin-like effects and to interact with TCDD. One of the first studies to examine the interactions of individual PCB congeners with TCDD used mouse teratogencity as an endpoint (Birnbaum et al., 1985, 1987). A mono-ortho PCB (2,3,4,5,3',4'-HxPCB or PCB 156) at doses of 20 mg/kg or higher (Birnbaum, 1991) induced hydronephrosis and cleft palate in mice. When mice were co-exposed to PCB 156 and 3.0 μg TCDD/kg the interactions resulted in strict additivity.

The interaction of TCDD with dioxin-like PCBs has been examined by van Birgelen et al. (1994a,b) in subchronic rat feeding studies. Concentrations of PCB 126 in the diet between 7

and 180 ppb induced several dioxin-like effects, including CYP1A1 induction, thymic atrophy, liver enlargement, and decreases in hepatic retinol concentrations, body weight gains, and plasma thyroxine concentrations. The REP for PCB 126 was estimated by the authors at between 0.01 and 0.1 (van Birgelen et al., 1994a). Co-exposure to PCB 126 and TCDD (0.4 or 5.0 ppb) in the diet demonstrated additivity for all responses except induction of CYP1A2 and decreases in hepatic retinol, where antagonism occurred at the highest doses of PCB 126 and TCDD tested. These nonadditive interactions were not observed at more environmentally relevant exposures, according to the author. In a similar study design, PCB 156 also induced dioxin-like effects with a REP estimated between 0.00004 and 0.001 (van Birgelen et al., 1994b). Similar to the interactions between PCB 126 and TCDD, additive interactions were observed in animals receiving mixtures of PCB 156 and TCDD in the low-dose region for all responses examined. However, at the highest exposures of PCB 156 and TCDD, the authors reported slight antagonistic interactions for decreases in hepatic retinol (van Birgelen et al., 1994b). For both PCB 126 and PCB 156, antagonistic interactions were observed with TCDD only at exposures that produced maximal CYP1A1 induction. The authors concluded that the antagonistic interactions are unlikely to occur at relevant human exposures.

In a series of studies examining the TEF methodology, TCDD (1.5-150 ng/kg/d), 1,2,3,7,8-PeCDD; 2,3,7,8-TCDF; 1,2,3,7,8-PeCDF; 2,3,4,7,8-PeCDF; OCDF; the coplanar PCBs 77, 126, and 169; and the mono-ortho substituted PCBs 105, 118, and 156 were administered to mice 5 days/week for 13 weeks. REPs were determined for EROD induction, a marker for CYP1A1, in liver, lung, and skin; ACOH activity, a marker for CYP1A2, in liver; and hepatic porphyrins (DeVito et al., 1997a; 2000; van Birgelen et al., 1996c). These data demonstrate that the dose-response curves for the PCDDs and PCDFs were parallel (DeVito et al., 1997a). Dose-response curves for some of the enzyme induction data for the individual PCBs displayed evidence of non-parallelism in the high-dose region (DeVito et al., 2000). A laboratory-derived mixture of these chemicals with congener mass ratios resembling those in food was administered to mice and rats, and indicated that despite the evidence of non- parallelism for the PCBs at high doses, the assumption of additivity predicted the potency of the mixture for enzyme induction, immunotoxicity, and decreases in hepatic retinoids (Birnbaum and DeVito, 1995; van Birgelen et al., 1996; 1997; DeVito et al., 1997; Smialowicz et al., 1996). In addition, the REPs estimated in mice also predicted the response of the mixture in rats for enzyme induction and decreases in hepatic retinyl palmitate concentrations (van Birgelen et al., 1997d; Ross et al., 1997; DeVito et al., 1997b). These studies indicate that not only do the REPs for enzyme induction in mice predict other responses, such as immunotoxicity and decreases in hepatic retinyl palmitate, they also can be used to predict responses of mixtures in another species.

The commercial PCB mixtures induce a variety of dioxin-like effects. Rats exposed to commercial Aroclors and observed for 2 weeks exhibited dose-dependent induction of hepatic CYP1A activity (EROD) but no thymic atrophy (Harris et al., 1993). Using REP values derived for EROD induction in rats, the TEF methodology provided good agreement with experimental estimates of the ED50 for enzyme induction. However, use of the conservative TEF values of Safe (1990) overestimated the potency of the Aroclor mixutres (Harris et al., 1993). In contrast, similar studies examining immunotoxicity as an endpoint demonstrate that both experimentally derived REP values and the conservative TEF values of Safe (1990) overestimate the potency of the Aroclor mixtures by a factor of 1.2 - 22 (Harper et al., 1995). These data demonstrate that there are nonadditive interactions between dioxin-like compounds and the non-dioxin-like PCBs and that these interactions are response specific and most likely are not due to AhR antagonism.

In in vitro systems, using H4IIe cells and rat hepatocytes, Schmitz et al. (1995, 1996) examined the assumption of additivity for individual congeners as well as commercial mixtures. After deriving REP values for enzyme induction, the authors concluded that a laboratory mixture of PCBs 77, 105, 118, 126, 156, and 169 demonstrated perfect additive behavior in these cell line systems (Schmitz et al., 1995). However, when the mixture was combined with a tenfold surplus of a mixture containing non-dioxin-like PCBs (PCB 28, 52, 101, 138, 153 and 180), the mixture demonstrated an approximate threefold higher TEQ than predicted. The authors concluded that a moderate synergistic interaction is responsible for the increased enzyme-inducing potency of the mixture containing dioxins and non-dioxin-like PCBs. Further studies by Schmitz et al. (1996) also demonstrated a slight synergistic deviation (less than threefold) from strict additivity when the calculated TEQ based on chemical analysis of Aroclor 1254 and Clophen A50 was compared to the CYP1A-induction TEQ derived in an established rat hepatoma cell line (H4IIE) (Schmitz et al., 1996).

Recently, Mayes et al. (1998) compared the carcinogenicity of Aroclor 1016, 1242, 1254 and 1260 in Sprague-Dawley rats. All four mixtures increased the incidence of hepatic tumors in female rats. The authors concluded that the female rats were more susceptible than the males to the hepatocarcinogenic effects of these mixtures. In the two-year bioassay of TCDD in Sprague-Dawley rats, the female rats were also more susceptible to the hepatocarcinogenic effects than the males (Kociba et al., 1978). Mayes and colleagues(1998) performed congener specific analysis of the Aroclor mixtures and calculated dioxin TEQ values for each of these mixtures. In order to compare the cancer induction potential of dioxin TEQ in PCB mixtures (Mayes et al. 1998) with that from TCDD (Kociba et al., 1978) in the same species of rat, the dose-response relationships are graphed and presented in figure 9-2. The dose-response relationship for hepatic tumors in female rats is similar between the Aroclor 1242, 1254, 1260 and TCDD dose regimen. This analysis demonstrates that the TEF methodology qualitatively and quantitatively predicts the

response of a complex mixture of PCBs. This is particularly important because the mass concentration of dioxin equivalents in the mixture is approximately 100,000 times less than the non-dioxin-like PCBs present in these mixtures. These data strongly support the ability of the TEF methodology to estimate the carcinogenic potency of a complex mixture of PCBs even in the presence of significant concentrations of non-dioxin-like PCBs.

Researchers have evaluated the applicability of the TEF methodology to mixtures containing dioxin-like PCBs by examining the interactions of binary mixtures, laboratory-derived mixtures, or commercial mixtures of PCBs. The studies examining the binary mixtures or laboratory-derived mixtures have demonstrated that the assumption of additivity provides good estimates of the potency of a mixture of PCBs and other dioxin-like compounds. In contrast, studies using commercial mixtures of PCBs suggest that the assumption of additivity may be endpoint specific, and that both synergistic and antagonistic interactions may occur for some mixtures of dioxins and PCBs for certain endpoints. A more detailed examination of these issues follows in the section on nonadditive interactions with non-dioxin-like compounds.

9.4.3. Examination of Environmental Samples Containing PCDDs, PCDFs, and/or PCBs

One of the first tests of the TEF methodology examined soot from a transformer fire in Binghamton, NY (Eadon et al., 1986). Benzene extracts of soot from a PCB transformer fire which contained a complex mixture of PCDDs, PCDFs, PCBs, and polychlorinated biphenylenes were administered to guinea pigs as single oral doses, and LD_{50} values were compared to TCDD. Relative potency values for the PCDDs and PCDFs based on guinea pig LD_{50} values were used to estimate the TCDD equivalents of the mixture. Eadon and co-workers exposed guinea pigs to either TCDD alone or the soot and determined their LD_{50}s. With these relative potency values, the soot extract had a TCDD equivalent concentration of 22 ppm. Comparison of the LD_{50}s for TCDD and the soot led to a TCDD equivalent of 58 ppm for the mixture. Other endpoints examined included alterations in thymus weight, body weight, serum enzymes, and hepatotoxicity. Experimentally the TCDD equivalents of the soot varied from 2 to 58 ppm. The authors concluded that because the benzene extract of the soot contained hundreds of chemicals including PCDDs, PCDFs, and PCBs, the difference between the calculated TEQ of 22 ppm and the experimentally derived TEQs between 2 and 58 seems minimal. (Note: the initial analytical TEQ value of soot [22 ppm] was calculated on the basis of guinea pig LD_{50} values of the respective components; using the current recommended TEF scheme [van den Berg et al., 1998], the “calculated” TCDD TEQ would be approximately 17 ppm.)

Shortly after the studies on the Binghamton transformer fire soot, investigators applied the TEF methodology to the leachate from Love Canal, NY. The organic phase of the leachate consisted of more than 100 different organic compounds including PCDDs and PCDFs. The

leachate did not contain PCBs or PAHs. The authors estimated the TEQ of the mixture on the basis of REP values for teratogenicity (cleft palate and hydronephrosis in mice) for the PCDDs and PCDFs present in the leachate. The authors state that the leachate contained the equivalent of 3 μg TCDD/g and that more than 95% of the TEQ was contributed by TCDD. There were two other PCDFs present in the leachate, and their contribution to the total TEQ was approximately 5% (Silkworth et al., 1989). When the TEQ of the mixture was based on dose-response analysis of the mixture compared to TCDD, the leachate was estimated to contain between 6.6 and 10.5 μg TCDD/g (Silkworth et al., 1989). The authors concluded there was a good agreement between the experimental TCDD equivalents (6.6-10.5 μg TCDD/g) and the analytical TEQs (3 μg TCDD/g). In addition, these studies illustrate that the non-AhR components of the leachate did not interfere with receptor-mediated teratogenicity (Silkworth et al., 1989). Additional investigations have shown that the same complex mixture of non-AhR agonists slightly potentiated TCDD-induced thymic atrophy and immunosuppression (plaque-forming cells/spleen response) while decreasing the hepatic CYP1A-inducing ability of the TCDD component (Silkworth et al., 1993).

The assumption of additivity was also examined using a PCDD/PCDF mixture extracted from fly ash from a municipal waste incinerator (Suter-Hofmann and Schlatter, 1989). As a purification step, rabbits were fed organic extracts from the fly ash. After 10 days the livers were removed and analyzed for PCDDs and PCDFs. The rabbit livers contained predominately 2,3,7,8-substituted PCDDs/PCDFs. Based on the chemical analysis of the liver, lyophilized and pulverized liver was added to the standard rat diet. This diet was fed to rats for 13 weeks and body weights and terminal thymus weights were recorded. The authors concluded that the mixture of PCDDs and PCDFs produced equivalent toxicities as TCDD, and the assumption of additivity was confirmed.

9.4.4. Nonadditive Interactions With Non-Dioxin-Like Compounds

For a number of toxicological responses, there appears to be evidence for nonadditive interactions in defined dose ranges by both commercial Aroclors and major congeners with little if any AhR agonist activity (i.e., PCB 153). Both commercial Aroclors and a PCB mixture comprised of major congeners found in human breast milk were shown to antagonize the immunotoxic effects of TCDD in mice (Biegel et al., 1989; Davis and Safe, 1989; Harper et al., 1995). When immunotoxicity-derived TEF values for a variety of PCB congeners were used in an additive manner to estimate TCDD TEQs for commercial Aroclors, in comparison to the experimental TEQs, they were approximately predictive for Aroclor 1254 and 1260 (Harper et al., 1995). However, the TEF approach tended to overestimate the immunotoxicity of Aroclors 1242 and 1248, suggesting some antagonism.

Typical responses to TCDD exposure in rodents include CYP1 enzyme induction and thymic atrophy. Rats consuming a diet containing 5 ppb TCDD for 13 weeks exhibited a 33-fold increase in hepatic CYP1A activity (EROD) and a greater than 50% reduction in relative thymus weight. Addition of PCB 153 to the diet at concentrations up to 100 ppm had no significant effect on either response (van der Kolk et al., 1992). Mice dosed simultaneously with TCDD and up to a 10^6-fold molar excess of PCB 153 (1 nmol/kg vs. 1 mmol/kg) exhibited no significant dose-dependent alteration in hepatic CYP1A1/A2 protein compared to the TCDD dose group alone (De Jongh et al., 1995). There was, however, an approximate twofold increase in hepatic EROD activity in the highest combined PCB 153:TCDD dose group. Subsequent tissue analysis revealed that the increase in EROD activity appeared related to PCB 153 increasing hepatic TCDD concentrations. The same PCB congener at high doses (358 mg/kg) is able to almost completely inhibit TCDD-induced suppression of the plaque-forming cell (PFC) response toward sheep red blood cells in male C57BL/6J mice (Biegel et al., 1989; Smialowicz et al., 1997). However, as PCB 153 displays negligible AhR binding affinity, the exact mechanism(s) behind these interactions is unknown. Recently, it has been shown that PCB 153 at high doses (greater than 100 mg/kg) actually enhances the PFC response in female B6C3F1 mice, thereby raising the "control" set point. When combined doses of TCDD and PCB 153 are then compared to the elevated PCB 153 response, an apparent block of the immunosuppressive effect of TCDD is observed (Smialowicz et al., 1997). The relevance of this functional antagonism is uncertain, as the doses required to inhibit the TCDD-like effects are at least 100 mg/kg of PCB 153. These doses of PCB 153 seem unlikely to occur in human populations except under extreme conditions.

Commercial PCBs and various PCB congeners have been shown to potentiate or antagonize the teratogenicity of TCDD depending upon the dose ranges and response examined (Biegel et al., 1989; Morrissey et al., 1992). Treatment of developing chicken embryos with TCDD and dioxin-like PCBs induces a characteristic series of responses, including embryo lethality and a variety of embryo malformations/deformities. Combined exposure of chicken embryos to both PCB 126 and PCB 153 (2 μg/kg and 25-50 mg/kg, respectively) resulted in protection from PCB 126-induced embryo malformations, edema, and liver lesions, but not mortality (Zhao et al., 1997). In mice, doses of 125 mg PCB 153/kg or higher inhibit the induction of cleft palate by TCDD (Biegel et al., 1989; Morrissey et al., 1992). The induction of hydronephrosis by TCDD was slightly antagonized by PCB 153, but only at doses of 500 mg/kg or higher. Once again, the environmental relevance of exposures of 100 mg/kg of PCB 153 or higher remains quite speculative, and nonadditive interactions are not expected at environmental exposures.

Nonadditive interactions have also been observed in rodents exposed to both TCDD and mixtures of various PCB congeners for hepatic porphyrin accumulation and alterations in

circulating levels of thyroid hormones. A strong synergistic response was seen with hepatic porphyrin accumulation in female rats following the combined dietary exposure to TCDD and PCB 153 (van Birgelen, 1996a). The mechanism accounting for the interaction was thought to be a combination of both AhR-dependent (CYP1A2 induction) and AhR-independent (δ-aminolevulinic acid synthetase [ALAS] induction) events. Additionally, subchronic exposure of mice to a mixture of PCDDs, PCDFs, and dioxin-like PCBs in a ratio derived from common foods also resulted in a highly synergistic response, when compared to an equivalent dose of TCDD alone, for both hepatic porphyrin accumulation and urinary porphyrin excretion (van Birgelen et al., 1996b). PCB 153, although not porphyrinogenic alone, when added to the mixture further enhanced the synergistic response of hepatic porphyrin accumulation. Non-AhR-mediated induction of ALAS activity by both the dioxin-like mono ortho-substituted PCBs in the mixture and by PCB 153 was hypothesized to partially explain the synergism.

Decreases in thyroid hormone levels have been observed in both experimental animals and humans following exposure to both dioxin-like and non-dioxin-like compounds (Nagayama et al., 1998; Koopman-Esseboom et al., 1997). It is currently thought that multiple mechanisms, including induction of specific isozymes of hepatic UDP-glucoronyl transferase (UDPGT) and binding to thyroid hormone transport proteins (thyroid binding globulin, transthryetin) could be involved. Exposure of female rats to a food-related mixture of PCDDs, PCDFs, and dioxin-like PCBs for 90 days resulted in an approximately 85% decrease in decrease in plasma levels of thyroxine. In contrast, the TCDD equivalent dose produced no effect on serum thyroxine (van Birgelen et al., 1997). Increased induction of several isoforms of UDPGT by the HAH mixture as compared to TCDD was thought to only partially explain the observed response with thyroxine levels.

Several studies examining the interactions of dioxins and non-dioxins for rat liver tumor promotion and additive and nonadditive interactions have been reported. Synergistic interactions for tumor promotion have been observed for combinations of PCB 77 and PCB 52 (2,2',5,5'-tetrachlorbiphenyl) in rat liver (Sargent et al., 1992). Bager et al. (1995) reported greater than additive interactions of PCBs 126 and 153 in a rat liver tumor promotion model.

The assumption of additivity was examined in a laboratory-derived mixture of PCDDs, PCDFs, and PCBs in a rat liver tumor promotion model (van der Plas et al., 1999). The mixture contained TCDD, 1,2,3,7,8-PeCDD, 2,3,4,7,8-PeCDF, and PCBs 126, 118, and 156. The composition of the mixture was based on concentrations of these chemicals in Baltic herring. PCB 126 and 1,2,3,7,8-PeCDD accounted for 65% of the TEQ in the mixture and TCDD accounted for approximately 6.6%. Both TCDD and the TEQ mixture increased mean foci volume and the volume fraction of foci in the liver. However, the response was statistically significantly greater in the TCDD treated animals by approximately 2-fold. While the TEQ

mixture did not produce the exact same response level as TCDD, it is difficult to quantify the overestimation of the TEF methodology in this study since only a single dose level was examined. The authors also did a dose-response study with the mixture. However, they added PCB 153 to the mixture used for the dose response study. The concentration of PCB 153 was 20,000 times the concentration of TCDD in these mixtures. Dose levels of 0.5, 1, and 2 ug TEQ/kg/week were administered to the animals. The presence of PCB 153 did not alter the effects of the 1 ug TEQ/kg/week dose since there was no statistical difference between the response of animals to the TEQ mixture with or without PCB 153. The highest dose examined, 2 ug TEQ/kg/week produced an effect that was statistically equivalent to the animals treated with TCDD alone. Van der Plas et al (1999) also determined the concentration of chemicals in the liver at the termination of the study. Their data suggest that the lower response level of the mixture is due to pharmacokinetic interactions. Animals administered 1 ug TEQ/kg/week had approximately one third of the liver TEQ concentrations as the animals treated with TCDD. Animals treated with 2 ug/kg/week had equivalent TEQ concentrations in the liver and also had similar responses as animal treated with 1 ug TCDD/kg/week. Van der Plas and colleagues concluded that the TEF methodology predicted the tumor-promoting potency of the mixture quite well, within a factor of two, but pharmacokinetic interactions between dioxins may alter the accuracy of the methodology (van der Plas et al., 1999).

In another study, van der Plas and colleagues (2000) examined the interactions of co-planar and non-coplanar components of Aroclor 1260 in a tumor promotion study. In these studies, Aroclor 1260 was separated into planar (0-1 ortho chlorines) and non-planar (2-4 ortho chlorines) components. Rats were then exposed to either 1 ug TCDD/kg/week, 1 mg 0-1ortho/kg/week, 9 mg 2-4 ortho/kg/week, 10 mg 0-4 ortho/kg/week or 10 mg aroclor 1260/kg/week. Mean foci volume and the volume fraction of the liver occupied by foci increased in animals treated with either TCDD, the 2-4 ortho mixture, the 0-4 ortho mixture and aroclor 1260. The 0-1 ortho mixture did not alter foci development compared to the control animals. Van der Plas et al (2000) concluded that the results from their study indicate that 80% of the carcinogenicity of Aroclor 1260 is due to the non-dioxin congeners in the mixture.

In the study described above, Van der Plas et al (2000) used the CALUX assay to determine the TEQ of the different mixtures. The lot of Aroclor 1260 used in this study had very low TEQs based on the CALUX assay. For example, 10 mg Aroclor 1260/kg/week was equivalent to 0.0012 ug TEQ/kg/week or approximately 0.12 ppm TEQ. In addition, the 1 mg 0-1 ortho/kg/week dose is equivalent to 0.09 ng TEQ/kg/d. In contrast, the lot of Aroclor 1260 used by Mayes et al (1998) had 7.2 ppm TEQ concentrations using the WHO TEF values and dose levels examined ranged from 10-42 ng TEQ/kg/d. The lot of Aroclor 1260 used by Mayes et al (1998) has approximately 60 times more TEQs than the lot used by van der Plas et al

(2000). In the Mayes et al (1998) studies the TEF methodology accurately predicts the carcinogenic response of the mixture. The differences in the van der Plas et al (2000) and the Mayes et al (1998) studies may be due to the different lots of Aroclor 1260 used by these two groups.

The interactions of dioxins with non-dioxin-like compounds results in additive and nonadditive responses. The antagonistic interactions, while endpoint specific, appear to occur at dose levels that greatly exceed most human exposures and should not affect the overall use of the TEF methodology. One of the difficulties in addressing the nonadditive interactions is understanding the mechanism behind these interactions. For the greater than additive interactions for induction of porphyria and decreases in serum thyroxine, there are hypotheses that may explain these effects. The mechanism of the antagonistic interactions of non-dioxin-like PCBs and TCDD on immunotoxicity and teratogenicity in mice is uncertain. For other responses, such as developmental reproductive toxicity, the interactions of PCDDs, PCDFs, and PCBs have not been examined. In addition, it has also been suggested that antagonism of Ah receptor-mediated events may be species specific. For example, addition of PCB 52, a congener commonly found in biotic samples, inhibited the TCDD-induced expression of a reporter gene under the regulatory control of the Ah receptor in mouse and rat cells, but not in guinea pig or human hepatoma cells (Aarts et al., 1995). Our limited understanding of the interactions between dioxins and non-dioxins for a variety of responses requires further research before their impact on the TEF methodology can be fully understood.

9.4.5. Examination of the TEF Methodology in Wildlife

Many wildlife species also exhibit toxic effects associated with exposure to halogenated aromatic hydrocarbons. Early life stage (ELS) or sac fry mortality in fish, characterized by edema, structural malformations, and growth reduction prior to fry mortality can be induced in trout species following exposure to dioxin-like PCDDs, PCDFs, and PCBs (Walker and Peterson, 1991). Binary combinations of a variety of PCDDs, PCDFs, and both dioxin and non-dioxin-like PCB congeners injected into fertilized trout eggs were also capable of inducing ELS mortality, with the majority of interactions between the congeners described as strictly additive (Zabel et al., 1995). When a synthetic complex mixture of PCDDs, PCDFs, and PCBs, in congener ratios that approximated Great Lakes fish residues, was tested in the ELS mortality assay, the lethal potency observed for the mixture, compared to TCDD, deviated less than twofold from an additivity approach (Walker et al., 1996). Recently, the TCDD TEQ of an environmental complex mixture of PCDDs, PCDFs, and PCBs extracted from lake trout and applied to the ELS bioassay could also be predicted by an additivity approach (Tillitt and Wright, 1997). These results suggest that additional halogenated aromatic compounds, including non-

dioxin-like PCBs, present in fish do not significantly detract from an additivity response for this AhR-mediated event.

There are also numerous studies that have examined the effects of environmental mixtures in marine mammals and avian species (Ross, 2000; Giesy and Kannan, 1998; Ross et al., 1996; Shipp et al., 1998a,b; Restum et al., 1998; Summer et al., 1996a,b). Ross and colleagues examined captive harbor seals fed herring from either the Atlantic Ocean (low levels of PCDDs/PCDFs/PCBs) or the Baltic Sea (high levels of PCDDs/PCDFs/PCBs). The seals fed herring from the Baltic Sea displayed immunotoxic responses including impaired natural killer cell activity and antibody responses to specific antigens. These effects were correlated with the TEQ concentrations in the herring. Using mink as a model, Aulerich, Bursian, and colleagues have also examined the TEF methodology. Minks were fed diets containing carp from Saginaw Bay to provide exposures of 0.25, 0.5, or 1 ppm PCB in the diet. In a series of reports, the authors demonstrated that the diet induced dioxin-like effects ranging from enzyme induction to reproductive and developmental effects, and that these effects were correlated with the dietary intake of TEQs (Giesy and Kannan, 1998). Similar studies in White Leghorn hens also demonstrated that the TEQ approach provided accurate estimates of the potency of the mixtures (Summer et al., 1996).

In summary, current experimental evidence suggests that for PCDDs, PCDFs, coplanar dioxin-like PCBs, and strictly AhR-mediated events, the concept of TEF additivity adequately estimates the dioxin-like toxicity of either synthetic mixtures or environmental extracts, despite the variations in relative contributions of each congener. Addition of the more prevalent mono- and di-ortho-substituted PCBs to a mixture, at least in the case of environmental extracts and wildlife, does not seem to significantly detract from this assumption of additivity. Interactions other than additivity (antagonism, synergism) have been observed with a variety of effects (teratogenicity, immunotoxicity, hepatic porphyrin accumulation, thyroid hormone metabolism) in both binary combinations and complex synthetic mixtures of dioxin and partial or non-Ah receptor agonists (commercial PCBs, PCB 153). However, it appears that at these high-dose exposures, multiple mechanisms of action not under the direct control of the Ah receptor are responsible for these nonadditive effects.

Additional research efforts should focus on complex mixtures common to both environmental and human samples and the interactions observed with biological and toxicological events known to be under Ah receptor control. In the interim, the additive approach with TEFs derived by scientific consensus of all available data appears to offer a good estimation of the dioxin-like toxicity potential of complex mixtures, keeping in mind that other effects may be elicited by non-dioxin-like components of the mixture.

9.4.6. Toxic Equivalency Functions

The TEF methodology has been described as an "interim" methodology. Since this interim method has been applied, there have been few proposed alternatives. One recent proposal suggests that the TEF value be replaced by a toxic equivalency function (Putzrath, 1997). It has been proposed that the REPs for PCDDs/PCDFs are better described by a function as compared to a factor or single-point estimate (Putzrath, 1996). The use of a factor to describe the relative potency of a chemical implies that its relative potency is independent of dose. Putzrath (1997) suggests that data exists which indicates that the REPs are dose dependent and that the REPs must be described as a function of dose. Recent studies have examined this possibility for a series of PCDDs/PCDFs and PCBs (DeVito et al., 1997; DeVito et al., 2000). For the PCDDs/PCDFs, the data indicate that the REPs estimated from enzyme induction data in mice are best described by a factor and not a function. For some of the PCBs examined, a function fit better, but the change in the REP was within a factor of two to five for most of the four enzymatic responses examined (DeVito et al., 2000). In addition, the dose dependency was observed only at the high-dose and not in the low-dose region (DeVito et al., 2000).

Even though these studies suggest that a TE function may be useful, there are numerous difficulties in applying this method. If the REPs are really functions and not factors, there must be a mechanistic basis for these differences, and these mechanisms would most likely be response specific and perhaps species specific. This would then require that for all critical responses, every chemical considered in the TEF methodology would have to be examined. Once again, it is highly unlikely that 2-year bioassays and multigenerational studies will be performed on all the TEF congeners in the foreseeable future. The use of a TEF function requires extensive data sets that are not available and are unlikely to be collected.

9.4.7. Species and Endpoint Specific TEFs

It is often suggested that species and endpoint TEFs may be required for the TEF concept to provide accurate estimates of risk. In fact, the WHO does have class specific TEFs based on fish, birds and mammals (van den Berg et al., 1998). The most notable differences are the lack of effect of some mono-ortho PCBs in fish (van den Berg et al., 1998). Hahn and colleagues recently examined the influence of affinity and intrinsic activity on the relative potency of PCBs in PLHC-1 cells (Hestermann et al., 2000). Using this cell line derived from fish, Hahn and colleagues demonstrated clear differences in the response of these cells to mono-ortho PCBs. The insensitivity of these fish cells to the mono-ortho PCBs is due to both reduced affinity and reduced intrinsic efficacy. Using information on affinity and intrinsic efficacy allowed for better predictions of mixtures of these chemicals than did the application of the TEF methodology (Hestermann et al., 2000). Future studies examining species differences applying the approach of

Herstermann et al., (2000) may provide insight into species specific TEFs as well as alternative approaches to the TEF methodology.

There are numerous examples of endpoint specific relative potencies for receptor mediated pharmacological agents, such as the antiestrogen, tamoxifen. It is reasonable to assume that the Ah receptor and its ligands would be no different from these other receptor systems. Examination of the WHO data base suggests that even for the chemicals with the largest data sets this question cannot be adequately addressed (See section 9.2.5). Endpoint specific TEFs would require a much more complete data set than is available at this time. In addition, these studies would have to be designed to test the hypothesis that the REPs are equivalent across endpoints. This requires controlling the species and dosing regimen employed as well as other factors. One of the reasons the TEF methodology was developed was because limited toxicity data was available for the other dioxin-like chemicals and it was unlikely that all relevant chemicals would be tested for all responses in all species, including humans. For example, it is extremely unlikely that 2-year bioassays for carcinogenesis or multi-generational studies will be performed on all chemicals included in the TEF methodology. Even though there are significant data demonstrating that a number of chemicals produce dioxin-like toxic effects, clearly the data set is not complete. For this reason, WHO recommends revisiting the TEF values every 5 years.

9.5. APPLICATION OF UNCERTAINTY ANALYSIS TO THE TEF METHODOLOGY

TEFs are presented as point estimates, in spite of the fact that variability in the REP values estimated from the supporting experimental data can range several orders of magnitude for a particular congener. It has been proposed that some of this variability in the REP values can be attributed to differences in exposure regimens, test species, or purity of the test compound. In addition, others have argued that the variability of the REPs may be due to differences in the REP across endpoints. The reasons for much of this variability have not been adequately examined experimentally and remain unknown. For example, in the WHO database, PCB 126 has the largest data set of REP values. However, while there are numerous studies estimating the REPs for this chemical, these individual studies were not designed to address the variability in the REP values. Close examination of theses studies indicates that it is difficult to attribute the variability of the REP to either species, endpoint, dosing regimen or laboratory differences. For example, there are four studies that examined the REP of 126 for immune effects in mice in the WHO data base (Harper et al., 1994; 1995; Mayura et al.,1993; Steinburg et al., 1993). The range of the REPs from these studies is 0.05 - 0.99 with a mean of 0.23 ± 0.22. It is not clear why the range is so large. In fact, three of the studies and the two extreme REPs (0.05 and 0.99) come from the same laboratory (Harper et al., 1994; 1995; Mayura et al., 1993). Similarly, there are four studies examining the REP of PCB 126 for hepatic EROD induction in mice following an acute

exposure and the REPs are 0.0005, 0.012, 0.38 and 0.55. Once again, there is no clear reason for the three order of magnitude range in the REPs for this endpoint. Because the experiments used to estimate the REPs were not designed to address the variability, further studies will be required to determine what is causing the variability.

One of the difficulties in quantitatively describing the uncertainties in the TEF methodology is due to the method by which the TEF values are assigned. First and foremost is the fact that TEFs are assigned and not derived. While there is a clear description of the qualitative weighting scheme used in assigning the TEFs, quantitatively describing how the actual committee actually assessed this weighting scheme is impossible. Consequently, the TEF approach, as currently practiced, does not provide for a quantitative description of the uncertainty for individual TEF values.

There has been several proposals for incorporating quantitative uncertainty descriptors into TEFs. Suggestions have been made to use meta-analytic approaches or Monte Carlo techniques, however (Finley et al., 1999), these approaches are only as good as the data available. For some chemicals, such as PCB 126, PeCDD and 4-PeCDF, there are sufficient data to apply these methods. In contrast, chemicals such as OCDD and OCDF have only a few studies and application of these statistical methods would be inappropriate. Another shortcoming to the application of meta-analytic approaches or Monte Carlo techniques is that they would also have to incorporate the weighting scheme described by the WHO workgroup (van den Berg et al., 1998). The weighting scheme gives qualitatively greater weight to studies that examine toxic endpoints following repeated exposures. Because our concern is generally for potential toxic effects following repeated exposures, this weighting scheme is appropriate. Incorporating a quantitative description of the weighting scheme into a meta-analytic approaches or a Monte Carlo approach to describe the uncertainty is not a trivial task (Finley et al., 2000). Future efforts by WHO or USEPA which develop guidelines and approaches to incorporating these weighting schemes into quantitative uncertainty analysis are an important step in understanding the uncertainties of the TEF methodology.

Qualitative statements of confidence are embodied in the discussions associated with the establishment and revision of TEFs. These qualitative judgments, when examined in the context of a specific risk assessment, can provide valuable insight into the overall uncertainty of some TEQ estimates. For example, using WHO TEFs (van den Berg et al., 1998) to look at background exposure from a typical U.S. diet, it is clear that only a limited number of congeners significantly contributed to the total TEQ. Approximately 80% of the TEQ-WHO_{98} associated with background dietary exposure (1 pg/kg/d) comes from only five congeners: 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 2,3,4,7,8-PeCDF, and PCB 126 (see Part I, Volume 3). The variability of the REP values found in the literature for these congeners is much lower than for congeners that are

minor contributors to background TEQ. Furthermore, the assigned TEF values for the chemicals contributing 80% to the TEQ intake are similar to the mean of their in vivo REP values. The confidence in the TEF methodology is also increased by empirical examination. A number of studies have examined complex mixtures of dioxin and non-dioxin-like compounds and the TEF methodology consistently results in TEQ estimates within a factor 2-3 for these mixtures. Based on these mixture studies it is unlikely that the estimated TEQ over or under estimates the "true" TEQ by more than a factor of five. Finally, the uncertainty in TEQ estimates is only one component of the overall uncertainty in a dioxin risk assessment. The TEQ uncertainty only addresses the confidences associated in ascribing 2,3,7,8-TCDD equivalents to a mixture. It does not address the uncertainty associated with quantitatively linking health effects to 2,3,7,8-TCDD exposure, or the uncertainties associated with exposure estimates themselves.

9.6. IMPLICATIONS FOR RISK ASSESSMENT

The TEF methodology provides a mechanism to estimate potential health or ecological effects of exposure to a complex mixture of dioxin-like compounds. However, the TEF method must be used with an understanding of its limitations. This methodology estimates the dioxin-like effects of a mixture by assuming dose-additivity and describes the mixture in terms of an equivalent mass of 2,3,7,8-TCDD. Although the mixture may have the toxicological potential of 2,3,7,8-TCDD it should not be assumed for exposure purposes to have the same environmental fate as 2,3,7,8-TCDD. The environmental fate of the mixture is still the product of the environmental fate of each of its constituent congeners. Different congeners have different physical properties such as vapor pressure, practical vapor partition, water octanol coefficient, photolysis rate, binding affinity to organic mater, water solubility, etc. Consequently, both the absolute concentration of a mixture in an environmental medium and the relative concentration of congeners making up an emission will change as the release moves through the environment. For some situations, treating emission as equivalent to exposure, which assumes that modeling fate and exposure can be reasonably accomplished by treating a mixture as if it were all 2,3,7,8,-TCDD, is a useful but uncertain assumption. However, for many risk assessments the differences in fate and transport of different congeners must be taken into consideration and TEQ must be calculated at the point of exposure if more accurate assessments are to be achieved. Similarly, many dioxin releases are associated with the release of non-dioxin-like compounds such as pesticides, metals, and non-dioxin-like PHAHs, and their risk potential may also need to be assessed in addition to dioxin-related risk.

There are instances where exposures to PCBs are the major problem. The TEF methodology provides risk assessors with a useful tool to estimate potential dioxin-related health risks associated with these exposures. Typically, the congener makeup of environmental

exposures to PCBs does not resemble the congener profile of any of the commercial mixtures produced. Because the environmental mixtures do not resemble the commercial mixtures, it is not clear that using total PCB concentrations and comparing them to any of the commercial mixtures provides an accurate assessment of the potential risks. However, the use of the TEF methodology allows for the estimation of the risk associated with the dioxin-like effects of the mixture and may provide a more accurate assessment of the risk in conjunction with the use of total PCBs. The Agency has recently published an application of this approach to the evaluation of PCB carcinogenicity (U.S. EPA, 1996; Cogliano, 1998)

9.7. SUMMARY

The AhR mediates the biochemical and toxicological actions of dioxin-like compounds and provides the scientific basis for the TEF/TEQ methodology. In its 20-year history, this approach has evolved, and decision criteria supporting the scientific judgment and expert opinion used in assigning TEFs have become more transparent. Numerous countries and several international organizations have evaluated and adopted this approach to evaluating complex mixtures of dioxin and related compounds. It has become the accepted, interim methodology, although the need for research to explore alternative approaches is widely endorsed. Although this method has been described as a "conservative, order of magnitude estimate" of the TCDD dose, experimental studies examining both environmental mixtures and laboratory-defined mixtures indicate that the method provides a greater degree of accuracy when all effects are considered and may not be as conservative as sometimes described. Clearly, basing risk on TCDD alone or assuming all chemicals are as potent as TCDD is inappropriate on the basis of available data. Although uncertainties in the TEF methodology have been identified, one must examine the utility of this method in the broader context of the need to evaluate the public health impact of complex mixtures of persistent bioaccumulative chemicals. The TEF methodology decreases the overall uncertainties in the risk assessment process (U.S. EPA, 1999); however, this decrease cannot be quantified. One of the limitations of the TEF methodology in risk assessment is that the risk from non-dioxin-like compounds is not evaluated. This applies to both industrial/synthetic as well as natural ligands which are not considered to be dioxin-like, in addition to non-AhR ligands which may be interacting with dioxin-like chemicals in modulating their impacts on biological systems. Future research should focus on the development of methods that will allow risks to be predicted when multiple mechanisms are present from a variety of contaminants.

Since TEFs were first proposed in the 1980's, there have been several expert panels charged with evaluating and assigning TEF values to dioxin-like congeners. The development of the TEF methodology can be seen as an iterative process in which as more data was collected and

our knowledge base on the mode of action and biological effects of these chemicals accumulated, the later panels provided more accurate assessments of the chemicals included in the TEF methodology. For example, the initial TEF proposals assigned values to all tetra-, penta-, hexa-, hepta- and octa-chlorinated dioxin and dibenzofuran congeners. Later evaluations assigned TEF values only to the 2,3,7,8-chlorine substituted congeners. The most recent expert panal to re-evaluate and assign TEF values to dioxin-like congeners was the WHO panel convened in 1997 (Van den berg, 1998). This group of experts assigned TEF values to dioxin-like PCBs and revised TEF values for several of the chlorinated dioxins and dibenzofurans. The WHO_{98} TEF values are based on the most recent data available and it is recommended that these values supercede previous TEF values.

Thus, in summary, the WHO_{98} TEF values, which include dioxins, furans and dioxin-like PCBs, are the recommended TEF values. These are the TEF values recommended for use in human health risk analysis.

Table 9-1. Estimated relative toxicity of PCDD and PCDF isomers to 2,3,7,8-T_4CDD[a]

Isomer groups	Toxicity factor relative to 2,3,7,8-T_4 CDD
DD	nontoxic
M_1CDD	0.0001
D_2CDD	0.001
T_3CDD	0.01
T_4CDD[b]	0.01
P_5CDD	0.1
H_6CDD	0.1
H_7CDD	0.01
O_8CDD	0.0001
DF	nontoxic
M_1CDF	0.0001
D_2CDF	0.0001
T_3CDF	0.01
T_4CDF	0.5
P_5CDF	0.5
H_6CDF	0.1
H_7CDF	0.01
O_8CDF	0.0001

[a] OME, 1984.
[b] Excluding 2,3,7,8-T_4CDD.

Table 9-2. Toxic equivalency factors (TEFs)

Congener		EPA/87 [a]	NATO/89 [b]	WHO/94 [c]	WHO/98[d]
PCDDs					
2,3,7,8-TCDD		1	1		1
1,2,3,7,8-PeCDD		0.5	0.5		1
1,2,3,4,7,8-HxCDD		0.04	0.1		0.1
1,2,3,7,8,9-HxCDD		0.04	0.1		0.1
1,2,3,6,7,8-HxCDD		0.04	0.1		0.1
1,2,3,4,6,7,8-HpCDD		0.001	0.1		0.01
1,2,3,4,6,7,8,9-OCDD		0	0.001		0.0001
PCDFs					
2,3,7,8-TCDF		0.1	0.1		0.1
1,2,3,7,8-PeCDF		0.1	0.05		0.05
2,3,4,7,8-PeCDF		0.1	0.5		0.5
1,2,3,4,7,8-HxCDF		0.01	0.1		0.1
1,2,3,7,8,9-HxCDF		0.01	0.1		0.1
1,2,3,6,7,8-HxCDF		0.01	0.1		0.1
2,3,4,6,7,8-HxCDF		0.01	0.1		0.1
1,2,3,4,6,7,8-HpCDF		0.001	0.01		0.01
1,2,3,4,7,8,9-HpCDF		0.001	0.01		0.01
1,2,3,4,6,7,8,9-OCDF		0	0.001		0.0001
PCBs					
IUPAC #	**Structure**				
77	3,3',4,4'-TCB			0.0005	0.0001
81	3,4,4',5-TCB			-	0.0001
105	2,3,3',4,4'-PeCB			0.0001	0.0001
114	2,3,4,4',5-PeCB			0.0005	0.0005
118	2,3',4,4',5-PeCB			0.0001	0.0001
123	2',3,4,4',5-PeCB			0.0001	0.0001
126	3,3',4,4',5-PeCB			0.1	0.1
156	2,3,3',4,4',5-HxCB			0.0005	0.0005
157	2,3,3',4,4',5'-HxCB			0.0005	0.0005
167	2,3',4,4',5,5'-HxCB			0.00001	0.00001
169	3,3',4,4',5,5'-HxCB			0.01	0.01
170	2,2',3,3',4,4',5-HpCB			0.0001	-
180	2,2',3,4,4',5,5'-HpCB			0.00001	-
189	2,3,3',4,4',5,5'-HpCB			0.0001	0.0001

[a] U.S. EPA, 1987.
[b] NATO/CCMS, 1989.
[c] Alhlborg et al., 1994.
[d] Van den Berg, 1998.

Table 9-3. The range of the in vivo REP values for the major TEQ contributors

Chemical	Number of in vivo endpoints	Range of REPs (mean±std)	Number of end points from subchronic studies	Range of REPs (mean±std)	TEF
1,2,3,7,8-PCDD	22	0.16-0.9 (0.5±0.22)	16	0.19-0.9 (0.53±0.24)	1
2,3,4,7,8-PCDF	40	0.018-4.0 (0.4±0.7)	20	0.018-0.6 (0.20±0.13)	0.5
1,2,3,6,7,8-HxCDD	3	0.015-0.16	1	0.04	0.1
PCB 126	62	0.0024-0.98 (0.20±0.20)	31	0.004-0.18 (0.13±0.13)	0.1

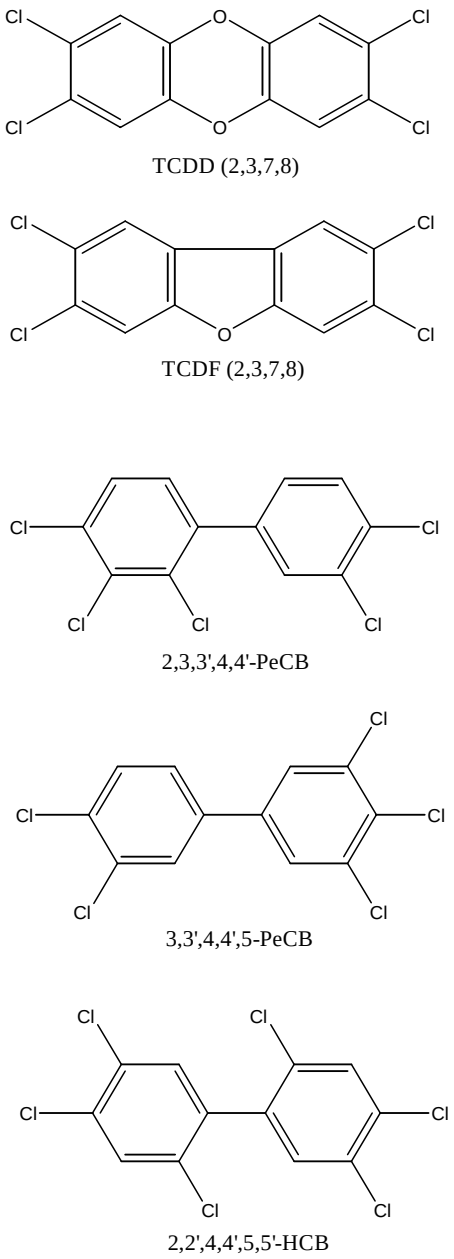

Figure 9-1. Structures of polychlorinated dibenzo-*p*-dioxins, dibenzofurans and biphenyls. The prototype chemical 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD[2,3,7,8]), and example of a dioxin-like dibenzofuran 2,3,7,8-tetrachlorodibenzfuran (TCDF[2,3,7,8]), a mono-ortho dioxin-like PCB, 2,3,3',4,4'-pentachlorobiphenyl (2,3,3',4,4'-PeCB), a dioxin-like coplanar PCB, 3,3',4,4',5-pentachlorobiphenyl (3,3',4,4',5-PeCB) and an example of a non-dioxin-like di-ortho substituted PCB, 2,2',4,4',5,5'-hexachlorobiphenyl (2,2',4,4',5,5'-HCB).

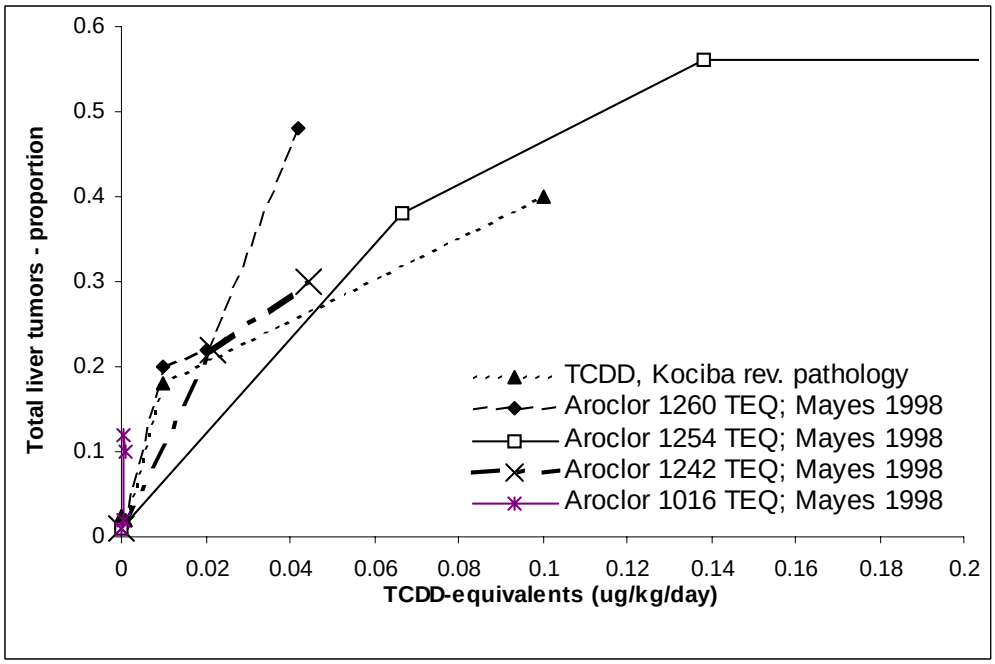

Figure 9-2: TEQ-based bioassay results. (Kociba et al.,1978 and Mayes et al.,1998) Presentation of the comparison of the dose-response relationship for hepatic tumors for TCDD (Kociba et al., 1978) with Aroclor 1016, 1242, 1254, and 1260 (Mayes et al., 1998) when dose is expressed as TCDD equivalents using the TEF methodology (Ahlborg et al., 1994).

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Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

Part III: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

NOTICE

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This document is a draft for review purposes only and does not constitute U.S. Environmental Protection Agency policy. It has been provided for review to the National Academy of Sciences (NAS). While the NAS review is being conducted and until a final agency assessment has been released, the draft dioxin reassessment (2003 version or other draft versions) remains draft, does not represent a final position, and is not intended to serve as the basis or rationale for regulatory and other policy action. However, EPA will continue its work to reduce human exposure to dioxin.

While the NAS review is underway and no final reassessment has been issued, in meeting their regulatory responsibilities, the agency will continue its current practice of utilizing the best available data that meet the EPA Information Quality Guidelines and the government-wide Information Quality Guidelines issued by OMB. T he Agency will consider all such data and associated uncertainty to determine the strength of the evidence in proposing regulatory actions related to dioxin and dioxin-like compounds.

Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds

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Ah	aryl hydrocarbon
AHF	altered heptacellular foci
AhR	aryl hydrocarbon receptor
ALK	alkaline phosphatase
ALT	alanine aminotransferase
Arnt	aryl hydrocarbon receptor nuclear translocator
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
BaP	benzo[a]pyrene
BDD	brominated dibenzodioxin
BDF	polybrominated dibenzofuran
BMD	benchmark dose
BW	body weight
CDC	Centers for Disease Control and Prevention
CDD	chlorinated dibenzodioxin
CFD	chlorinated dibenzofuran
CI	confidence interval
CTL	cytotoxic T lymphocyte
CYP1A1	cytochrome P4501A1 enzyme
CYP1A2	cytochrome P4501A2 enzyme
CYP1B1	cytochrome P4501B1 enzyme
DFP (subscript)	dioxins, furans, PCBs
DEN	diethylnitrosamine
DHT	5α-dihydrotestosterone
DNA	deoxyribonucleic acid
ED	effective dose
ED_{01}	effective dose at the 1% response level
EDC/VC	ethylene dichloride/vinyl chloride
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EPA	U.S. Environmental Protection Agency
FSH	follicle-stimulating hormone
g	gram
GD	gestation day
GGT	gamma glutamyl transferase
HAH	halogenated aromatic hydrocarbons
HCDD	hexachlorodibenzo-*p*-dioxin
HIF	hypoxia-inducible factor
HpCDD	heptachlorodibenzo-*p*-dioxin

hr	hairless
IARC	International Agency for Research on Cancer
ID	immunosuppressive dose
IgA	immunoglobulin A
I-P	initiation-promotion
IPCS	International Programme on Chemical Safety (WHO)
I-TEQ	international TEF scheme adopted by EPA in 1989
kg	kilogram
L	liter
LABB	lifetime average body burden
LED_{01}	lower bound of the effective dose at the 1% response level
LH	luteinizing hormone
LMS	linearized multistage
LOAEL	lowest-observed-adverse-effect level
MOE	margin of exposure
mRNA	messenger ribonucleic acid
MRL	minimal risk level (ATSDR)
NHANES	National Health and Nutrition Examination Survey
NHATS	National Human Adipose Tissue Survey
ng	nanogram
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OCDD	octachlorodibenzo-*p*-dioxin
pg	picogram
PAH	polycyclic aromatic hydrocarbon
PBPK	physiologically based pharmacokinetic
PBDD	polybrominated dibenzodioxin
PBDF	polybrominated dibenzofuran
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCP	pentachlorophenol
PCQ	polychlorinated quaterphenyl
PeCDD	pentachlorodibenzo-*p*-dioxin
PeCDF	pentachlorodibenzo-*p*-furan
PK	pharmacokinetic
POD	point of departure
POTW	publicly-owned treatment works

ppt	part per trillion
PVC	polyvinyl chloride
REP	relative potency
RfD	reference dose (EPA)
RR	relative risk
SAB	U.S. EPA's Science Advisory Board
SMR	standardized mortality ratio
SRBC	sheep red blood cells
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
TDG	thyroid binding globulin
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCP	trichlorophenol
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalent
TEQ-WHO_{94}	1994 WHO extension of the I-TEF scheme to include 13 dioxin-like PCBs
TEQ-WHO_{98}	1998 WHO update to the previously established TEFs for dioxins, furans, and dioxin-like PCBs
TPA	tetradecanoyl phorbol acetate
TNP-LPS	trinitrophenyl-lipopolysaccharide
TSH	thyroid stimulating hormone
URL	unit risk level
WHO	World Health Organization

~	approximately
>	greater than
<	less than
≥	greater than or equal to
≤	less than or equal to
µg	microgram

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1. INTRODUCTION

This document presents an integrated summary of available information related to exposure to and possible health effects of dioxin and related compounds. It also presents a short risk characterization, which is a concise statement of dioxin science and the public health implications of both general population exposures from environmental "background"[1] and incremental exposures associated with proximity to sources of dioxin and related compounds. Even though this document is a summary of key findings developed in the exposure and health assessment portions (Parts I and II, respectively) of the U.S. Environmental Protection Agency's (EPA *or* Agency) dioxin reassessment, it is meant to be detailed enough to stand on its own for the average reader. Readers are encouraged to refer to the more detailed documents, cited below, for further information on the topics covered here and to see complete literature citations.

Estimating Exposure to Dioxin-Like Compounds: This document, hereafter referred to as Part I, the Exposure Document, is divided into 3 volumes: (1) Sources of Dioxin-Like Compounds in the United States; (2) Properties, Environmental Levels, and Background Exposures; and (3) Site-Specific Assessment Procedures.

Health Assessment for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds: This document, hereafter referred to as Part II, the Health Document, contains two volumes with nine chapters covering pharmacokinetics, mechanisms of action, epidemiology, animal cancer and various noncancer effects, toxic equivalency factors (TEFs), and dose-response.

Parts of this integrative summary and risk characterization go beyond individual chapter findings to reach general conclusions about the potential impacts of dioxin-like compounds on human health. This document specifically identifies issues concerning the risks that may be occurring in the general population at or near population background exposure levels. It

[1]The term "background exposure" has been used throughout this reassessment to describe exposure that regularly occurs to members of the general population from exposure media (food, air, soil, etc.) that have dioxin concentrations within the normal background range. Most (> 95%) background exposure results from the presence of minute amounts of dioxin-like compounds in dietary fat, primarily from the commercial food supply. The origin of this background exposure is from three categories of sources: naturally formed dioxins, anthropogenic dioxins from contemporary sources, and dioxins from reservoir sources. The term "background exposure" as used in this document should not be interpreted as indicating the significance or acceptability of risk associated with such exposures.

articulates the strengths and weaknesses of the available evidence for possible sources, exposures, and health effects, and it presents assumptions made and inferences used in reaching conclusions regarding these data. The final risk characterization provides a synopsis of dioxin science and its implications for characterizing hazard and risk for use by risk assessors and managers inside and outside the EPA and by the general public.

This document (Part III) is organized as follows:

1. Introduction. This chapter describes the purpose/organization of and the process for developing the report, defines dioxin-like compounds in the context of the EPA reassessment, and explains the toxic equivalence (TEQ) concept.

2. Effects Summary. This chapter summarizes the key findings of the Health Document and provides links to relevant aspects of exposure, mechanisms, and dose-response.

3. Mechanisms and Mode of Dioxin Action. This chapter discusses the key findings on effects in terms of mode of action. It uses the "Mode-of-Action Framework" recently described by the World Health Organization/(WHO) International Programme on Chemical Safety (IPCS) Harmonization of Approaches to Risk Assessment Project and contained in the Agency's draft guidelines for carcinogen risk assessment as the basis for the discussions.

4. Exposure Characterization. This chapter summarizes the key findings of the Exposure Document and links them to the effects, mechanisms, and dose-response characterization.

5. Dose Response Characterization. This chapter summarizes approaches to dose-response that are found in the Health Document and provides links to relevant aspects of exposure and effects.

6. Risk Characterization. This chapter presents conclusions that are based on an integration of the exposure, effects, mechanisms, and dose-response information. It also highlights key assumptions and uncertainties.

The process for developing this risk characterization and companion documents has been open and participatory. Each of the documents has been developed in collaboration with

scientists from inside and outside the Federal Government. Each document has undergone extensive internal and external review, including review by EPA's Science Advisory Board (SAB). In September 1992, early drafts of all the background chapters underwent external peer review. This was followed by extensive revision and re-review of the epidemiology chapter in September 1993. In September 1994, drafts of each document, including an earlier version of this risk characterization, were made available for public review and comment, which included a 150-day comment period and 11 public meetings around the country to receive oral and written comments. These comments, along with those of the SAB, have been considered in the drafting of this final document. The dose-response chapter of the Health Document underwent peer review in 1997; an earlier version of this Integrated Summary and Risk Characterization underwent development and review in 1997 and 1998, and comments have been incorporated.

In addition, as requested by the SAB, a chapter on toxic equivalency has been developed and underwent external peer review in parallel with the Integrated Summary and Risk Characterization in July 2000. Review by the SAB of the dose-response chapter, the toxic equivalency chapter, and the Integrated Summary and Risk Characterization occurred in November 2000. The report of that review was submitted to the EPA Administrator on May 31, 2001. These sections of the document, as well as a few of the other background chapters in Parts I and II, have been revised to reflect the comments of the SAB and the public. The comprehensive set of background documents and this integrative summary and risk characterization are now being published as final reports to replace previous dioxin assessments as the scientific basis for EPA decision making.

1.1. DEFINITION OF DIOXIN-LIKE COMPOUNDS

As defined in Part I of this document, this assessment addresses specific compounds in the following chemical classes: polychlorinated dibenzo-*p*-dioxins (PCDDs or CDDs), polychlorinated dibenzofurans (PCDFs or CDFs), polybrominated dibenzo-*p*-dioxins (PBDDs or BDDs), polybrominated dibenzofurans (PBDFs or BDFs), and polychlorinated biphenyls (PCBs); these chemicals are described as "dioxin-like." Dioxin-like refers to the fact that these compounds have similar chemical structure and physical-chemical properties, and they invoke a common battery of toxic responses. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans.

The CDDs include 75 individual compounds; CDFs include 135 different compounds. These individual compounds are referred to technically as congeners. Likewise, the BDDs include 75 different congeners, and the BDFs include an additional 135 congeners. Only 7 of the 75 congeners of CDDs or of BDDs are thought to have dioxin-like toxicity: those with

chlorine/bromine substitutions in, at a minimum, the 2, 3, 7, and 8 positions. Only 10 of the 135 possible congeners of CDFs or of BDFs are thought to have dioxin-like toxicity; also those with substitutions in the 2, 3, 7, and 8 positions. This suggests that 17 individual CDDs/CDFs and an additional 17 BDDs/BDFs exhibit dioxin-like toxicity. The database on many of the brominated compounds regarding dioxin-like activity has been less extensively evaluated, and these compounds are not explicitly considered in this assessment. (For a review of this topic see Birnbaum et al., 2003.)

There are 209 PCB congeners, only 12 of which are thought to have dioxin-like toxicity: PCBs with four or more lateral chlorines, with one or no substitution in the ortho position. These compounds are sometimes referred to as coplanar, meaning that they can assume a flat configuration, with rings in the same plane. Similarly configured polybrominated biphenyls (PBBs) are likely to have similar properties. However, the database on these compounds with regard to dioxin-like activity has been less extensively evaluated, and these compounds are not explicitly considered in this assessment. Mixed chlorinated and brominated congeners of dioxins, furans, and biphenyls also exist, increasing the number of compounds potentially considered dioxin-like within the definitions of this assessment. The physical/chemical properties of each congener vary according to the degree and position of chlorine and/or bromine substitution. Very little is known about occurrence and toxicity of the mixed (chlorinated and brominated) dioxin, furan, and biphenyl congeners. Again, these compounds are not explicitly considered in this assessment.

Generally speaking, this assessment focuses on the 17 CDDs/CDFs and a few of the coplanar PCBs that are frequently encountered in source characterization or environmental samples. The Agency recognizes that other dioxin-like compounds exist in the chemical classes discussed above (e.g., brominated or chlorinated/brominated congeners) or in other chemical classes (e.g., polyhalogenated naphthalenes or benzenes, azo- or azoxybenzenes), but this evaluation focuses on the two dozen chlorinated congeners that are generally considered to be most associated with environmental and human health risks.

The chlorinated dibenzodioxins and dibenzofurans are tricyclic aromatic compounds with similar physical and chemical properties. Certain of the PCBs (the so-called coplanar or mono-ortho coplanar congeners) are also structurally and conformationally similar. The most widely studied of this general class of compounds is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). This compound, often simply called “dioxin,” represents the reference compound for this class of compounds. The structure of TCDD and several related compounds is shown in Figure 1-1. Although sometimes confusing, the term “dioxin” is often also used to refer to the complex mixtures of TCDD and related compounds emitted from sources or found in the environment or

in biological samples. It can also be used to refer to the total TCDD "equivalents" found in a sample. This concept of toxic equivalency is discussed extensively in Part II, Chapter 9, Section 9.4, and is summarized below.

1.2. TOXIC EQUIVALENCY FACTORS

CDDs, CDFs, and PCBs are commonly found as complex mixtures when detected in environmental media and biological tissues or when measured as environmental releases from specific sources. Humans are likely to be exposed to variable distributions of CDDs, CDFs, and dioxin-like PCB congeners that vary by source and pathway of exposures. This complicates the human health risk assessment that may be associated with exposures to variable mixtures of dioxin-like compounds. In order to address this problem, the concept of toxic equivalency has been considered and discussed by the scientific community, and TEFs have been developed and introduced to facilitate risk assessment of exposure to these chemical mixtures.

On the most basic level, TEFs compare the potential toxicity of each dioxin-like compound in the mixture to the well-studied and understood toxicity of TCDD, the most toxic member of the group. The use of the TEF methodology has been EPA policy since 1987, when the Agency "adopted an interim procedure, based on dioxin 'toxicity equivalence' factors (TEFs), for estimating the hazard and dose-response of complex mixtures containing CDDs and CDFs in addition to 2,3,7,8-TCDD" (EPA 1987, 1989a). The background and historical perspective regarding this procedure is described in detail in Part II, Chapter 9, Section 9.1, 9.2, and in Agency documents (U.S. EPA, 1987, 1989a, 1991a). This procedure involves assigning individual TEFs to the 2,3,7,8-substituted CDD/CDF congeners and dioxin-like PCBs. To accomplish this, scientists have reviewed the toxicological databases and considered chemical structure, persistence, and resistance to metabolism and have agreed to ascribe specific "order of magnitude" TEFs for each dioxin-like congener relative to TCDD, which is assigned a TEF of 1.0. The other congeners have TEF values ranging from 1.0 to 0.00001. Thus, these TEFs are the result of scientific judgment of a panel of experts who used all of the available data, and they are selected to account for uncertainties in the available data and to avoid underestimating risk. In this sense, they can be described as "public health-conservative" values.

It is important to understand that this process results in values that represent the scientific judgment of experts working with specified criteria. As described below, these values rely more heavily on in vivo than in vitro data and on chronic or subchronic exposures rather than acute exposures. Attempts to replicate or critique individual TEF values on the basis of distributional analysis of relative potency (REP) estimates from individual endpoints or all data have been undertaken (Finley et al., 2003), suggesting possible benefits from the analysis of REP

distributions. It remains important, however, to recognize the emphasis placed by WHO on the above noted weighting factors and on the expert scientific judgment used to derive the existing TEF values.

The TEQ concept is applied by multiplying the TEF of each congener present in a mixture by the respective mass concentration and the products are summed to represent the 2,3,7,8-TCDD TEQ of the mixture, as determined by equation 1-1.

$$TEQ \cong \sum_{i-n}\left(Congener_i \times TEF_i\right)+\left(Congener_j \times TEF_j\right)+\ldots\ldots\left(Congener_n \times TEF_n\right) \qquad (1\text{-}1)$$

The TEF values for PCDDs and PCDFs were originally adopted by international convention (U.S. EPA, 1989a). Subsequent to the development of the first international TEFs for CDD/CDFs, these values were further reviewed and/or revised and TEFs were also developed for PCBs (Ahlborg et al., 1994; van den Berg et al., 1998). A problem arises in that past and present quantitative exposure and risk assessments may not have clearly identified which of three TEF schemes was used to estimate the TEQ. This reassessment introduces a new uniform TEQ nomenclature that clearly distinguishes between the different TEF schemes and identifies the congener groups included in specific TEQ calculations. The nomenclature uses the following abbreviations to designate which TEF scheme was used in the TEQ calculation:

1. I-TEQ refers to the International TEF scheme adopted by EPA in 1989 (U.S. EPA, 1989a). See Table 1-1.

2. TEQ-WHO_{94} refers to the 1994 WHO extension of the I-TEF scheme to include 13 dioxin-like PCBs (Ahlborg et al., 1994). The TEF values for the dioxins and furans are identical to the I-TEQ. See Table 1-2.

3. TEQ-WHO_{98} refers to the 1998 WHO update to the previously established TEFs for dioxins, furans, and dioxin-like PCBs (van den Berg et al., 1998). There are numerous changes in the TEF values for the dioxins, furans and PCBs. See Table 1-3.

The nomenclature also uses subscripts to indicate which family of compounds is included in any specific TEQ calculation. Under this convention, the subscript D is used to designate dioxins, the subscript F to designate furans, and the subscript P to designate PCBs. For example, "TEQ_{DF}-WHO_{98}" would be used to describe a mixture for which only dioxin and furan congeners were determined and where the TEQ was calculated using the WHO_{98} scheme. If PCBs had also

been determined, the nomenclature would be "TEQ_{DFP}-WHO_{98}." Note that the designations TEQ_{DF}-WHO_{94} and I-TEQ_{DF} are interchangeable, as the TEFs for dioxins and furans are the same in each scheme. Note also that in the current draft of this document, I-TEQ sometimes appears without the D and F subscripts. This indicates that the TEQ calculation includes both dioxins and furans.

This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxic equivalency to complex environmental mixtures for assessment and regulatory purposes. Later sections of this document describe the mode(s) of action by which dioxin-like chemicals mediate biochemical and toxicological actions. These data provide the scientific basis for the TEF/TEQ methodology. In the 20-year history of the TEF/TEQ concept, the approach has evolved, and decision criteria supporting the scientific judgment and expert opinion used in assigning TEFs have become more transparent. Numerous states and countries and several international organizations have studied and consequently adopted this approach to evaluating complex mixtures of dioxin and related compounds (Part II, Chapter 9, Section 9.2). It has become the accepted methodology, although the need for research to explore alternative approaches is widely endorsed. Clearly, basing risk on TCDD alone or assuming that all chemicals are equally as potent as TCDD is inappropriate on the basis of available data. Although uncertainties in the use of the TEF methodology have been identified and are described later in this document and in detail in Part II, Chapter 9, Section 9.5, one must examine the use of this method in the broader context of the need to evaluate the potential public health and environmental impact of complex mixtures of persistent, bioaccumulative chemicals.

It can be generally concluded that the use of TEF methodology for evaluating complex mixtures of dioxin-like compounds decreases the overall uncertainties in the risk assessment process, as compared to alternative approaches. Use of the latest consensus values for TEFs assures that the most recent scientific information informs this "useful, interim approach" (U.S. EPA, 1989a; Kutz et al., 1990) to dealing with complex environmental mixtures of dioxin-like compounds. As stated by the EPA's SAB (U.S. EPA, 1995), "The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the TEFs and the availability of representative and reliable exposure data." EPA will continue to work with the international scientific community to update these TEF values to ensure that the most up-to-date and reliable data are used in their derivation and to evaluate their use on a periodic basis.

A chemical is assigned a TEF value on the basis of all the available data comparing the REP of a chemical to 2,3,7,8-TCDD. REP values are obtained from individual studies available in the peer-reviewed literature. In addition, there are weighting criteria that place more emphasis

on REP values from chronic and subchronic studies that examine toxic endpoints (van den Berg et al., 1998). There is a broad range in the quantity and quality of the data available for individual congeners. For example, the TEF for PCB 126 is based on over 60 REP values from in vivo endpoints that examine responses as diverse as enzyme induction, developmental toxicity, immunotoxicity, hepatic toxicity, alterations in hormones, and tumor promotion, whereas the TEF for 3,4,4',5-tetrachlorobiphenyl (PCB 81) is based on REP values for in vitro CYP1A induction and QSAR calculations. Fortunately, the uncertainty in the PCB 81 TEF based on limited data has minimal effect on the risk characterization of complex mixtures of dioxin-like compounds since it does not contribute significantly to human TEQ exposures.

Five congeners contribute approximately 80% of the total TEQ in humans: 2,3,7,8-TCDD; 1,2,3,7,8-PCDD; 1,2,3,6,7,8-HxCDD; 2,3,4,7,8-PCDF; and PCB 126 (see Part I, Volume 2 and Section 4.4.3 of this document). With the exception of 1,2,3,6,7,8-HxCDD, the TEFs for these chemicals are based on a number of different endpoints examined in multiple studies performed in different laboratories (Table 1-4). The TEF for 1,2,3,6,7,8-HxCDD is based heavily on a two-year bioassay in which rats were exposed to a mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD. The TEFs for 2,3,4,7,8-PCDF and PCB 126 are similar to the mean REP value for all in vivo endpoints and are similar to their REPs for tumor promotion. The TEF for 1,2,3,7,8-PCDD is based largely on its REP for tumor promotion in rats, supported by studies of its biochemical effects in a subchronic mouse study (DeVito et al., 1997).

From these data, it is clear that the chemicals that contribute approximately 80% to the total human TEQ are well studied and that the assigned TEFs provide reasonable estimates of the relative potency of these chemicals. In contrast, although some chemicals in the TEF methodology have minimal data sets with which to reliably assess their relative potency, they do not contribute substantially to the background human blood TEQ.

The ability of the TEF methodology to predict the biological effects of mixtures containing dioxin-like chemicals has been evaluated in a number of experimental systems. These studies generally demonstrate that the assumption of additivity provides a reasonable estimate of the dioxin-like potential of a mixture (Part II, Chapter 9, Section 9.4). Hamm et al. (2003) demonstrated that a mixture of TCDD, PeCDD, TCDF, 1-PeCDF, 4-PeCDF, OCDF, and PCBs 77, 126 and 169 at doses approximating the relative abundance in the food supply, as described by Birnbaum and DeVito (1995), induced a similar spectrum of reproductive toxicity in rat offspring as does TCDD, and that the TEF methodology did reasonably well at predicting the dose-response relationship of the mixture. A close relationship was evident for maternal EROD enzyme induction between TCDD and the equivalent TEQ mixture, with a slightly lowered dose-response for fetal effects from the mixture (~2 fold lower), attributed to decreased transfer of

mixture components to the offspring. A recent statistical modeling exercise of EROD enzyme induction in the NTP bioassays (Toyoshiba et al., 2004) reported that from a statistical standpoint the consensus WHO_{98} TEFs were "significantly different from the maximum likelihood-based estimates, but not very different in actual magnitude." Graphing of the non-log-scaled summary data reported in Toyoshiba et al. (2004) reveals differences of less than 2 - 3 fold from predicted TEQ-based activities, for individual congeners and the mixture. There are examples of nonadditive interactions between dioxins and nondioxins. Both greater-than-additive and less-than-additive interactions have been observed in these studies. In general the nonadditive interactions between the dioxins and nondioxins have been observed at doses that are considerably higher than present background human exposures (Part II, Chapter 9, Section 9.4).

There are a number of natural chemicals that bind and activate the aryl hydrocarbon (Ah) receptor (AhR) and induce some dioxin-like effects. It has been proposed by some scientists that these chemicals contribute significantly to total TEQ exposures and that these exposures far outweigh those from PCDDs, PCDFs, and PCBs (Safe, 1995a). There are several limitations to these analyses, as detailed in Part II, Chapter 9, Section 9.3.5. The hypothesis is built on AhR binding studies and a few other in vitro studies that compared natural ligands to the dioxin-like chemicals. Under these circumstances, neither biological half-life nor toxicity profile is considered.

The in vivo data on the natural AhR ligands is limited to enzyme induction and a single developmental study. Few if any toxicology studies demonstrating clear dioxin-like toxicities have been published. The natural AhR ligands are rapidly metabolized and result in both transient tissue concentrations and transient effects. More recent data demonstrate that these potent in vitro AhR agonists (e.g., indolo[2,3-b]carbazole) neither elicit dioxin-like toxicity nor alter the effects of dioxin in vivo (Pohjanvirta et al., 2002). This may occur because of short persistence times in target organs or inadequate/inappropriate conformational changes induced as a result of AhR-ligand binding (Henry and Gasiewicz, 2003). The natural ligands also have their own distinct biological effects that are independent of the AhR, and it is not clear as to the role of the AhR in the biological effects of these chemicals. Because of the relative concentration of these compounds in the daily diet, their in vitro binding characteristics, and the limited toxicological information in vivo, this issue requires further research in order to better understand the uncertainty surrounding the relative potential health effects of dioxin and related chemicals as compared to natural AhR ligands.

One of the limitations of the use of the TEF methodology in risk assessment of complex environmental mixtures is that the risk from nondioxin-like chemicals is not evaluated in concert with that of dioxin-like chemicals. Another limitation of the TEF methodology is the application

of TEFs to nonbiological samples. The fate and distribution of PCDDs, PCDFs, and PCBs are not necessarily related to their TEFs. Thus, the use of the TEF for assessing potential hazard and risk based on dioxin-like compounds passing through nonbiological media must be done cautiously. Fate and transport of the mixture and likelihood and route of exposure will have important impacts on such assessments. Future approaches to the assessment of environmental mixtures should focus on the development of methods that will allow risks to be predicted when multiple mechanisms are present from a variety of contaminants coming into contact with humans and other environmental receptors through multiple routes.

There are a number of uncertainties in the application of the TEF methodology which are discussed in greater detail in Part II, Chapter 9. In 1998, the U.S. EPA and the U.S. Department of the Interior sponsored a workshop on the use of the TEF methodology in ecological risk assessment. This workshop involved panel members from academia, industry and state and federal governments. This panel concluded that "the uncertainties associated with using RePs or TEFs are not thought to be larger than other sources of uncertainty within the [ecological] risk assessment process (e.g., dose-response assessment, exposure assessment, and risk characterization)" (U.S. EPA, 2001a). In addition, despite the uncertainties in the TEF methodology, the use of this methodology decreases the overall uncertainty of the risk assessment. The panel had difficulty in quantitatively expressing the uncertainty in the TEF methodology. While the panel supported the use of the TEF methodology, they also recommended continued research focusing on a better understanding of the uncertainty in the TEF methodology.

1.3. UNDERSTANDING EXPOSURE/DOSE RELATIONSHIPS FOR DIOXIN-LIKE COMPOUNDS

Risk assessment requires the scaling of exposure/dose across endpoints and across species. Given the many responses to TCDD and its congeners, the selection of dose metrics for use in quantitative risk assessments is a complex problem. The biochemical and toxicological responses to TCDD and related chemicals are initiated by their interaction with the Ah receptor. Some responses, such as enzyme induction, require short periods (minutes to hours) of AhR activation. Other responses, such as cancer, require prolonged (months to many years) activation of this pathway. Still other responses, such as the developmental toxicities, require receptor activation during specific windows of sensitivity. Because of the different mechanisms involved in these diverse responses, it is unlikely that a single dose metric will be adequate for all of these endpoints.

A number of studies have proposed a variety of dose metrics for a number of different responses. These studies have taken different approaches, ranging from simple curve-fitting exercises (Hurst et al., 2000; van Birgelen et al., 1996) to more complex physiologically based pharmacokinetic (PBPK) modeling approaches (Jusko et al., 1995; Andersen et al., 1997; Kohn et al., 1993; Portier and Kohn, 1996). Area under the curve (AUC) has been used traditionally in the drug literature as a dose metric of choice when the dose and the time related to effects in humans are known.

The choice of dose metric not only considers mechanistic data but must consider pragmatic approaches as well. The use of the dose metric plays a role in its choice. Because of differences in lifespan and uncertainties in the windows of sensitivity for various endpoints, lifetime AUC may not be a useful dose metric for cross-species extrapolation in the risk assessment of dioxin and related compounds. For instance, reported interspecies differences in rat liver versus human lung cancer risks based on lifetime AUC are heavily influenced by different lifespans of humans (~70 yrs) versus rats (~2 years), and are mitigated though the use of peak levels or average concentrations (Aylward et al., 1996). Notably, there are no interspecies differences in risk calculations between humans and rats when applying average body burden to the same endpoint, all cancers combined, coupled with more detailed exposure data from the epidemiology studies (see Table 5-4). Because cross-species scaling is not required when the analysis is confined to humans, lifetime AUC has been used in the analysis of human cancer data on TCDD (Becher et al., 1998) and may be a useful dose metric when applied to accidental or occupational exposures.

The choice of dose metric is also dependent on the data available. A number of dose metrics, such as AhR occupancy, induction of CYP1A2, and decreases in epidermal growth factor (EGF) receptor (EGFR) have been proposed on the basis of PBPK models (Jusko et al., 1995; Andersen et al.,1997; Kohn et al., 1993; Portier and Kohn, 1996). Although these dose metrics have been useful in hypothesis testing in experimental systems, they are not useful in animal-to-human extrapolations due to the difficulty in measuring these parameters in humans. In the following section, the strengths and weaknesses of a variety of proposed dose metrics are presented.

1.3.1. Administered Dose

In experimental studies, animals are administered a defined dose through a variety of routes. A default method used by EPA (U.S. EPA, 1992a, 1996) to estimate the human equivalent dose when scaling across species is to use allometric scaling based on the following equation:

$$Dose_{human} = Dose_{rat} (BW_{rat}/BW_{human})^{0.25} \quad (1\text{-}2)$$

where BW is the body weight in kilograms and Dose is the daily administered dose in rats or the scaled human daily dose expressed as mg/kg/day, or in the case of TCDD ng/kg/day. This method, in the absence of data to select a more appropriate dose metric, is thought to scale administered dose in such a way as to result in equivalent effective doses in humans and experimental animals (U.S. EPA, 1992). Using this equation, a dose of 1 ng TCDD/kg/day in a 0.35 kg rat would result in a scaled human dose of 0.27 ng TCDD/kg/day for a 70 kg human. If this scaling method applies to TCDD and related chemicals, then 1 ng TCDD/kg/day in the rat should produce similar effective doses in a human exposed to 0.27 ng TCDD/kg/day, some 3.8 times lower. However, this method fails to take into account differences in the elimination half-life of the chemical in the two species. In the case of dioxin-like compounds, this is an important consideration.

Assuming similar sensitivity between rats and humans at the tissue level, effective doses should be a function of tissue concentration. Tissue concentrations of TCDD and related chemicals are directly related to the concentration of TCDD in the body. The steady-state concentration of TCDD in the body, or steady-state body burden, can be estimated in rats and humans using the following equation.

$$\text{Steady-state body burden (ng/kg)} = \frac{[\text{Dose (ng TEQ/kg)} * \text{half-life (days)}]}{\text{Ln}(2)} * F \quad (1\text{-}3)$$

where Dose is the daily administered dose, F is the fraction absorbed, and $t_{½}$ is the species-specific half-life of TCDD. In the present example, we will assume that the species-specific half-life of TCDD is 25 days for rats and 2593 days for humans. We also assume for this illustration that F is 50% for both human and animal studies. The fraction absorbed varies from ~50–100% of administered dose, depending on dosing matrix (pellets, oil, food, breast milk; greater variability from soil) and study species. For standardization elsewhere in Part III, Risk Characterization, the Agency has adopted 50% absorption from animal food pellets and 80%

from human dietary intake (see Part II, Chapter 1; Poiger and Schlatter, 1986; Abraham et al., 1996). The fraction absorbed linearly impacts the calculation of resulting body burden, with 80% absorption leading to a 1.6-fold higher value than 50% absorption.

Starting with an administered dose of 1 ng/kg/day in rats and the scaled human dose of 0.27 ng/kg/day, the steady-state body burdens are presented in Table 1-5. The steady-state body burden of TCDD using the scaled human dose is approximately 28 times that of the steady-state body burden in the rat (Table 1-5). Using equation 1-3 to estimate equivalent steady-state body burdens (i.e., 18 ng/kg), a human equivalent administered dose comparable to 1 ng/kg/day administered to the rat was estimated at 0.0096 ng/kg/day, over 100 times less.

Clearly, the default scaling method results in an estimated human equivalent dose that produces much greater estimated human tissue concentrations (505 ng/kg) than the rat's tissue concentration (18 ng/kg). The default scaling approach accounts for a difference of ~ 3.7 times, based on allometric considerations, yet the half-life of TCDD in humans alone is approximately 100-fold greater than in rats. This exercise suggests that administered dose may not provide a useful dose metric for cross-species extrapolation even if the dose is scaled using the EPA default methodology. However, administered dose can be used to compare chronic exposures between human populations in order to describe potential human health risks, because the species differences in half-life would not exist in this case. Adjustments will still need to be made, however, to compare short-term exposures expressed as intake as a function of body weight per day to more typical daily intake values in the general population.

1.3.2. Area Under the Curve

AUC is frequently used as a dose metric for reversible responses of pharmaceutical agents. Typically, these agents have half-lives on the order of minutes to hours. In addition, the pharmacological actions of the drug and the length of time of the response is clearly defined in both animals and humans. For example, for anesthetics, sleep time is used as the length of time for determining the AUC. In essence, plasma concentrations are readily determined and the time span is easily defined. In contrast, TCDD has a prolonged half-life in both humans and experimental animals and some of the adverse effects that are of concern in the hazard characterization are not reversible responses. Because of these differences it is unclear whether the AUC is the best dosemetric.

Mechanistic considerations suggest that AUC may be a useful dose metric for carcinogenesis. TCDD and related chemicals are thought to induce tumors through promotional mechanisms as opposed to acting as direct initiators. The promotional effects of TCDD and related chemicals are associated with altered gene expression, resulting in alterations in growth

and differentiation. This promotional process requires sustained tissue concentrations of TCDD sufficient to maintain increased gene expression. One recent study examined AUC as a dose metric for the tumor promotional responses of TCDD. Kim et al. (2003) compared AUC and peak concentrations in rats as a dose metric for liver tumor promotion. Animals receiving a single high exposure to TCDD had greater numbers of altered hepatic foci than animals receiving repeated low dose exposures, even though the AUC was equivalent between the two exposures. These data suggest that the peak concentrations of TCDD may play a significant role in TCDD carcinogenicity and that future dose-response modeling exercises should incorporate measures of dose timing and peak concentrations.

It is possible that AUC could be an appropriate dose metric for cancer in humans, and it may also involve the incorporation of a threshold concentration (Hays et al., 1997). However, the use of AUC for species extrapolation for TCDD is more complicated. Although blood or plasma concentrations of TCDD can be determined in both humans and animals, the determination of the time span for which the AUC is to be calculated is much less certain. For some of the toxic responses to TCDD, such as induction of cleft palate, the window of sensitivity is clearly defined in rodents and humans. For other responses, such as the developmental reproductive alterations observed in male rats, the window of sensitivity has been narrowed to exposures between gestational day 15 and 20 in the rats, but the human window of sensitivity is uncertain. For many of the chronic toxic effects of TCDD, the length of time required to induce the response remains uncertain in both experimental animals and humans. In order to apply AUC for species comparisons of sensitivity to TCDD, one must have a better understanding of the species differences in the windows of sensitivity to the various biological effects of TCDD.

In addition, differences in lifespan also must be considered. Brody and Reid (1967) proposed that the biological activity of a drug is related to its plasma concentrations. If animals and humans had the same plasma concentrations for their entire lives, the human AUC would be greater because humans have a longer half-life of elimination for TCDD. However, because the plasma concentrations would be the same, according to Brody and Reid (1967), the responses should be similar. Hence, in order to use AUC for chronic toxicities, such as cancer, a correction for the difference in lifespan must be applied. Typically, this involves the derivation of a lifetime average serum lipid concentration, which is calculated by dividing the AUC by the time period of exposure (Aylward et al., 1996). An estimation of the average daily AUC is directly related to steady-state body burdens. Hence, once the AUC is corrected for life-span differences, these values are equivalent to steady-state body burdens.

Although AUC may not be an appropriate dose metric for animal-to-human extrapolations, it may be a useful tool for comparing populations exposed to high concentrations

of dioxins over a short period of time to the background population. Becher et al. (1998) and Steenland et al. (2001) used this approach to examine dose-response relationships for cancer in occupationally exposed cohorts. One difficulty in determining AUC is the accuracy of the intake measurements. Past exposures through the diet are uncertain, although they have been estimated (Pinsky and Lorber, 1998). Future exposures are thought to be decreasing, although the exact magnitude of this decrease is uncertain. Hence, determination of AUC carries a number of uncertainties that must be considered.

1.3.3. Plasma or Tissue Concentrations

Brodie and Reid (1967) have argued that the response to a drug is determined by the amount bound to its biological receptor, and because the drug-receptor complex is in dynamic equilibrium with the free drug in the plasma, the biological response of a drug will be related to its plasma concentrations. There is no reason to believe that this relationship will not be true for TCDD and related chemicals. However, there are several data gaps that may prohibit the use of plasma or blood concentrations for species extrapolation. First, few animal studies have determined blood or plasma concentrations of TCDD, particularly in the subchronic, chronic, and lifetime exposures. PBPK models can be used to estimate blood concentrations and should provide reasonable estimates of these values. In contrast, the human exposure data are based predominantly on blood, serum, or plasma dioxin concentrations.

One limitation of the human data is that it is mostly presented on a lipid-adjusted basis. Hence, in order to compare the human and animal plasma or blood concentrations, one would have to first estimate the blood concentrations in the animals using a PBPK model. Then, either the animal data would have to be expressed as a lipid basis or the human data would have to be expressed as a wet-weight basis. In either case, assumptions of the percent lipid in the blood would have to be applied, as would a number of other assumptions typically used in the construction of PBPK models. Recent work by Salvan et al. (2001) has attempted to account for some of these assumptions in an analysis of cancer mortality in the National Institute for Occupational Safety and Health (NIOSH) cohort (Steenland et al., 1999, 2001) using data on age-related body mass index (BMI) and historical background exposures and tissue half-lives from the Ranch Hand cohort (Michalek and Tripathi, 1999).

The use of tissue concentrations as a dose metric has also been examined by van Birgelen et al. (1996) and Hurst et al. (1998, 2000). van Birgelen et al. presented data demonstrating that target tissue concentrations provided an accurate prediction of enzyme induction regardless of the exposure scenario (i.e., acute vs. subchronic). Similarly, Hurst et al. (2000) presented data demonstrating that fetal tissue concentrations of TCDD on gestation day 16 predicted decreases

in sperm counts, delays in puberty in males, urethra-phallus distance, and the incidence of vaginal threads in rats prenatally exposed to TCDD on either gestational day 9 or 15. These data suggest that target tissue concentrations may be a reasonable dose metric for these responses. Although target tissue concentrations may aid in estimating risks, these data are unlikely to be collected in humans in sufficient numbers to be useful, particularly for fetal concentrations.

Plasma (or serum) concentrations are also a useful tool for comparing exposures in different human populations. Application of plasma concentration as a dose metric for species extrapolation requires some level of assumptions, as described above, but reasonable comparisons could be made, particularly for steady-state in humans and animals. Comparing plasma or blood concentrations following acute exposures in experimental animals directly to steady-state human blood or plasma concentrations is problematic.

One problem with the use of plasma, blood, or target tissue concentrations as a dose metric is the limitations of current human PBPK models to predict these values on the basis of changes in intake patterns. Further work will be required to develop such models.

1.3.4. Steady-State Body Burdens

Body burden is defined as the concentration of TCDD and related chemicals in the body and is typically expressed as ng/kg body weight. In animals, these values are calculated from studies at or approaching steady-state. These values are calculated on the basis of knowledge of the species-specific half-life and the exposure or they are estimated on the basis of the TCDD tissue concentration, the size of the tissues, and the weight of the animal. In humans the values are typically presented as steady-state body burdens and are estimated on the basis of an intake rate and the half-life of TCDD in humans. Alternatively, body burdens in humans are estimated on the basis of lipid-adjusted serum or adipose tissue TCDD or TEQ concentrations (See Part I, Volume 2, Chapter 4).

Steady-state body burdens provide a useful dose metric for several reasons. First, tissue and blood concentrations are directly related to body burdens. Thus, body burdens are surrogates for tissue concentrations. Second, the differences in the half-life of TCDD between species are accounted for, because these body burdens are estimated at steady-state conditions. Third, DeVito et al. (1995) have demonstrated that for a multitude of in vitro, biochemical, and toxic responses, including chloracne and cancer, species have similar rates of responses when dose is expressed on a body burden basis. Finally, body burdens provide flexibility, because they can be estimated on the basis of either intake rates or on measured tissue concentrations.

Use of steady-state body burdens also has some limitations. In order to estimate steady-state body burdens from lipid-adjusted tissue concentrations, an assumption of the percent body

fat must be used. In the reassessment, a value of 25% has been used for humans. It should be noted that there are human populations with body fat compositions as low as 10% and greater than 35%. Also, when estimating the body burden on the basis of intake rates and half-lives, the uncertainty of these parameters should be considered. In the reassessment, the estimated current steady-state body burden of approximately 5 ng TEQ_{DFP}-WHO_{98}/kg is based on measured serum concentrations from several populations in the mid 1990's.

Although measured concentrations should eliminate some of the uncertainties in estimates using intake rates and half-life assumptions, it is likely that these measured values represent a past history of higher exposure, and we must anticipate a continued downward trend to represent a "true" lifetime average concentration associated with current dose intake rates. Caution must be used when using body burden as a dose metric for species extrapolation when comparing short-term animal studies to steady-state human exposures. Under acute exposure conditions in the animals, the relationship between tissue concentrations and body burden may not be the same as under the steady-state conditions.

1.3.5. Mechanistic Dose Metrics

Several groups have proposed a variety of dose metrics based on mechanistic considerations, such as concentration of occupied AhR (Jusko, 1995), induced CYP1A2 (Andersen et al., 1997; Kohn et al., 1993) and reduced EGFR (Portier and Kohn, 1996). Although these dose metrics are intellectually appealing, it must be kept in mind that they are still hypothesized dose metrics and require further research to demonstrate their utility for cross-species extrapolations. In addition, these dose metrics are unlikely to be measured in sufficient human samples to be useful.

1.3.6. Summary

A variety of dose metrics have been proposed for estimating potential human health effects following exposure to dioxins. Many of them, such as tissue concentrations and the mechanistic dose metrics, have practical limitations that inhibit their use. Others, such as AUC, have limited utility for species extrapolations because of our limited understanding of the concept of physiological time. Some, such as AUC and administered dose, can be used to compare different human exposures, but are not necessarily suitable for cross-species extrapolations. Others, such as steady-state body burdens or blood concentrations, are useful for species extrapolations because they are directly related to tissue concentrations and can be estimated in both animals and humans. All of these dose metrics require more research to improve cancer and

noncancer risk prediction. This research could include efforts to quantify impacts of dose timing, peak concentrations, and AUC above a baseline.

The use of any of these dose metrics requires a number of assumptions, discussed above and in various chapters in Parts I and II. The choice of dose metric requires an understanding of the data available and their application in the intended use of the dose metric. Future research efforts could provide better guidance in choosing the dose metrics for dioxins and related chemicals. However, in the meantime, the use of steady-state body burdens can provide a reasonable description of dose for use in species extrapolations and risk assessments for many chronic effects and is clearly preferable to intake levels.

Table 1-1. The toxic equivalency factor (TEF) scheme for I-TEQ_{DF}[a]

Dioxin congener	TEF	Furan congener	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1
1,2,3,4,6,7,8,9-OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1
		1,2,3,4,6,7,8-HpCDF	0.01
		1,2,3,4,7,8,9-HpCDF	0.01
		1,2,3,4,6,7,8,9-OCDF	0.001

[a] Note that the scheme does not include dioxin-like PCBs. The nomenclature for this scheme is I-TEQ_{DF}, where "I" represents "International," TEQ represents the 2,3,7,8-TCDD toxic equivalence of the mixture, and the subscript DF indicates that only dioxins (D) and furans (F) are included in the TEF scheme.

Table 1-2. The toxic equivalency factor (TEF) scheme for TEQ_{DFP}-WHO_{94}[a]

Dioxin congener	TEF	Furan congener	TEF	Dioxin-like PCB	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1	PCB-77	0.0005
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.05	PCB-126	0.1
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5	PCB-169	0.01
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1	PCB-105	0.0001
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1	PCB-118	0.0001
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1	PCB-123	0.0001
1,2,3,4,6,7,8,9-OCDD	0.001	2,3,4,6,7,8-HxCDF	0.1	PCB-156	0.0005
		1,2,3,4,6,7,8-HpCDF	0.01	PCB-157	0.0005
		1,2,3,4,7,8,9-HpCDF	0.01	PCB-167	0.00001
		1,2,3,4,,6,7,8,9-OCDF	0.001	PCB-114	0.0005
				PCB-170	0.0001
				PCB-180	0.00001
				PCB-189	0.0001

[a] The nomenclature for this TEF scheme is TEQ_{DFP}-WHO_{94}, where TEQ represents the 2,3,7,8-TCDD toxic equivalency of the mixture, and the subscript DFP indicates that dioxins (D), furans (F), and dioxin-like PCBs (P) are included in the TEF scheme. The subscript 94 following WHO displays the year changes were made to the TEF scheme.

Table 1-3. The toxic equivalency factor (TEF) scheme for TEQ_{DFP}-WHO_{98}[a]

Dioxin congener	TEF	Furan congener	TEF	Dioxin-like PCB	TEF
2,3,7,8-TCDD	1.0	2,3,7,8-TCDF	0.1	PCB-77	0.0001
1,2,3,7,8-PeCDD	1.0	1,2,3,7,8-PeCDF	0.05	PCB-81	0.0001
1,2,3,4,7,8-HxCDD	0.1	2,3,4,7,8-PeCDF	0.5	PCB-126	0.1
1,2,3,6,7,8-HxCDD	0.1	1,2,3,4,7,8-HxCDF	0.1	PCB-169	0.01
1,2,3,7,8,9-HxCDD	0.1	1,2,3,6,7,8-HxCDF	0.1	PCB-105	0.0001
1,2,3,4,6,7,8-HpCDD	0.01	1,2,3,7,8,9-HxCDF	0.1	PCB-118	0.0001
1,2,3,4,6,7,8,9-OCDD	0.0001	2,3,4,6,7,8-HxCDF	0.1	PCB-123	0.0001
		1,2,3,4,6,7,8-HpCDF	0.01	PCB-156	0.0005
		1,2,3,4,7,8,9-HpCDF	0.01	PCB-157	0.0005
		1,2,3,4,6,7,8,9-OCDF	0.0001	PCB-167	0.00001
				PCB-114	0.0005
				PCB-189	0.0001

[a] The nomenclature for this TEF scheme is TEQ_{DFP}-WHO_{98}, where TEQ represents the 2,3,7,8-TCDD toxic equivalency of the mixture, and the subscript DFP indicates that dioxins (D), furans (F), and dioxin-like PCBs (P) are included in the TEF scheme. The subscript 98 following WHO displays the year changes were made to the TEF scheme. Note that the changes to the TEFs since 1994 are as follows:

- for 1,2,3,7,8-PeCDD, the new WHO TEF is 1 and the I-TEF is 0.5;
- for OCDD, the new WHO TEF is 0.0001 and the I-TEF is 0.001;
- for OCDF, the new WHO TEF is 0.0001 and the I-TEF is 0.001;
- for PCB 77, the new TEF is 0.0001;
- the addition of PCB 81 (i.e., 3,4,4',5-TCB); and
- for the two di-ortho substituted HpCBs in the 1994 TEF scheme (i.e., PCBs 170 and 180), no TEFs have been assigned in the new WHO TEF scheme.

Table 1-4. The range of the in vivo relative potency estimates (REP) values for the major toxic equivalency contributors

Chemical	Number of in vivo endpoints	Range of REPs (mean ± std)	Number of endpoints from subchronic studies	Range of REPs (mean ± std)	TEF
1,2,3,7,8-PCDD	22	0.16–0.9 (0.5 ± 0.22)	16	0.19–0.9 (0.53 ± 0.24)	1
2,3,4,7,8-PCDF	40	0.018–4.0 (0.4 ± 0.7)	20	0.018–0.6 (0.20 ± 0.13)	0.5
1,2,3,6,7, 8-HxCDD	3	0.015–0.16	1	0.04	0.1
PCB 126	62	0.0024–0.98 (0.20 ± 0.20)	31	0.004–0.18 (0.13 ± 0.13)	0.1

TEF = toxic equivalency factor

Table 1-5. Comparison of administered dose and body burden in rats and humans[a]

	(A) Rat daily administered dose/body burden	(B) Human scaled administered dose/body burden[b]	(C) Human equivalent administered dose/body burden[c]	(A/B) Ratio of rat-to-human scaled dose	(A/C) Ratio of rat-to-human equivalent Dose
Dose (ng/kg/day)	1	0.27	0.0096	3.7	104
Body burden (ng/kg)	18	505	18	0.036	1

[a] This matrix compares the effects of different interspecies scaling factors between rats and humans. Column A indicates that a dose of 1 ng/kg/day to a rat leads to a steady-state body burden (BB) of 18 ng/kg, using the formula BB = half-life*dose*absorption fraction (0.5)/ln2. Columns B and C then use different interspecies scaling factors to convert the rat dose to a human equivalent dose. Column B uses body weight to the 3/4 power as the interspecies scaling factor to convert the rat dose of 1 ng/kg/day (from the column A dose row) to the equivalent human scaled dose of 0.27 ng/kg/day, which in turn corresponds to a human body burden of 505 ng/kg based on the human half-life of 7.1 years and f = 0.5 (used in this table for consistency). Column C uses body burden as the interspecies scaling factor to convert the rat body burden of 18 ng/kg (from column A body burden row) to the equivalent 18 ng/kg BB in humans, and then derives the human dose that would correspond with this body burden, i.e., 0.0096 ng/kg/day. The fifth column divides column A results by column B results, revealing that the $BW^{3/4}$ interspecies factor leads to a rat/human ratio of 3.7-fold. The last column divides column A by column C results, revealing that when body burden is used as the interspecies scaling factor the rat dose is over 100 times the equivalent human dose.

[b] Assumes administered dose scales across species as a function of $BW^{3/4}$

[c] Assumes administered dose scales across species as a function of equivalent body burdens

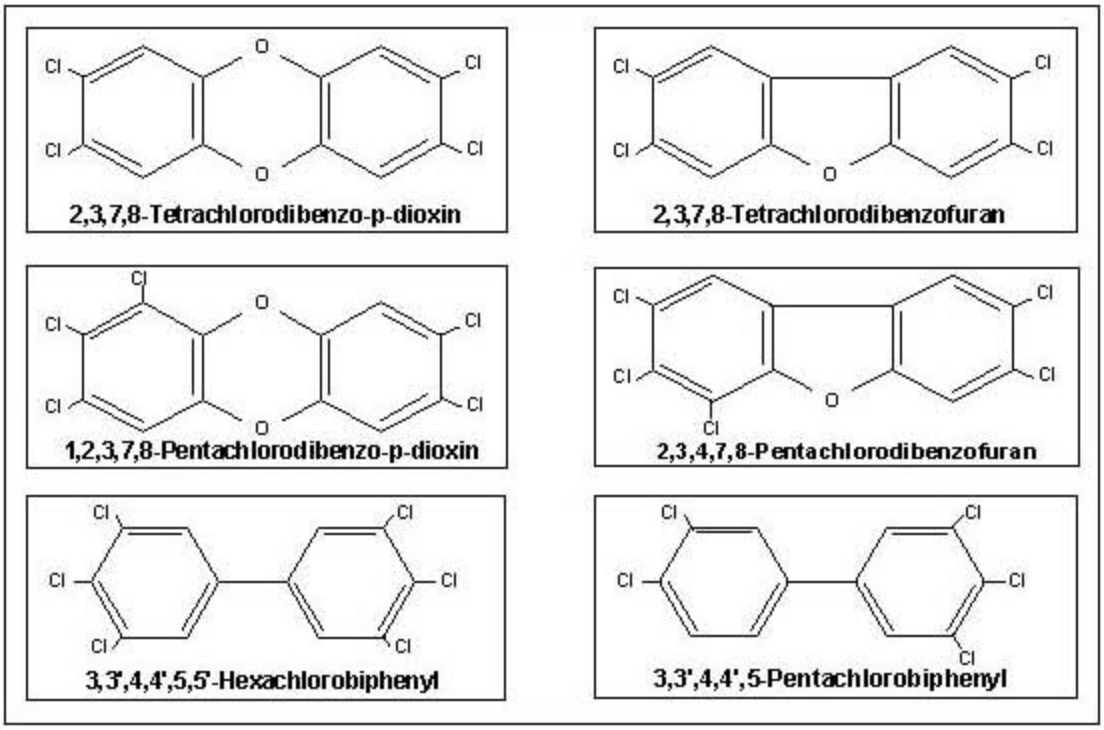


Figure 1-1. Chemical structure of 2,3,7,8-TCDD and related compounds.

2. EFFECTS SUMMARY

Since the identification in 1957 of 2,3,7,8-TCDD as a chloracnegen, more than 5000 publications have discussed its biological and toxicological properties. A large number of the effects of dioxin and related compounds have been discussed in detail throughout the chapters in Part II of this assessment. These discussions illustrate the wide range of effects produced by this class of compounds. The majority of effects have been identified in experimental animals; some have also been identified in exposed human populations. Although past EPA risk assessments have focused on cancer estimates based on extrapolation models as the major concern for dioxin and related compounds, more recent data suggest that noncancer effects may be occurring at or near human background steady-state body burden levels in animals and in humans. Evaluation of noncancer effects and their relationship to past and current body burdens and intake levels is an important feature of this reassessment. Direct comparisons between various noncancer effects and cancer in animals and humans and exposures of interest are presented in the form of *margins of exposure* (MOE).

Cross-sectional studies have been conducted to evaluate the prevalence or extent of disease in living 2,3,7,8-TCDD-exposed groups (Suskind and Hertzberg, 1984; Moses et al., 1984; Lathrop et al., 1984, 1987; Roegner et al., 1991; Grubbs et al., 1995; Sweeney et al., 1989; CDC Vietnam Experience Study, 1988; Webb et al., 1989; Ott and Zober, 1994). The limitations of the cross-sectional study design for evaluating hazard and risk are discussed in Part II, Chapter 7b, Section 7.11. Many of the earliest studies were unable to define exposure-outcome relationships owing to a variety of shortcomings, including small sample size, poor participation, short latency periods, selection of inappropriate controls, and the inability to quantify exposure to 2,3,7,8-TCDD or to identify confounding exposures.

Cohort and case-control studies have been used to investigate hypothesized increases in malignancies among the various 2,3,7,8-TCDD-exposed populations (Fingerhut et al., 1991a, b; Manz et al., 1991; Eriksson et al., 1990). In more recent analyses of occupational cohorts (Steenland et al., 1999; Ott and Zober, 1996; Flesch-Janys et al., 1998), cross-sectional studies of U.S. chemical workers (Sweeney et al., 1989), U.S. Air Force Ranch Hand personnel (Roegner et al., 1991; Grubbs et al., 1995), and Missouri residents (Webb et al., 1989), serum or adipose tissue levels of 2,3,7,8-TCDD were measured to evaluate 2,3,7,8-TCDD-associated effects in exposed populations. The ability to measure tissue or serum levels of 2,3,7,8-TCDD for all or a large sample of the subjects confirmed exposure to 2,3,7,8-TCDD and permitted the investigators to test hypothesized dose-response relationships.

A large number of effects of exposure to TCDD and related compounds have been documented in the scientific literature. Although many effects have been demonstrated in multiple species (see Table 2-1), other effects may be specific to the species in which they are measured and may have limited relevance to the human situation. Although the potential species-specific responses are an important consideration for characterizing potential hazard, all the observed effects of 2,3,7,8-TCDD illustrate the multiple sequelae that are possible when primary impacts are at the level of signal transduction and gene transcription. Even though not all observed effects may be characterized as "adverse" (i.e., some may be responses within the normal range or adaptive or compensatory and of unknown or neutral consequence), they represent a continuum of response expected from the fundamental changes in biology caused by exposure to dioxin-like compounds. As discussed in the following sections, the doses associated with this plethora of effects are best compared across species using a common measurement unit of steady-state body burden of 2,3,7,8-TCDD and other dioxin-like compounds, as opposed to the level or rate of exposure/intake.

The low end of the range of experimental lowest-observed-adverse-effect levels (LOAELs), no-observed-adverse-effect levels (NOAELs), and effective doses at the 1% response level (ED_{01}s) for critical endpoints from animal studies is compiled in Table 5-6 and Appendix A. These selected endpoints cover a spectrum from overt toxicity (e.g., fetal mortality, cancer), through developmental and reproductive toxicity endpoints, to enzyme induction as a marker of intracellular dioxin activity. Many of the studies report multiple statistically significant effects related to dioxin exposure. From these results, the values tabulated were selected on the basis of the lowest dose at which significant effects occurred—findings that were generally highlighted by the authors of the publication. In the event that multiple endpoints were elicited at the same dose, the effect considered of most consistency across studies and relevance to human risk assessment was selected (e.g., decreased sperm counts).

A variety of methods were employed to estimate body burdens corresponding to the LOAELs/NOAELs/ED_{01}s, including using measured body burden and lipid concentration data, absorption adjustments for single-dose studies, and first-order pharmacokinetic modeling estimates using absorbed dose and halflife. Additional details on study design, endpoint selection, and calculation of body burdens are included in Appendix A and can also be found in Sections 5.2 and 6.0 of this document and in other chapters of the dioxin reassessment. Human equivalent intakes for the body burden endpoints were calculated according to formulae discussed in Part II, Chapter 8 of this report and are displayed in order corresponding to the preceding three results columns in Table 5-6 and Appendix A. These comparisons result in the finding that, when animal data associated with effects at the low end of the range of experimental

observation (NOAELs/LOAELs/ED_{01}s) are compared to current average human body burdens of approximately 5 ng TEQ_{DFP}-WHO_{98}/kg—representing lifetime average intake values of approximately 3 pg TEQ_{DFP}-WHO_{98}/kg/day—or to current intake values of 1 pg TEQ_{DFP}-WHO_{98}/kg/day, relatively small MOEs are obtained. Similarly, some human noncancer effects (e.g., developmental delay, neurobehavioral outcomes, and impact on thyroid function in Dutch children) and cancer outcomes show comparatively small MOEs.

In the following sections which discuss these general effects, the focus is on developing an understanding of dioxin hazard and risk. This discussion is, by its nature, selective of findings that inform the risk assessment process. Readers are referred to the more comprehensive chapters for further discussion of the broader epidemiologic and toxicologic database.

2.1. BIOCHEMICAL RESPONSES (Cross-reference: Part II, Chapters 2, 3, and 8)

As described later in Section 3, mechanistic studies can reveal the biochemical pathways and types of biological events that contribute to adverse effects from exposure to dioxin-like compounds. For example, much evidence indicates that 2,3,7,8-TCDD acts via an intracellular protein, AhR, which is a ligand-dependent transcription factor that functions in partnership with a second protein (known as the AhR nuclear translocator, or Arnt) to alter gene expression. In addition, receptor binding may result in release of cytoplasmic proteins that, in turn, alter the expression or activity of cell-regulatory proteins (e.g., increases in Src activity). Therefore, from a mechanistic standpoint, TCDD's adverse effects appear likely to reflect alterations in gene expression or protein activity that occur at an inappropriate time and/or for an inappropriate length of time. Mechanistic studies also indicate that several other proteins (e.g. hif α, Rb, relA, src, sim, etc.) contribute to TCDD's gene-regulatory effects and that the response to 2,3,7,8-TCDD involves a relatively complex interplay between multiple genetic and environmental factors. This model is illustrated in Figure 2-1 (from Part II, Chapter 2). Comparative binding studies and other data suggest that biochemical events observed in response to TCDD exposure are also seen with other dioxin-like compounds in proportion to their TEFs.

Comparative data from animal and human cells and tissues suggest a strong qualitative similarity across species in response to dioxin-like chemicals. This further supports the applicability to humans of the generalized model of initial events in response to dioxin exposure. These biochemical and biological responses are sometimes considered adaptive or reflective of exposure to dioxin-like compounds. When they are seen within normal homeostatic limits, these biochemical changes are often not considered adverse in and of themselves. However, many of these changes are potentially on a continuum of dose-response relationships that leads to adverse responses and, considering the potential to shift population distributions in response, may be of

concern. Because of the distribution of responses and sensitivity within a population, it is possible that adaptive responses for some are frankly adverse for those at the tails of the distribution. For this reason, a balanced approach must be used when describing these events, recognizing that they may be adaptive or simply biomarkers of exposure to dioxin-like compounds, or they may represent early events in a pathway resulting in a risk of adverse effects in some humans.

If, as we can infer from the evidence, 2,3,7,8-TCDD and other dioxin-like compounds operate through these mechanisms, there are constraints on the possible models that can plausibly account for dioxin's biological effects and also on the assumptions used during the risk assessment process. For instance, the linear relationship expected between ligand concentration and receptor binding may or may not be reflective of dose-response relationships for downstream events requiring complex interactions of other regulatory proteins with the activated receptor. Puga et al. (2000a) have shown that interactions of TCDD with the AhR alters expression of over 300 genes in a single cell line at one time point and one dose. These data suggest that mechanisms of toxic action may be very complicated and that additional research will be necessary to further unravel the mechanistic relationships underpinning dioxin's toxicity.

Mechanistic knowledge of dioxin action may also be useful in other ways. For example, knowledge of genetic polymorphisms that influence 2,3,7,8-TCDD responsiveness may also allow the identification of individuals either refractory to or at particular risk from exposure to dioxin. In addition, knowledge of the biochemical pathways that are altered by dioxin-like compounds may help in the development of approaches to intervention or to drugs that can prevent dioxin's adverse effects.

As described in Part II, Chapter 2, biochemical and genetic analyses of the mechanisms by which dioxin modulates particular genes have revealed the outline of a novel regulatory system whereby a chemical signal can alter cellular regulatory processes. Future studies of dioxin action have the potential to provide additional insights into mechanisms of mammalian gene regulation that are of relatively broad interest. Additional perspectives on dioxin action can be found in several recent reviews (Birnbaum, 1994a, b; Schecter, 1994; Hankinson, 1995; Schmidt and Bradfield, 1996; Rowlands and Gustafsson, 1997; Gasiewicz, 1997; Hahn, 1998; Denison et al., 1998; Wilson and Safe, 1998; Schecter and Gasiewicz, 2003).

The ability of 2,3,7,8-TCDD and other dioxin-like compounds to modulate a number of biochemical parameters in a species-, tissue-, and temporal-specific manner is well recognized. Despite the ever-expanding list of these responses from the past 20 years and the elegant work on the molecular mechanisms mediating some of these, there still exists a considerable gap between our knowledge of individual biochemical changes and the degree to which they are related to the

more complex biological and toxicological endpoints elicited by these chemicals. A framework for considering these responses in a mode of action context is discussed later in this document.

TCDD-elicited activation of the AhR has been clearly shown to mediate altered transcription of a number of genes, including several oncogenes and those encoding growth factors, receptors, hormones, and drug-metabolizing enzymes. Table 2-2 provides an illustrative list of gene products whose regulation or activity is modulated by 2,3,7,8-TCDD. Although this list is not meant to be exhaustive, it demonstrates the range of potential dioxin impacts on pathways with potential to lead to adverse effects.

As discussed in Part II, Chapter 2, it is possible that the TCDD-elicited alteration of activity of these genes may occur through a variety of mechanisms. The transcription of some genes may be directly regulated by the activated AhR. Other alterations in gene expression may be secondary to the initial biochemical events directly regulated transcriptionally by the AhR. Some of the changes may also occur by post-transcriptional processes such as messenger ribonucleic acid (mRNA) stabilization or altered protein phosphorylation (Gaido et al., 1992; Matsumura, 1994). Nie et al. (2001) described cross-talk between Arnt-requiring pathways resulting in interactions between the AhR and the hypoxia signaling pathways. Thus, the molecular mechanisms by which many if not most of the biochemical processes discussed herein are altered by 2,3,7,8-TCDD treatment remain to be determined. Nevertheless, it is assumed, based on the cumulative evidence available, that all of these processes are mediated by the binding of 2,3,7,8-TCDD to the AhR. Although evidence has accumulated for the involvement of the AhR in many but not all of these processes, structure-activity relationships, genetic data, and reports from the use of biological models such as "knockout" mice that are lacking the AhR ($AhR^{-/-}$) are consistent with the involvement of the AhR as the initial step leading to these biochemical alterations. In fact, for every biochemical response that has been well studied, the data are consistent with the particular response being dependent on the AhR.

The dioxin-elicited induction of certain drug-metabolizing enzymes such as CYP1A1, CYP1A2, and CYP1B1 is clearly one of the most sensitive responses observed in a variety of different animal species, including humans, and it occurs at body burdens as low as 3–8 ng TCDD/kg in animals (see Part II, Chapter 8, Sections 8.3 and 8.4). These and other enzymes are responsible for the metabolism of a variety of exogenous and endogenous compounds. Several lines of experimental evidence suggest that these enzymes may be responsible for either enhancing or protecting against the toxic effects of a variety of agents, including known carcinogens as well as endogenous substrates such as hormones. These interactive effects are dependent on the compounds and the experimental system examined.

Several reports (Kadlubar et al., 1992; Esteller et al., 1997; Ambrosone et al., 1995; Kawajiri et al., 1993) provide evidence that human polymorphisms in CYPIA1 and CYPIA2 that result in higher levels of enzyme activity are associated with increased susceptibility to colorectal, endometrial, breast, and lung tumors. Also, exposure of AhR-deficient ("knockout") mice to benzo[a]pyene (BaP) results in no tumor response, suggesting a key role for the AhR—and perhaps CYPIA1 and CYPIA2—in BaP carcinogenesis (Dertinger et al., 1998; Shimizu et al., 2000). Modulation of these enzymes by dioxin may play a role in chemical carcinogenesis. However, the exact relationship between the induction of these enzymes and any toxic endpoint observed following dioxin exposure has not been clearly established.

In addition to what is known about the P450 isozymes (CYP1A1, CYP1A2, and CYP1B1), there exists some evidence from experimental animal data to indicate that the alteration of certain other biochemical events might have a more direct relationship to sensitive toxic responses observed following TCDD exposure. Some of these may be relevant to responses observed in humans, and further work in these areas is likely to lead to data that would assist in the risk characterization process. For example, changes in EGFR have been observed in tissues from dioxin-exposed animals and humans (see Part II, Chapter 3, Section 3.5, and Chapter 6, Section 6.5). EGF and its receptor possess diverse functions relevant to cell transformation and tumorigenesis, and changes in these functions may be related to a number of dioxin-induced responses, including neoplastic lesions, chloracne, and a variety of reproductive and developmental effects. Likewise, the known ability of TCDD to directly or indirectly alter the levels and/or activity of other growth factors and hormones, such as estrogen, thyroid hormone, testosterone, and gonadotropin-releasing hormone and their respective receptors as well as enzymes involved in the control of the cell cycle (Safe, 1995b), may affect growth patterns in cells/tissues, leading to adverse consequences. In fact, most of the effects that the dioxins produce at the cellular and tissue levels are due not to cell/tissue death but to altered growth patterns (Birnbaum, 1994b). Many of these alterations may occur at critical times in development and/or maturation and thus may be irreversible.

There does not yet exist a precise understanding of the relationships between the alteration of specific biochemical processes and particular toxic responses observed in either experimental animals or humans exposed to the dioxins. This is due predominantly to our incomplete understanding of the complex and coordinated molecular, biochemical, and cellular interactions that regulate tissue processes during development and under normal homeostatic conditions. A further understanding of these processes and how 2,3,7,8-TCDD may interfere

with them remains an important goal that would greatly assist in the risk characterization process. In particular, knowledge of the causal association of these responses coupled with dose-response relationships may lead to a better understanding of sensitivity to various exposure levels of the dioxin-like compounds. Nevertheless, it is important to recognize that many of the biochemical and biological changes observed are consistent with the notion that 2,3,7,8-TCDD is a powerful growth dysregulator. This hypothesis may play a considerable role in the risk characterization process by providing a focus on those processes, such as development, reproduction, immunity, and carcinogenesis, that are highly dependent on coordinated growth regulation.

2.2. ADVERSE EFFECTS IN HUMANS AND ANIMALS

2.2.1. Cancer (Cross-reference: Part II, Chapters 6, 7, and 8)

2.2.1.1. *Epidemiologic Studies*

Since the last formal EPA review in 1988 of the human database relating to the carcinogenicity of TCDD and related compounds, a number of new follow-up mortality studies have been completed. This body of information is described in Part II, Chapter 7a, Section 7.5, of this assessment, and summaries appear in an International Agency for Research on Cancer monograph (IARC, 1997), the Agency for Toxic Substances and Disease Registry (ATSDR) ToxProfile (ATSDR, 1999a), and the National Toxicology Program's report on carcinogens (NTP, 2001). Among the most important of these are the ones by Fingerhut et al. (1991a) and Steenland et al. (1999, 2001) from NIOSH of 5172 U.S. chemical manufacturing workers and the independent analyses by Aylward et al. (1996) and Salvan et al. (2001) and followup of the Dow sub-cohort by Bodner et al. (2003); a study of 2479 German workers involved in the production of phenoxy herbicides and chlorophenols by Becher et al. (1996, 1998) and by others in separate publications (Manz et al., 1991; Nagel et al., 1994; Flesch-Janys et al., 1995, 1998); a study of more than 2000 Dutch workers in two plants involved in the synthesis and formulation of phenoxy herbicides and chlorophenols (Bueno de Mesquita et al., 1993) and subsequent follow-up and expansion by Hooiveld et al., 1998); a smaller study by Zober et al. (1990) of 247 workers involved in a chemical accident cleanup and subsequent follow-up (Ott and Zober, 1996b); and an international study by Saracci et al. (1991) of more than 18,000 workers exposed to phenoxy herbicides and chlorophenols, with subsequent follow-up and expansion by Kogevinas et al. (1997). Recent reports also indicate increased cancer risks among the Seveso population (Bertazzi et al. 2001a, Warner et al. 2002).

Although uncertainty remains in interpreting these cohort results because not all potential confounders have been ruled out and coincident exposures to other carcinogens are likely (see Cole et al., 2003 for a critique), all provide support for an association between exposure to dioxin

and related compounds and increased cancer mortality. Strong inference regarding carcinogenic hazard often relies on the availability of studies with well-documented exposures. One of the strengths of these studies is that each has some exposure information that permits an assessment of dose response. Some of these data have, in fact, served as the basis for fitting the dose-response models in Part II, Chapter 8, Section 8.4.

In addition, during the development of its monograph on PCDDs/PCDFs (IARC, 1997), the IARC Working Group abstracted from the published literature data concerning the most highly exposed populations in the world. The group focused its attention on the most exposed subcohorts within cohorts with adequate latency. IARC suggests that if associations between exposure and risk are truly causal, they will become more apparent in these highly exposed subcohorts with adequate latency. Increased risk for all cancers combined and lung cancer mortality were consistent findings in the occupational cohort studies. Although the increase was generally low (20–50%), it was highest in the subcohorts with the presumed heaviest exposure. The results of the IARC Working Group's analysis regarding all cancer and lung cancer mortality in the recent studies are summarized in Table 2-3. Observed numbers of cases, standardized mortality ratios (SMR) and 95% confidence intervals (CI) are given for each of these two findings for each study.

In addition, the Working Group developed overall SMRs for the combined studies. The group state clearly that, although these total SMRs are low (1.4, 95% CI = 1.2–1.6 for all cancers and 1.4, 95% CI = 1.1–1.7 for lung cancer), these results are unlikely to be due to chance, nor can confounding by cigarette smoking likely account for the increase in lung cancer. Positive dose-response trends in the German studies and increased risk in the longer duration U.S. subcohort and the most heavily exposed Dutch workers support this view. In the opinion of these experts, increases of this magnitude in all cancers combined have rarely been found in occupational cohorts. These results are also supported by significantly increased mortality from lung and liver cancers subsequent to the Japanese rice oil poisoning accident where exposure to high levels of PCDFs and PCBs occurred (Kuratsune et al., 1988; Kuratsune, 1989).

Although smoking as a confounder cannot be totally eliminated as a potential explanation of the occupational studies results, analyses conducted to date (Fingerhut et al., 1991b; Ott and Zober, 1996b) suggest that smoking is not likely to explain the entire increase in lung cancer and may even suggest synergism between occupational exposure to dioxin and smoking. These analyses have not been deemed entirely satisfactory by some reviewers of the literature. The question of confounding exposures such as to asbestos and other chemicals in addition to smoking has not been entirely ruled out and must be considered as potentially adding to the observed increases. Although increases of cancer at other sites (e.g., non-Hodgkin's lymphoma,

soft tissue sarcoma, gastrointestinal cancer) have been reported (see Part II, Chapter 7a, Section 7.5), the data for an association with exposure to dioxin-like chemicals are less compelling due to the limited numbers of observed tumors at any specific site.

As discussed by IARC (McGregor et al., 1998) and Smith and Lopipero (2001), it is unusual for a cancer hazard characterization to focus on the "all cancers combined" category of epidemiological results, and continuing uncertainties regarding site-specific cancer increases following dioxin exposure remain a factor in concluding that the epidemiological information is limited. McGregor et al. (1998) note, however, that the predominant cancer promotion mechanism of action for dioxin will theoretically elicit pre-existing initiated cell lines. These promotional effects would be expected in multiple tissues, especially those most sensitive to the effects of dioxin. In epidemiological studies, there may not be a statistically increased tumor site(s), but rather a pattern of smaller increases that could vary across study populations because of differences in life histories, exposures, and pre-existing initiating events.

The cancer-promotion mechanism may also serve to accentuate existing tumor rate increases following other carcinogenic exposures, thereby acting in a synergistic manner. Timing of tumor induction may differ between a cancer promoter and initiator, where the effects of a promoter may not be monotonic with time, but rather may exhibit an earlier onset, harvesting effect, where the total cancer burden may not have changed but the onset has been accelerated. These timing issues are exacerbated by the pharmacokinetics of dioxin elimination, where initial peak body burdens during employment or after accidental exposures decline gradually after cessation of exposure.

Mathematically, a net carcinogenic effect in one or more organ sites must, by definition, increase the "all cancers combined" risk for the exposed population if the exposed and control groups are matched (i.e., they have the same background cancer rate absent the exposure). Thus, an increase in the all cancers category should be considered an expected result of a carcinogen exposure, not an unusual event. The statistical power of a study to detect such an effect is, however, the limiting factor in the presence of stochastic events and imperfect matching. This constraint is particularly applicable to rare tumor sites, but it also occurs for common tumor sites such as lung, colon, breast (♀), and prostate (♂) or for mechanistically linked sites (e.g., hormonally related breast, ovary, uterus), where substantial increases in site-specific relative risks are necessary to impact the all cancer category.

Ionizing radiation (a mutagenic carcinogen) provides an example where small increased relative risks at multiple sites lead to a significantly increased relative risk for "all nonleukemic cancers." In atomic bomb survivors, the relative risk for all nonleukemic cancers at 100 rads was 1.17 ($p<0.01$), comprised principally of small but statistically significant increases in stomach

(relative risk [RR] = 1.11), lung (1.33), breast (1.69), ovary (1.52), and bladder-kidney (1.55) cancers and nonstatistically significant increases in esophagus (1.23), liver (1.35), ovary (1.52), and multiple myeloma (1.51). Although the relative risk for leukemia was 3.95 ($p<0.01$), the excess cancer burden from nonleukemic sites in the exposed population was over twice that due to the leukemias (Hoel, 1987).

Some studies that are discussed in Part II, Chapter 7a, report small or no increased risk of cancer from exposure to 2,3,7,8-TCDD or its congeners. These studies generally suffer from one or more deficiencies that limit their ability to determine the carcinogenic hazard of dioxins. These deficiencies fall into the following categories: little statistical power to detect an effect of exposure because the measured exposures are lower than those seen in the studies cited above and are more similar to those of the comparison population; no measurements of internal exposure to 2,3,7,8-TCDD and potential for misclassification of exposure; and inadequate latency or follow-up.

The Ranch Hand study of U.S. Air Force personnel who sprayed the defoliant Agent Orange during the Vietnam War provides an illustrative example of statistical power constraints in the presence of low predicted relative risks. Statistical power is the ability of a study to detect a real difference between two groups at pre-defined levels of statistical significance (usually $p \leq 0.05$) and relative risk. Statistical power analysis based on the detailed dosimetry and health status data available for this cohort indicates insufficient statistical power to detect an elevated all-cancers risk at levels consistent with the occupational dose-response data. A predicted relative risk for all cancers combined can be estimated for the Ranch Hands by calculating the difference between their dose and that of the control group (mean background of 4.25 ppt TCDD in lipid) (Michalek et al., 1998) and then multiplying this dose increment by an estimated cancer risk slope factor for TCDD. The median AUC increment value for the overall Ranch Hand group is 468 ng TCDD/kg lipid * years, and for the high dioxin group the median is 2280 ng TCDD/kg lipid * years. Using the Becher et al. (1998) linear formula (RR = 1 + 0.000016 x AUC ng-TCDD/kg lipid * years, which equals ~ 3×10^{-3} risk/pg/kg/day) described in Section 5.3 and Table 5-2 of this document, the estimated all-cancers relative risk for the overall Ranch Hand cohort is approximately 1.01, and for the high-exposure group it is 1.04 as compared to the control population. Using formulae in Fleiss (1981) and Cohen (1977) and assuming two-sided testing at a significance level of 5%, the study has no power to detect 1 to 4% increases in relative risk. Data on the overall prevalence of cancer in the comparison group (18.9%) and sample sizes (all Ranch Hand 845 vs. 1224 controls; high category 241 vs. 1200 controls) used in the above analysis were obtained from the 1997 Ranch Hand morbidity report (http://www.brooks.af.mil/AFRL/HED/hedb/afhs/.html).

Recent suggestive cancer findings from the Ranch Hand database are consistent with these calculations, both in the magnitude of the risk ratios under review and in the constraints on statistical methods to detect such levels of incremental risk. Akhtar et al. (2003) provide results that suggest exposure to dioxin-contaminated herbicides may be associated with cancer, based on a statistically significant positive trend in "any site" cancer relative risk with exposure group, accompanied by a non-significant increase in the any site cancer standardized incidence ratio of 1.09 (Obs. 134, Exp 123.34, p=0.34).

In addition, one of the earliest reported associations between exposure to dioxin-like compounds in dioxin-contaminated phenoxy herbicides and increased cancer risk involved an increase in soft tissue sarcomas (Hardell and Sandstrom, 1979; Eriksson et al., 1981; Hardell and Eriksson, 1988; Eriksson et al., 1990). In this and in other recent evaluations of the epidemiologic database, many of the earlier epidemiological studies that suggested an association between dioxin exposure and soft tissue sarcoma have been criticized for a variety of reasons. Arguments regarding selection bias, lack of exposure or differential exposure misclassification, confounding, and chance in each individual study, which increases uncertainty around this association, have been presented in the scientific literature. Nonetheless, the incidence of soft tissue sarcoma is elevated, although not statistically so, in several of the most recent studies (Bertazzi et al., 1993, 1997, 1999; Fingerhut et al., 1991a; Hertzman et al., 1997; Kogevinas et al., 1997; Lampi et al., 1992; Lynge, 1998; Pesatori et al., 1999; Saracci et al., 1999; Vineis et al., 1986). It is probable that soft tissue sarcomas are not unlike other site-specific cancers whose risks from exposure to TCDD are difficult to define because of small numbers and lack of measures of internal exposure.

The accidental exposure of the population at Seveso, Italy, serves as an example of a more highly exposed group where, in previous assessments, latency was considered to be inadequate. Although Bertazzi and coworkers published results of cancer mortality after 10 and 15 years of latency, results are suggestive but not definitive regarding an association between exposure to TCDD and cancer deaths. Results of the analysis of 20 years of follow-up have recently been published (Bertazzi et al., 2001). This more recent follow-up of the same group of residents in zones A and B was completed after 20.5 years to December 31, 1996. The authors stated that their results support the evaluation of TCDD as a human carcinogen, especially with the increased estimates of relative risk for all cancer mortality and for several specific sites of cancer in the >15 year latency period. No soft tissue sarcomas were observed in zones A and B. However, less than one case would have been expected to occur by the end of the follow-up. In Zone A, where exposure was highest, the expectation of a soft tissue sarcoma was only 0.1. There was little power to detect a significant risk in that region.

In a commentary by Smith and Lopipero (2001) on this study, two "key" problems were identified. The "likely" exposure levels back-calculated to the time when the exposures occurred indicate that the weighted average for the two highest exposure zones in Seveso is only 136 ng/kg TCDD (lipid adjusted) versus a mean of 3600 ng/kg TCDD (lipid adjusted) in the combined U.S. industrial cohorts. This interpretation is consistent with the data in Figure 5-1 of this document. On this basis, one would not expect to find significant increases in all cancers combined based on extra risk estimates from the occupational cohorts. This situation is not unlike the one described above for the Ranch Hand cohort. However, in this case, associations with exposure to TCDD and cancer risk are being reported.

The other issue raised by these authors is the potential for smoking-related causes of disease to be confounders in this study. The relatively low dioxin exposure and the increase in major smoking-related causes of death raise questions regarding the attribution of these cancer effects to TCDD exposure. Other data are consistent with potential dioxin hazard in this exposed population, for example, the finding of increased diabetes mortality among women. Bertazzi (2001b) takes exception to these interpretations and argues against the perception of "low" exposure and smoking as a confounder. It is clear that the question of whether the Bertazzi (2001a) study contributes to the weight of evidence for carcinogenicity awaits further follow-up and improved exposure assessment.

In general, both past and more recent human studies have focused on males. Although males comprise all the case-control studies and the bulk of the cohort study analyses, animal and mechanism studies suggest that males and females might respond differently to TCDD. There are now, however, some limited data suggesting carcinogenic responses associated with dioxin exposure in females. The only report of a female cohort that had good TCDD exposure surrogate information was that of Manz et al. (1991), which found a borderline statistically significant increase in breast cancer. Although Saracci et al. (1991) did report reduced female breast and genital organ cancer mortality, the finding was based on few observed deaths and on chlorophenoxy herbicide rather than TCDD exposures. In the later update and expansion of this cohort, Kogevinas et al. (1997) provided evidence of a reversal of this deficit and reported a borderline significant excess risk of breast cancer in females.

Bertazzi et al. (1993, 1997, 1998) reported nonsignificant decreases in breast cancer and endometrial cancer in women living in geographical areas around Seveso that were contaminated by dioxin. Breast cancer rates in women who had been exposed as infants at the time of the Seveso explosion were increased. On the basis of 15 (1.5%) confirmed breast cancer cases in the Seveso Women's Health Study, a Cox proportional hazard ratio for breast cancer of 2.1 fold (95% CI 1.0 - 4.6) was reported for a ten-fold increase in serum TCDD levels (Warner et al.,

2002). Although Kogevinas et al. (1993) saw an increase in cancer incidence among female workers most likely exposed to TCDD, no increase in breast cancer was observed in their small cohort. In short, TCDD cancer experience for women may differ from that of men, but currently there are few data to adequately address this question.

Both laboratory animal data and mechanistic inferences suggest that males and females may respond differently to the carcinogenic effects of dioxin-like chemicals. Further data will be needed to address this question of differential response between sexes, especially to hormonally mediated tumors. In addition, studies by Brown et al. (1998) demonstrated that prenatal exposure of rats to 2,3,7,8-TCDD enhances their sensitivity as adults to chemical carcinogenesis. A mechanistic understanding of the impact of gestational dioxin exposure on mammary tissue development has been provided by the work of Fenton and coworkers (Fenton et al., 2002; Vorderstrasse et al., 2004). The experimental data in laboratory animals suggest that exposure to women or perinatal exposures may result in carcinogenic responses. The epidemiological data examining the association between exposure of adult women to dioxin and cancer is limited. No epidemiological data are available to address the question of the potential impact of exposure to dioxin-like compounds on childhood cancers or the effects of perinatal exposures on the development of cancers later in life. The epidemiological data to date have not adequately addressed these issues.

In summary, 2,3,7,8-TCDD and, by inference from more limited data, other dioxin-like compounds are described as potentially multisite carcinogens in the more highly exposed human populations—consisting primarily of adult males that have been studied. Although the epidemiologic data by themselves are not sufficient to infer a causal association between exposure to TCDD and other dioxin-like chemicals and increased cancer in humans (IARC, 1997; ATSDR, 1999a; DHHS, 2001), this "limited" epidemiologic database has been strengthened by emerging data that reflect further follow-up and better exposure metrics. Although uncertainty remains, the cancer findings in the epidemiologic literature are generally consistent with results from studies of multiple laboratory animal species, where dioxin-like compounds have clearly been identified as multisite carcinogens and tumor promoters.

2,3,7,8-TCDD has also been demonstrated to promote dose-dependent clonal expansion and neoplastic transformation in human epidermal keratinocytes immortalized by simian adenovirus SV40 exposure, leading to fixed alterations in regulatory gene expression (Yang et al., 1999) and squamous cell carcinoma when inoculated into athymic nude mice (Yang et al., 1992). These phenomena did not occur in the absence of SV40 virus induction or in control cell lines, including the immortalized cell culture.

Thus, the findings of increased risk at multiple sites in occupationally exposed humans appear to be plausible, given what is known about mechanisms of dioxin action and the fundamental level at which this class of compounds appears to act on gene expression and cellular regulation in target tissues. Although several studies found a positive trend in dose-response and have been the subject of empirical risk modeling (see Part II, Chapter 8, and Becher et al., 1998, and Steenland et al., 2001), the epidemiologic data alone provide little insight into the shape of the dose-response curve below the range of observation in these occupationally exposed populations. However, Mackie et al. (2003) suggest that there is no evidence of a dioxin cancer threshold from the epidemiology data. Steenland and Deddens (2003) also reported that the results of quantitative exposure-response analyses for low environmental levels based on the NIOSH cohort are consistent with the results from the Becher cohort and demonstrate that a doubling of background levels of exposure will increase lifetime risk of cancer death between 0.1 and 1%. The issue of the shape of the dose-response curve in occupational cohorts is further discussed in Section 5.2.1 of this document.

2.2.1.2. *Animal Carcinogenicity (Cross-reference, Part II: Chapters 6 and 8)*

An extensive database on the carcinogenicity of dioxin and related compounds in laboratory studies exists and is described in detail in Part II, Chapter 6. There is adequate evidence that 2,3,7,8-TCDD is a carcinogen in laboratory animals, based on long-term bioassays conducted in both sexes of several strains of rats and mice, hamsters, and fish (U.S. EPA, 1985; Huff et al., 1991; Zeise et al., 1990; IARC, 1997; DHHS, 2001). All the studies produced positive results, leading to conclusions that TCDD is a multi-site carcinogen that increases the incidence of tumors at sites distant from the site of treatment and at doses well below the maximum tolerated dose. Since this issue was last reviewed by the Agency, in 1988, TCDD has been shown to be a carcinogen in hamsters (Rao et al., 1988), which are relatively resistant to the lethal effects of TCDD. Other preliminary data have also shown TCDD to be a liver carcinogen in the small fish *Medaka* (Johnson et al., 1992).

In the past, limited attempts had been made to demonstrate the carcinogenicity of other dioxin-like compounds. A mixture of two isomers of hexachlorodibenzo-*p*-dioxin (HCDDs) produced liver tumors in both sexes of rats and mice when given by the gavage route (NTP, 1980), but not by the dermal route in Swiss mice (NTP, 1982a,b). Reports from Rozman (1999, 2000) and Rozman et al. (2000) demonstrated lung cancer in female rats given gavage exposures of 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin(HpCDD).

Recently, the National Toxicology Program (NTP, 2003 a-d) has conducted chronic bioassays to test the relative carcinogenic potency of four dioxin-like congeners (TCDD,

2,3,4,7,8-PeCDD, PCB 118, and PCB 126), both alone and in combination. In these studies, TCDD, PCB 126 and 2,3,4,7,8-PeCDF, were tested individually or in an equally potent mixture of all three chemicals in a 2-year bioassay in female Sprague-Dawley rats. The NTP study also included PCB 118, but the results and interpretation of this bioassay remain under review due to substantial contamination by PCB 126. Initial reports from the NTP study indicate that there is clear evidence of carcinogenicity for both TCDD and PCB 126. In these studies, both TCDD and PCB 126 exposures increases the incidence of cholangiocarcinoma of the liver, cystic keratinizing epithelioma of the lung, and gingival squamous cell carcinoma of the oral mucosa. Under the conditions of the 2-year study, there was some evidence of carcinogenic activity for the 2,3,4,7,8-PeCDF based on increased incidences of cholangiocarcinoma of the liver, cystic keratinizing epithelioma of the lung and gingival squamous cell carcinoma of the oral mucosa. The results from the mixture study also indicate clear evidence of carcinogenicity as evidenced by dose dependent increases in cholangiocarcinomas in the liver and cystic keratinizing epitheliomas of the lung. The data on the three individual chemicals and mixtures demonstrate consistent increases in the incidence of three tumor types. This evidence provides support that the carcinogenicity of dioxin-like chemicals is mediated through their interactions with the Ah receptor and that the TEF methodology may provide a useful tool in estimating the potential carcinogenic risks of dioxin-like chemicals.

TCDD is characterized as a nongenotoxic carcinogen because it is negative in most assays for DNA-damaging potential and is a potent "promoter" and a weak initiator or noninitiator in two-stage initiation-promotion (I-P) models for liver, skin, and lung. The liver response is characterized by increases in altered hepatocellular foci (AHF), which are considered to be preneoplastic lesions because increases in AHFs are associated with liver cancer in rodents. The results of the multiple I-P studies enumerated in Table 6-5 and in Part II, Chapter 6, Section 6.3, have been interpreted as showing that induction of AHFs by TCDD is dose-dependent (Maronpot et al., 1993; Teeguarden et al., 1999), exposure-duration dependent (Dragan et al., 1992; Teeguarden et al., 1999; Walker et al., 2000), and partially reversible after cessation of treatment (Dragan et al., 1992; Tritscher et al., 1995; Walker et al., 2000).

Other studies indicate that other dioxin-like compounds have the ability to induce AHFs. These studies showed that the compounds demonstrate a rank-order of potency for AHF induction that is similar to that for CYP1A1 (Flodstrom and Ahlborg, 1992; Waern et al., 1991; Schrenk et al., 1994). Non-ortho-substituted, dioxin-like PCBs have also induced the development of AHFs according to their potency to induce CYP1A1 (Hemming et al., 1995; van der Plas et al., 1999). It is interesting to note that liver I-P studies carried out in ovariectomized rats demonstrated the influence that the intact hormonal system has on AHF development. AHF

were significantly reduced in the livers of ovariectomized female rats (Graham et al., 1988; Lucier et al., 1991).

I-P studies on skin have demonstrated that TCDD is a potent tumor promoter in mouse skin as well as rat liver. Early studies demonstrated that TCDD is at least two orders of magnitude more potent than the "classic" promoter tetradecanoyl phorbol acetate (Poland et al., 1982), that TCDD skin tumor promotion is AhR dependent (Poland and Knutsen, 1982), that TCDD had weak or no initiating activity in the skin system (DiGiovanni et al., 1977), and that TCDD's induction of drug-metabolizing enzymes is associated with both metabolic activation and deactivation of initiating agents, as described by Lucier et al. (1979). More recent studies show that the skin tumor-promoting potencies of several dioxin-like compounds reflect relative AhR binding and pharmacokinetic parameters (Hebert et al., 1990).

Although few I-P studies have demonstrated lung tumors in rats or mice, the study by Clark et al. (1991) is particularly significant because of its use of ovariectomized animals. In contrast to liver tumor promotion, lung tumors were seen only in initiated (diethylnitrosamine [DEN]), TCDD-treated rats. No tumors were seen in DEN-only, TCDD-only, control, or DEN/TCDD intact rats. Liver tumors are ovary dependent, but ovaries appear to protect against TCDD-mediated tumor promotion in female rat lung. Perhaps the use of transgenic animal models will allow further understanding of the complex interaction of factors associated with carcinogenesis in rodents and, by extension, in humans. Several such systems are being evaluated (Eastin et al., 1998; van Birgelen et al., 1999; Dunson et al., 2000).

The tumor-promoting ability of a number of dioxin-like chemicals has been examined. As discussed in Part II, Chapter 6, Section 6, 1,2,3,7,8-PCDD; 1,2,3,4,6,7,8-HpCDD; 2,3,4,7,8-PCDF; 1,2,3,4,7,8-HCDF; PCB126; and PCB105 all promote the development of AHF within rodent liver, suggesting that they, like TCDD, are tumor promoters. (For a summary of positive tumor-promotion studies for PCDDs and PCDFs in rats, see Part II, Chapter 6, Table 6-5). In addition, complex mixtures of dioxins and furans and commercial PCB mixtures act as promoters of liver AHF. For the five principle dioxins, furans, and coplanar PCBs that comprise approximately 80% of the current, total dioxin/furan/PCB TEQ in human blood, all are positive in either rodent bioassays or rodent liver tumor-promotion studies or mouse skin tumor-promotion studies. Although the majority of dioxin-like congeners have not been tested for carcinogenicity in chronic rodent bioassays, these data suggest that it is likely that those individual congeners and mixtures of dioxin-like compounds that comprise the majority of the dioxin-like activity in human tissues are likely to be carcinogenic to rodents.

van den Berg et al. (2000) present a summary of the data (their Table 1) relied on by WHO's European Centre for Environment and Health (WHO-ECEH) and IPCS in their joint

consensus re-evaluation of the TEFs for PCDDs, PCDFs, and dioxin-like PCBs for mammals. These TEFs were derived using a tiered approach in which in vivo toxicity data were given more weight than in vitro data, toxicity more than biochemical endpoints, and chronic more than acute data. Table 2-4 summarizes the tumor incidence and promotion data that were cited in the development of these $TEFs_{DFP}$-WHO_{98}. The data presented are for those congeners that are principal contributors to the background body burden of dioxin TEQs in the United States (see Part I, Chapter 3). For 1,2,3,7,8-PeCDF and 2,3,4,7,8-PeCDF, the TEF was used to adjust the dose from the studies by Waern et al. (1991), and for PCB 126 similar dose adjustments are included from Hemming et al. (1995; their Fig. 4). For the comparison of TCDD to the HxCDDs, the primary TCDD data points from the Kociba et al. (1978) bioassay were graphed for both the original tumor count data and for the revised tumor counts from Goodman and Sauer (1992). This presentation of both the original and the revised tumor counts for TCDD reflects the contemporaneous performance and analysis of the HxCDD and TCDD bioassays and pathology and the recognition that the HxCDD pathology has not been re-analyzed.

Table 2-3 illustrates the comparability of the TCDD and other congener data sets based on TEFs. This analysis also demonstrates that the development of the TEFs for all of the congeners that contribute substantially to the background dioxin TEQ appropriately reflect either cancer bioassay or tumor promotion data. Furthermore, when one considers the impact of current TEF values on compounds that made up the majority of the TEQ prior to 1990, it is clear that more than 80% of the TEQ for either dioxins/furans or PCBs was made up of compounds for which the current TEF is supported by data on relative potencies which included tumor promotion or carcinogenic endpoints. This point is illustrated in Part II, Chapter 6, Table 6-10.

2.2.1.3. *Plausible Mode(s) of Carcinogenic Action*

Several potential mechanisms for TCDD carcinogenicity are discussed above and in Part II, Chapter 6, Section 6.4. These include oxidative stress, indirect DNA damage, endocrine disruption/growth dysregulation/altered signal transduction, and cell replication/apoptosis leading to tumor promotion. All of these mechanisms are biologically plausible as contributors to the carcinogenic process in humans, and none are mutually exclusive. Several biologically based models that encompass many of these activities are described in Part II, Chapter 8, Section 8.4. Further work is needed to elucidate a detailed mechanistic model for any particular carcinogenic response in animals or in humans; however, plausible modes of action with probable relevance to human carcinogenicity are discussed below.

TCDD is a potent tumor promoter in rat and mouse liver and in initiated human skin cells. In general terms, it is believed that cancer is likely due to the clonal expansion of damaged

cells that have a heritable genetic defect. Increased growth and accumulation of damage in critical genes ultimately aid in the progression into tumors. Consequently, promotion of carcinogenesis by TCDD may occur at several steps: (1) increased formation of initiated/susceptible cells through DNA mutation and/or increase rate of fixation of damaged DNA into the genome, (2) reduced loss of initiated cells through a suppression of apoptosis, (3) increase in growth rate and clonal expansion of initiated cells, and (4) accumulation of DNA damage in critical genes resulting in the progression of clonally expanded cell populations into tumors. Within this framework, it is hypothesized that TCDD may be acting as a tumor promoter through multiple mechanisms. Primarily, the activation of the AhR leads to alteration in genes that are involved in normal cell growth and differentiation pathways.

TCDD may contribute to the formation and accumulation of DNA damage via an indirect mechanism involving the production of reactive oxygen species. These reactive oxygen species may be formed as a result of autooxidation during futile metabolism of TCDD by the induction of CYP1 enzymes or via the CYP1-dependent production of estrogen metabolites capable of redox cycling. The clonal expansion of these damaged cells by TCDD and related chemicals is likely to occur through the altered expression and activity of a number of genes that regulate the cell-cycle. Activation of the AhR by TCDD results in altered expression or activity of the EGF receptor, retinoblastoma protein, TGF-beta, and many others. These proteins all regulate the cell cycle, and alterations of these proteins would alter cell growth properties.

The contribution of these two pathways in the carcinogenic actions of TCDD remains uncertain. However, Portier et al. (1996) have proposed a model in which the contribution of TCDD to the number of DNA damaged or initiated cells plays a significant role in its carcinogenic response. In contrast, Conolly and Andersen (1997) have proposed a tumor promotion model based on a negative selection mechanism in which the actions of TCDD are focused on its ability to alter cell growth properties. Descriptions of these models are provided in Part II, Chapter 8. Interestingly, the use of the model by Portier and colleagues leads to a result that is consistent with low-dose linearity, whereas the Andersen and Conolly model predicts highly nonlinear dose response relationships in the low-dose region. Presently, the available data do not allow for adequate discrimination between these two models.

TCDD causes a dose-related increase in thyroid follicular cell adenomas and carcinomas in rats and mice. One hypothesis for the induction of thyroid tumors involves the disruption of thyroid hormone homeostasis via the induction of the phase II enzymes UDP-glucuronosyltransferases (UGTs) (Hurley, 1998; Hill et al., 1998). Dioxin-like compounds induce the synthesis of UDP-glucuronosyltransferase-1 (UGT1) mRNA by an AhR-dependent transcriptional mechanism (Bock et al., 1998; Nebert et al., 1990). It is proposed that dioxin-like

chemicals increase the incidence of thyroid tumors through an extrathyroidal mechanism. Dioxin-like chemicals induce hepatic UGT, resulting in increased conjugation and elimination of thyroxine (T4) and leading to reduced serum T4 concentrations. T4 production is controlled by thyroid stimulating hormone (TSH), which is under negative and positive regulation from the hypothalamus, pituitary, and thyroid by thyrotrophin releasing hormone (TRH), TSH itself, thyroxine (T4), and triiodothyronine (T3). Consequently, the reduced serum T4 concentrations would lead to a decrease in the negative feedback inhibition on the pituitary gland. This would then lead to a rise in secreted TSH and stimulation of the thyroid. The persistent induction of UGT by dioxins and subsequent prolonged stimulation of the thyroid would result in thyroid follicular cell hyperplasia and hypertrophy of the thyroid, thereby increasing the risk of progression to neoplasia.

In support of this hypothesis, Kohn et al. (1996) modeled the effect of 2,3,7,8-TCDD on UGTs and thyroid hormones in female rats within the framework of a PBPK model. This mathematical model described release and uptake of thyroid hormones, metabolism, 2,3,7,8-TCDD induction of UGT1, regulation of TSH release from the pituitary by T4, and feedback on TRH and somatostatin, which inhibits TSH release. The model successfully reproduced the observed effects of 2,3,7,8-TCDD on serum T3, T4, and TSH and UGT1 mRNA and enzyme activity, suggesting that this is a plausible mechanism for an indirect role of 2,3,7,8-TCDD on the thyroid. This model is supported by the more recent experimental work of Schuur et al. (1997), which demonstrated the extrathyroidal effects of 2,3,7,8-TCDD on thyroid hormone turnover.

Although this discussion illustrates that there is no defined molecular mechanism leading to cancer in either liver or thyroid, it does demonstrate the concept of "mode of action" as defined in the Agency's proposed cancer guidelines (U.S. EPA, 1996, 1999, 2003). In each case, critical "key events" that correlate with carcinogenicity can be identified and measured, and these same events occur in both animals and humans. Although these relationships and linkages remain to be detailed, they form plausible, testable hypotheses whose acceptance by the scientific community is growing.

Despite this lack of a defined mechanism at the molecular level, there is a consensus that 2,3,7,8-TCDD and related compounds are receptor-mediated carcinogens in that (1) interaction with the AhR is a necessary early event; (2) 2,3,7,8-TCDD modifies a number of receptor and hormone systems involved in cell growth and differentiation, such as the EGFR and estrogen receptor; and (3) sex hormones exert a profound influence on the carcinogenic action of 2,3,7,8-TCDD.

2.2.1.4. *Other Data Related to Carcinogenesis*

Despite the relatively large number of bioassays on 2,3,7,8-TCDD, those by Kociba et al. (1978) and NTP (1982a), because of their multiple dose groups and wide dose range, continue to be the focus of dose-response modeling efforts and of additional review. Goodman and Sauer (1992) reported a re-evaluation of the female rat liver tumors in the Kociba study using the latest pathology criteria for such lesions. The review confirmed only approximately one-third of the tumors of the previous review (Squire, 1980). Although this finding did not change the determination of carcinogenic hazard—as 2,3,7,8-TCDD induced tumors in multiple sites in this study—it did have an effect on evaluation of dose-response and on estimates of risk at low doses. These issues are discussed in a later section of this document.

One of the more intriguing findings in the Kociba bioassay was reduced tumor incidences of the pituitary, uterus, mammary gland, pancreas, and adrenals in exposed female rats as compared to controls. Although this finding, coupled with evaluation of epidemiologic data, has led some authors to conclude that dioxin possesses "anticarcinogenic" activity (Kayajanian, 1997, 1999), it should be noted that in the Kociba study, the decreased incidence of tumors, with the exception of mammary gland tumors, is associated with significant weight loss in these rats. Examination of the data from NTP also demonstrates a significant decrease in these tumor types when there is a concomitant weight loss in the rodents, regardless of the chemical administered (Haseman and Johnson, 1996). It is also worth noting that the decrease in mammary tumors was only observed in one of seventeen rodent carcinogenesis studies, and was not observed in the recent NTP studies on TCDD, PCB 126, and 2,3,4,7,8-PeCDF (NTP, 2003 a-d).

As discussed in Section 3.2.3, under certain circumstances exposure to 2,3,7,8-TCDD may elicit beneficial effects. For example, 2,3,7,8-TCDD protects against the subsequent carcinogenic effects of polycyclic aromatic hydrocarbons (PAHs) in mouse skin, possibly reflecting induction of detoxifying enzymes (Cohen et al., 1979; DiGiovanni et al., 1980). In other situations, 2,3,7,8-TCDD-induced changes in estrogen metabolism may alter the growth of hormone-dependent tumor cells, producing a potential anticarcinogenic effect (Spink et al., 1990; Gierthy et al., 1993). While TCDD has been shown to inhibit the growth of certain breast cancer cell lines, Warner et al. (2002) have demonstrated an increase in breast cancer in highly exposed women from Seveso. Because the mechanism of the decreases in the tumor cells is unknown, extrapolation of these effects to humans is premature.

In considering overall risk, one must take into account factors such as the range of doses to target organs and hormonal state to obtain a complete picture of hazard and risk. Although exposure to dioxins may influence cancer response directly or indirectly and positively or negatively, it is unlikely that such data will be available to argue that dioxin exposure provides a

net benefit to human health. It is also important to note that the doses at which the incidence of certain tumors may decrease is in the same range at which adverse noncancer effects occur (see Appendix A).

2.2.1.5. *Cancer Hazard Characterization*

TCDD, CDDs, CDFs, and dioxin-like PCBs are a class of well-studied compounds whose human cancer potential is supported by a large database, including "limited" epidemiological support, unequivocal animal carcinogenesis, and biologic plausibility based on mode of action data. In 1985, EPA classified 2,3,7,8-TCDD and related compounds as "probable" human carcinogens, based on the available data. During the intervening years, the database relating to the carcinogenicity of dioxin and related compounds has grown and strengthened considerably. In addition, EPA guidance for carcinogen risk assessment has evolved (U.S. EPA, 1996, 1999, 2003). Under EPA's current approach, complex mixtures of dioxin and related compounds are considered "likely to be carcinogenic to humans," as are individual dioxin-like congeners other than TCDD. This descriptor is based primarily on the concept of toxic equivalency but also on the data available to support this characterization for individual congeners. Positive lifetime bioassays are available for a number of the principal congeners contributing to human TEQ body burden, specifically TCDD, 2,3,4,7,8-PeCDF, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, and PCB 126 (Kociba et al., 1978; NTP, 1980; NTP, 2003 a-d).

2,3,7,8-TCDD is best characterized as "carcinogenic to humans." This means that, based on the weight of all of the evidence (human, animal, mode of action), 2,3,7,8-TCDD meets the stringent criteria that allows EPA and the scientific community to accept a causal relationship between exposure and cancer hazard. The guidance (see EPA, 2003, section 2.6) suggests that "carcinogenic to humans" is an appropriate descriptor of carcinogenic potential when there is an absence of conclusive epidemiologic evidence to clearly establish a cause-and-effect relationship between human exposure and cancer but there is compelling carcinogenicity data in animals and mechanistic information in animals and humans demonstrating similar modes of carcinogenic action.

The "carcinogenic to humans" descriptor is suggested for 2,3,7,8-TCDD because *all* of the following conditions are met:

- Occupational epidemiologic studies all show an association between 2,3,7,8-TCDD exposure and increases in the all-cancers-combined category, in lung cancer, and perhaps in cancers at other sites, but the data are insufficient on their own to demonstrate a causal association.

- There is extensive carcinogenicity in both sexes of multiple species of animals at multiple sites.

- There is general agreement that the mode of 2,3,7,8-TCDD's carcinogenicity is AhR dependent and proceeds through modification of the action of a number of receptor and hormone systems involved in cell growth and differentiation, such as the EGFR and estrogen receptors.

- The human AhR and the rodent AhR are similar in structure and function and, once transformed, both bind to the same DNA response elements, designated DRE's.

- Human and rodent tissue and organ cultures respond to TCDD and related chemicals in a similar manner and at similar concentrations.

Other dioxin-like compounds are characterized as "likely to be carcinogenic to humans," primarily because of the lack of epidemiological evidence associated with their carcinogenicity, although there is a strong inference based on toxic equivalency that they would behave in humans as 2,3,7,8-TCDD does. Each of the congeners that contributes substantially to human body burden has been evaluated in vivo in cancer bioassays or tumor promotion assays. Each has a large database demonstrating AhR-mediated dioxin-like activities. Each has physico-chemical properties that contribute to their persistence. For each congener, the degree of certainty of carcinogenic hazard is dependent on the available congener-specific data and its consistency with the generalized mode of action that underpins toxic equivalency for 2,3,7,8-TCDD and related compounds. For the congeners most frequently encountered in human blood, milk, and adipose tissue, the database in support of 2,3,7,8-TCDD-like carcinogenic hazard is strong; those with weaker data supporting 2,3,7,8-TCDD-like carcinogenicity contribute relatively little to total TEQ.

On the basis of this logic, all complex environmental mixtures of 2,3,7,8-TCDD and dioxin-like compounds would be characterized as "likely" carcinogens, but the degree of certainty of the cancer hazard would be dependent on the major constituents of the mixture. For instance, the hazard potential, although still considered "likely," would be characterized differently for a mixture whose TEQ was dominated by octachlorodibenzo-*p*-dioxin as compared to one dominated by other PCDDs.

2.2.2. Reproductive and Developmental Effects

Several sections of this reassessment (Part II, Chapter 5 and Chapter 7b) have focused on the variety of effects that dioxin and dioxin-like agents can have on human reproductive health and development. The emphasis in each of these chapters has been on the discussion of the more recent reports of the impact of dioxin-like compounds on reproduction and development. These reports have been put into context with previous reviews of the literature applicable in risk assessment (Hatch, 1984; Sweeney, 1994; Kimmel, 1988) to develop a profile of the potential for dioxin and dioxin-like agents to cause reproductive or developmental toxicity, based on the available literature. An earlier version of the literature review and discussion contained in Part II, Chapter 5, has been previously published (Peterson et al., 1993).

The origin of concerns regarding a potential link between exposure to chlorinated dioxins and adverse developmental events can be traced to early animal studies reporting increased incidence of developmental abnormalities in rats and mice exposed early in gestation to 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (Courtney and Moore, 1971). 2,4,5-T is a herbicide that contains dioxin and related compounds as impurities. Its use was banned in the late 1970s, but exposure to human populations continued as a result of past production, use, and disposal.

2.2.2.1. *Human Effects*

The literature base with regard to potential human effects is detailed in Part II, Chapter 7b, Section 7.13. In general, there is limited epidemiological evidence to make a direct association between exposure to TCDD or other dioxin-like compounds and effects on human reproduction or development. One effect that may illustrate this relationship is the altered sex ratio (increased females) seen in the 6 years after the Seveso, Italy, accident (Mocarelli et al., 1996, 2000), and in a heavily exposed occupational cohort in Russia (Ryan et al., 2002). Particularly intriguing in these evaluations is the observation that exposure before and during puberty is linked to this sex ratio effect, and predominantly through the paternal side. Other sites have been examined for the effect of TCDD exposure on sex ratio with mixed results but with smaller numbers of offspring. Data on these sites are still preliminary, but effects similar to the Seveso findings are being reported. Continued evaluation of the Seveso population may provide other indications of impacts on reproduction and development but, for now, such data are limited and further research is needed.

Positive human data on developmental effects of dioxin-like compounds are limited to a few studies of populations exposed to a complex mixture of potentially toxic compounds (e.g., developmental studies from the Netherlands and effects of ingestion of contaminated rice oil in Japan [Yusho] and Taiwan [Yu-Cheng]). In the latter studies, however, all four manifestations

of developmental toxicity (reduced viability, structural alterations, growth retardation, and functional alterations) were observed to some degree following exposure to dioxin-like compounds as well as other agents. Data from the Dutch cohort of children exposed to PCBs and dioxin-like compounds (Huisman et al., 1995a, b; Koopman-Esseboom et al., 1994a-c; 1995a, b, 1996; Pluim et al., 1992, 1993, 1994; Weisglas-Kuperus et al., 1995; Patandin et al., 1998, 1999; ten Tusscher et al., 2003; Vreugdenhil et al., 2002) suggest impacts of background levels of dioxin and related compounds on neurobehavioral outcomes, thyroid function, immune function, and liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Although these effects cannot be attributed solely to dioxin and related compounds, several associations suggest that these are, in fact, likely to be AhR-mediated effects. Similarly, it is highly likely that the developmental effects in human infants exposed to a complex mixture of PCBs, PCDFs, and polychlorinated quaterphenyls (PCQs) in the Yusho and Yu-Cheng poisoning episodes may have been caused by the combined exposure to those PCB and PCDF congeners that are AhR agonists (Lü and Wong, 1984; Kuratsune, 1989; Rogan, 1989). However, it is not possible to determine the relative contributions of individual chemicals to the observed effects.

The incidents at Yusho and Yu-Cheng resulted in increased perinatal mortality and low birth weight in infants born to women who had been exposed. Rocker bottom heal was observed in Yusho infants, and functional abnormalities have been reported in Yu-Cheng children. Not all the effects that were seen are attributable only to dioxin-like compounds. The similarity of effects observed in human infants prenatally exposed to this complex mixture with those reported in adult monkeys exposed only to TCDD suggests that at least some of the effects in the Yusho and Yu-Cheng children are due to the TCDD-like congeners in the contaminated rice oil ingested by the mothers of these children. The similar responses include a clustering of effects in organs derived from the ectodermal germ layer, referred to as ectodermal dysplasia, including effects on the skin, nails, and Meibomian glands and developmental and psychomotor delay during developmental and cognitive tests (Chen et al., 1992). Some investigators believe that because some of the effects in the Yusho and Yu-Cheng cohorts do not correlate with TEQ, such effects could be exclusively due to nondioxin-like PCBs or to an interaction between the dioxins and the nondioxin-like congeners.

Of particular interest is the common developmental origin (ectodermal layer) of many of the organs and tissues that are affected in humans. An ectodermal dysplasia syndrome involving hyperpigmentation, deformation of the fingernails and toenails, conjunctivitis, gingival hyperplasia, and abnormalities of the teeth has been clearly associated with the Yusho and Yu-Cheng episodes, and in the non-human primate studies. Alaluusua et al. (1996, 1999)

investigated dioxin exposure and tooth development in Finnish children as a result of studies of dental effects in dioxin-exposed rats, mice, and nonhuman primates (Part II, Chapter 5, Section 5.2) and in PCB-exposed children (Rogan et al., 1988). The Finnish investigators examined enamel hypomineralization of permanent first molars in 6–7-year-old children. The length of time that infants breast-fed was not significantly associated with either mineralization changes or with TEQ levels in the breast milk. However, when the levels and length of breast-feeding were combined in an overall score, a statistically significant association was observed (r= 0.3, p=0.003, regression analysis). These data are discussed further in Part II, Chapter 7b, Section 7.13. Follow-up mechanistic studies on tooth development in TCDD sensitive and resistant rats revealed a relatively high dose impact on epithelial-mesenchymal interactions, particularly the mesenchymal odontocytes. This effect that was not associated with differential resistance to acute TCDD toxicity (Kiukkonen et al., 2002).

Other investigations into noncancer effects of human exposure to dioxin have provided human data on TCDD-induced changes in circulating reproductive hormones. This was one of the effects judged as having a positive relationship with exposure to TCDD in Part II, Chapter 7b, Section 7.13. Levels of reproductive hormones have been measured with respect to exposure to 2,3,7,8-TCDD in three cross-sectional medical studies. Testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured in trichlorophenol (TCP) and 2,4,5-T production workers from the NIOSH cohort (Egeland et al., 1994), in Army Vietnam veterans (CDC Vietnam Experience Study, 1988), and in Air Force Ranch Hands, who handled and/or sprayed Agent Orange during the Vietnam War (Roegner et al., 1991; Grubbs et al., 1995). A recent study also demonstrated an inverse correlation between TCDD levels and prolactin in 2,4,5,-T herbicide sprayers (Johnson et al., 2001). Alterations in breast development have been reported in young women, where a doubling of the serum dioxin concentration (CALUX assay) increased the odds of not having reached the adult stage of breast development by 2.3 fold (P<0.02) in the women (~17 yo) studied (Den Hond et al., 2002). Alterations in menstrual duration and flow have been reported in women exposed as premenarcheal girls 20 years previously as a result of the Seveso incident (Eskenazi et al., 2002a).

The risk of abnormally low testosterone was two to four times higher in exposed workers who had serum 2,3,7,8-TCDD levels above 20 ng/g than in unexposed referents (Egeland et al., 1994). In both the 1987 and 1992 examinations, mean testosterone concentrations were slightly but not significantly higher in Ranch Hands (Thomas et al., 1990; Grubbs et al., 1995). FSH and LH concentrations were no different between the exposed and comparison groups. No significant associations were found between Vietnam experience and altered reproductive

hormone levels (CDC Vietnam Experience Study, 1988). Only the NIOSH study (Egeland et al., 1994) found an association between serum 2,3,7,8-TCDD level and increases in serum LH.

The findings of the NIOSH and Ranch Hand studies are plausible, given the pharmacological and toxicological properties of 2,3,7,8-TCDD in animal models, which are discussed in Part II, Chapters 5 and 7. One plausible mechanism responsible for the effects of dioxins may involve their ability to influence hormone receptors. The AhR, to which 2,3,7,8-TCDD binds, and the hormone receptors are signaling pathways that regulate homoeostatic processes. These signaling pathways are integrated at the cellular level, and there is considerable "cross-talk" between these pathways. For example, studies suggest that 2,3,7,8-TCDD modulates the concentrations of numerous hormones and/or their receptors, including estrogen (Romkes and Safe, 1988; Romkes et al., 1987), progesterone (Romkes et al., 1987), glucocorticoid (Ryan et al., 1989), and thyroid hormones (Gorski and Rozman, 1987; Pavuk et al., 2003).

In summary, the results from both the NIOSH and the Ranch Hand studies are limited by the cross-sectional nature of the data and the type of clinical assessments conducted. However, the available data provide evidence that small alterations in human male reproductive hormone levels are associated with serum 2,3,7,8-TCDD.

2.2.2.2. *Experimental Animal Effects*

The extensive experimental animal database with respect to reproductive and developmental toxicity of dioxin and dioxin-related agents is discussed in Part II, Chapter 5. Dioxin exposure has been observed to result in both male and female reproductive effects as well as developmental effects. These latter effects are among the most responsive health endpoints to dioxin exposure (see Part II, Chapter 8, Section 8.3). In general, the prenatal and developing postnatal animal is more sensitive to the effects of dioxin than is the adult. In several instances (e.g., fetotoxicity in hamsters, rats, mice, and guinea pigs), the large species differences seen in acute toxicity are greatly reduced when developing animals are evaluated. Most of the data reviewed are from studies of six genera of laboratory animals. Although much of the data come from animals exposed only to TCDD, more recent studies of animals exposed to mixtures of PCDD/PCDF/ PCB congeners provide results that are consistent with the studies of TCDD alone.

2.2.2.2.1. *Developmental toxicity.* Dioxin exposure results in a wide variety of developmental effects; these are observed in three different vertebrate classes and in several species within each class. All four of the manifestations of developmental toxicity have been observed following

exposure to dioxin: reduced viability, structural alterations, growth retardation, and functional alterations. As summarized previously (Peterson et al., 1993), increased prenatal mortality (rat and monkey), functional alterations in learning (rat, mouse, and monkey) and sexual behavior (rat), and changes in the development of the reproductive system (rat, hamster, and mouse) occur at the lowest exposure levels tested (see also Part II, Chapter 8, Section 8.3).

Dioxin exposure has resulted in reduced prenatal or postnatal viability in virtually every species in which it has been tested. Previously, increased prenatal mortality appeared to be observed only at exposures that also resulted in maternal toxicity. However, the studies of Olson and McGarrigle (1990) in the hamster and Schantz and Bowman (1989) in the monkey suggested that this was not the case in all species. Although the data from these two studies were limited, prenatal death was observed in cases where no maternal toxicity was evident. In the rat, Peterson's laboratory (Bjerke et al., 1994a, b; Roman et al., 1995) reported increased prenatal death following a single exposure to TCDD during gestation that did not cause maternal toxicity, and Gray et al. (1995a) observed a decrease in postnatal survival under a similar exposure regimen. Although identifying the presence or absence of maternal toxicity may be instructive as to the specific origin of the reduced prenatal viability, it does not alter the fact that pre- and postnatal deaths were observed. In either case, the Agency considers these effects as being indicators of developmental toxicity in response to the exposure (U.S. EPA, 1991b).

Some of the most striking findings regarding dioxin exposure relate to the effects on the developing reproductive system in laboratory animals. Only a single, low-level exposure to TCDD during gestation is required to initiate these developmental alterations. Mably et al. (1992a-c) originally reported that a single exposure of the Holtzman maternal rat to as little as 0.064 μg/kg could alter normal sexual development in the male offspring. A dose of 0.064 μg/kg in these studies resulted in a maximal body burden in the maternal animal of 64 ng/kg during critical windows in development. More recently, these findings of altered normal sexual development have been further defined (Bjerke et al., 1994a, b; Gray et al., 1995a; Roman et al., 1995) and extended to female offspring and other strains (Faqi et al., 1998; Ohsako et al., 2001) and species (hamsters and mice) (Gray et al., 1995b; Theobald et al., 1997). In general, the findings of these later studies have produced qualitatively similar results that define a significant effect of dioxin on the developing reproductive system.

In the developing male rat, TCDD exposure during the prenatal and lactational periods results in delay of the onset of puberty, as measured by age at preputial separation. There is a reduction in testis weight, sperm parameters, and sex accessory gland weights. In the mature male exposed during the prenatal and lactational periods, there is an alteration of normal sexual behavior and reproductive function. Males exposed to TCDD during gestation are

demasculinized. Feminization of male sexual behavior and a reduction in the number of implants in females mated with exposed males have also been reported, although these effects have not been consistently found. These effects do not appear to be related to reductions in circulating androgens, which were shown in the most recent studies to be unaffected by TCDD. Most of these effects have occurred in a dose-related fashion, some at doses of 0.05 μg/kg and 0.064 μg/kg, the lowest doses tested (Mably et al., 1992c; Gray et al., 1997a).

In Part II, Chapter 8, ED_{01} values were estimated from the Mably et al. (1992a-c) and Gray et al. (1997a) reports. In these two studies more than 44 data sets were modeled, and 17 of these data sets had body burden ED_{01}s lower than 50 ng/kg. For the 12 endpoints in the Mably et al. studies that were modeled in Part II, Chapter 8, the median body burden ED_{01} estimate is 5.2 ng TCDD/kg. Although not modeled in Part II, Chapter 8, the data from Faqi et al. (1998) and Ohsaka et al. (2001) have LOAELs and NOAELs for developmental reproductive effects of TCDD in male rats ranging from body burdens of 12.5–200 ng TCDD/kg, which is consistent with the Mably et al. and Gray et al. studies.

In the developing female rat, Gray and Ostby (1995) demonstrated altered sexual differentiation in both the Long Evans and Holtzman strains. The effects observed depended on the timing of exposure. Exposure during early organogenesis altered the cyclicity, reduced ovarian weight, and shortened the reproductive lifespan. Exposure later in organogenesis resulted in slightly lowered ovarian weight, structural alterations of the genitalia, and a slight delay in puberty. However, cyclicity and fertility were not affected with the later exposure. The most sensitive dose-dependent effects of TCDD in the female rat were the structural alterations of the genitalia that occurred at 0.20 μg TCDD/kg administered to the dam (Gray et al., 1997b).

As described above, studies demonstrating adverse health effects from prenatal exposures often involved a single dose administered at a discrete time during pregnancy. The production of prenatal effects at a given dose appears to require exposure during critical times in fetal development. This concept is well supported by a recent report (Hurst et al., 2000) that demonstrated the same incidence of adverse effects in rat pups born to dams with a single exposure of 0.2 μg TCDD/kg body weight on gestation day 15 versus 1.0 μg TCDD/kg body weight on gestation day 8. Both of these experimental exposure paradigms resulted in the same fetal tissue concentrations and body burdens during the critical window of sensitivity. For example, exposure to 0.2 μg TCDD/kg on day 15 resulted in 13.2 pg TCDD/g fetal tissue on day16; exposure to 1.0 μg TCDD/kg on day 8 resulted in 15.3 pg TCDD/g fetus on day 16. This study demonstrates the appropriateness of the use of body burden to describe the effects of TCDD when comparing different exposure regimens. The uncertainties introduced when trying to compare studies with steady-state body burdens with single-dose studies may make it difficult

to determine a lowest effective dose. Application of pharmacokinetic models (described in Parts I and II) to estimate body burdens at the critical time of development is expected to be a sound method for relating chronic background exposures to the results obtained from single-dose studies.

Structural malformations, particularly cleft palate and hydronephrosis, occur in mice administered TCDD. The findings, although not representative of the most sensitive developmental endpoints, indicate that exposure during the critical period of organogenesis can affect the processes involved in normal tissue formation. The TCDD-sensitive events appear to require the AhR. Mouse strains that produce AhRs with relatively high affinity for TCDD respond to lower doses than do strains with relatively low-affinity receptors. Moreover, congeners that have a greater affinity for the AhR are more developmentally toxic than those that have a lower affinity. This is consistent with the rank ordering of toxic potency based on affinity for the receptor, as discussed in Part II, Chapter 9, Section 9.3. In addition, mice in which the Ah receptor has been knocked out do not develop cleft palate.

Recent work, not elaborated upon here, has demonstrated that developmental exposure of rodents to dioxin also permanently alters the development of the prostate in wild type but not AhR null mutant mice (Lin et al., 2003), and mammary development in rats and mice (Fenton et al, 2002; Vorderstrasse et al., 2003). The key role of the Ah receptor has also been demonstrated in the developing heart of AhR null mice (Lund et al., 2003).

2.2.2.2.2. ***Adult female reproductive toxicity.*** The primary effects of TCDD on female reproduction in animals appear to be decreased fertility, inability to maintain pregnancy for the full gestational period, and, in the rat, decreased litter size. In some studies of rats and of primates, signs of ovarian dysfunction such as anovulation and suppression of the estrous cycle have been reported (Kociba et al., 1976; Barsotti et al., 1979; Allen et al., 1979; Li et al., 1995a, b). Although the majority of reproductive effects are associated with high-dose exposures in experimental animals, the induction of endometriosis in primates occurs at body burdens near background human exposures. This effect is discussed further below.

2.2.2.2.3. ***Adult male reproductive toxicity.*** TCDD and related compounds decrease testis and accessory sex organ weights, cause abnormal testicular morphology, decrease spermatogenesis, and reduce fertility when given to adult animals in doses sufficient to reduce feed intake and/or body weight. In the testes of these different species, TCDD effects on spermatogenesis are characterized by loss of germ cells, the appearance of degenerating spermatocytes and mature spermatozoa within the lumens of seminiferous tubules, and a reduction in the number of tubules

containing mature spermatozoa (Allen and Lalich, 1962; Allen and Carstens, 1967; McConnell et al., 1978; Chahoud et al., 1989). This suppression of spermatogenesis is not a highly sensitive effect when TCDD is administered to postweanling animals, as an exposure of 1 μg/kg/day over a period of weeks appears to be required to produce these effects.

2.2.2.3. ***Other Data Related to Developmental and Reproductive Effects***

2.2.2.3.1. ***Endometriosis.*** The association of dioxin with endometriosis was first reported in a study of rhesus monkeys that had been exposed for 4 years to dioxin in their feed and then held for an additional 10 years (Rier et al., 1993). There was a dose-related increase in both the incidence and severity of endometriosis in the exposed monkeys as compared to controls. Follow-up on this group of monkeys revealed a clear association with total TEQ. A study in which rhesus monkeys were exposed to PCBs for up to 6 years failed to show any enhanced incidence of endometriosis (Arnold et al., 1996). However, many of these monkeys were no longer cycling, and the time may not have been adequate to develop the response. In the TCDD monkey study, it took 7 years before the first case of endometriosis was noted (Rier et al., 1993).

A recent study in Cynomolgus monkeys showed promotion of surgically induced endometriosis by TCDD within 1 year after surgery (Yang et al., 2000). Studies using rodent models for surgically induced endometriosis have also shown the ability of TCDD to promote lesions in a dose-related manner (Cummings et al., 1996, 1999; Johnson et al., 1997; Bruner-Tran et al., 1999). This response takes at least 2 months to be detected (Cummings et al., 1996, 1999; Johnson et al., 1997). Another study in mice that failed to detect dioxin promotion of surgically induced endometriosis held the mice for only 1 month, not long enough to detect a response (Yang et al., 1997). Prenatal exposure of mice also enhanced the sensitivity of the offspring to the promotion of surgically induced endometriosis by TCDD (Cummings et al., 1999).

The effects of TCDD in the murine model of endometriosis appear to be AhR-mediated, as demonstrated in a study in which AhR ligands were able to promote the lesions, whereas non-AhR ligands, including a nondioxin-like PCB, had no effect on surgically induced endometriosis (Johnson et al., 1997). Dioxin has also been shown to result in endometriosis with human endometrial tissue implanted in nude mice (Bruner-Tran et al., 1999).

Data on the relationship of dioxins to endometriosis in humans is intriguing, but preliminary. Studies in the early 1990s suggested that women who had higher levels of persistent organochlorines were at increased risk for endometriosis (Gerhard and Runnebaum, 1992). This was followed by the observation that Belgian women, who have the highest levels of dioxins in their background population, had higher incidences of endometriosis than those reported from

other populations (Koninckx et al., 1994). A study from Israel then demonstrated that there was a correlation between detectable TCDD in women who had surgically confirmed endometriosis in comparison to those who had no endometriosis (Mayani et al., 1997).

Recent studies from Belgium indicate that women with higher body burdens, based on serum TEQ determinations, are at greater risk for endometriosis (Pauwels et al., 1999). No association was seen with total PCBs in this study. A small study in the United States that did not involve surgically confirmed endometriosis saw no association between TCDD and endometriosis (Boyd et al., 1995). Likewise, a study in Canada saw no association between total PCBs and endometriosis (Lebel et al., 1998). The lack of an association with total PCBs is not surprising, because the rodent studies have indicated that this response is AhR-mediated (Johnson et al., 1997). The Seveso Women's Health Study reported "...a doubled, non-significant risk for endometriosis among women with serum TCDD levels of 100 ppt or higher, but no clear dose-response. Unavoidable disease misclassification in a population-based study may have led to an underestimate of the true risk of endometriosis"(Eskenazi et al., 2002b).

The animal results lend biological plausibility to the epidemiology findings (Birnbaum and Cummings, 2002). Endometriosis is not only an endocrine disorder, it is also associated with immune system alterations (Rier et al., 1995; Rier and Foster, 2002). Dioxins are known to be potent modulators of the animal immune system and to affect estrogen homeostasis. Further studies are clearly needed to provide additional support to this association of endometriosis and dioxins, as well as to demonstrate causality.

2.2.2.3.2. ***Androgenic deficiency.*** The effects of TCDD on the male reproductive system when exposure occurs in adulthood are believed to be due in part to an androgenic deficiency. This deficiency is characterized in adult rats by decreased plasma testosterone and 5α-dihydrotestosterone concentrations, unaltered plasma LH concentrations, and unchanged plasma clearance of androgens and LH (Moore et al., 1985, 1989; Mebus et al., 1987; Moore and Peterson, 1988; Bookstaff et al., 1990a). The cause of the androgenic deficiency was believed to be due to decreased testicular responsiveness to LH and increased pituitary responsiveness to feedback inhibition by androgens and estrogens (Moore et al., 1989, 1991; Bookstaff et al., 1990a, b; Kleeman et al., 1990). The single dose used in some of those earlier studies (15 µg TCDD/kg body weight) is now known to affect Leydig cells (Johnson et al., 1994).

2.2.2.4. *Developmental and Reproductive Effects Hazard Characterization*

There is limited direct evidence addressing the issues of how or at what levels humans will begin to respond to dioxin-like compounds with adverse impacts on development or reproductive function. The series of published Dutch studies suggest that pre- and early postnatal exposures to PCBs and other dioxin-like compounds may impact developmental milestones at levels at or near current average human background exposures. Although it is unclear whether these measured responses indicate a clearly adverse impact, if humans respond to TCDD similarly to animals in laboratory studies, there are indications that exposures at relatively low levels might cause developmental effects and at higher levels might cause reproductive effects. There is especially good evidence for effects on the fetus from prenatal exposure. The Yusho and Yu-Cheng poisoning incidents are clear demonstrations that dioxin-like compounds can produce a variety of mild to severe developmental effects in humans that resemble the effects of exposure to dioxins and dioxin-like compounds in animals.

Humans do not appear to be particularly sensitive or insensitive to effects of dioxin exposure in comparison to other animals. Therefore, it is reasonable to assume that human responsiveness would lie across the middle ranges of observed responses. This assumption still does not address the issues surrounding the potentially different responses that humans (or animals) might have to the more complex and variable environmental mixtures of dioxin-like compounds. One additional key point is that most of the epidemiology studies have focused on TCDD, and not the total TEQ. Eskenazi et al. (2004) have shown that background exposure to dioxins, furans and PCBs in the referent population (zone non-ABR) cohort at Seveso was substantial,with non-ABR residents having average serum 2,3,7,8-TCDD and TEQ levels of 20.2 ppt and 100.4 ppt, respectively. The exposure zone A median serum TCDD level was 272 ppt and zone B was 47 ppt. The authors suggest that previous Seveso studies "that considered only TCDD exposure, may have underestimated health effects due to total TEQ concentrations."

TCDD and related compounds have reproductive and developmental toxicity potential in a broad range of wildlife and domestic and laboratory animals. Many of the effects have been shown to be TCDD dose-related. The effects on perinatal viability and male reproductive development are among the most sensitive effects reported, occurring at a single prenatal exposure range of as little as 0.05–0.075 μg/kg, resulting in calculated fetal tissue concentrations of 3–4 ng/kg in the rat (Hurst et al., 2000). In these studies, effects were often observed at the lowest exposure level tested, thus a NOAEL has not been established for several of these endpoints. In general, the structure-activity results are consistent with an AhR-mediated mechanism for the developmental effects that are observed in the low-dose range. The structure-activity relationship in laboratory mammals appears to be similar to that for AhR binding. This

is especially the case with cleft palate in the mouse, but has also been seen with hydronephrosis in the mouse, and developmental reproductive effects in rats.

It is assumed that the responses observed in animal studies are indicative of the potential for reproductive and developmental toxicity in humans. This is an established assumption in the risk assessment process for developmental toxicity (U.S. EPA, 1991b). It is supported by the number of animal species and strains in which effects have been observed. The limited human data are consistent with an effect following exposure to TCDD or TCDD-like agents. In addition, the phylogenetic conservation of the structure and function of the AhR also increases our confidence that these effects may occur in humans.

There is extensive evidence in experimental animals (mice, rats, monkeys) that exposure to dioxin-like chemicals during development produces neurobehavioral effects. In fact, recent studies in rodents demonstrate effects on brain development (Zareba et al., 2002), attention (Markowski et al., 2002), and behavior (Hojo et al., 2002) at doses close to current human body burdens. The situation in humans is more complex. Studies in humans demonstrate associations between dioxin exposure and alterations in neurological development. These same studies often show similar associations between exposure to nondioxin-like PCBs and these same effects. On the basis of the human studies, it is possible that the alterations in neurological development are due to an interaction between the dioxins and the nondioxin-like PCBs. At present there are limited data that define the roles of the dioxins versus the nondioxin-like PCBs in these effects on neurological development.

In general, the structure-activity results on dioxin-like compounds are consistent with an AhR-mediated mechanism for many of the developmental effects that are observed. The structure-activity relationship in laboratory mammals appears to be similar to that for AhR binding. This is especially the case with teratogenesis in the mouse. However, a direct relationship with AhR binding has not yet been proven for those involving the developing nervous system.

2.2.3. Immunotoxicity

2.2.3.1. *Epidemiologic Findings*

The available epidemiologic studies on immunologic function in humans relative to exposure to 2,3,7,8-TCDD do not describe a consistent pattern of effects among the examined populations. Two studies of German workers in which one cohort was exposed to 2,3,7,8-TCDD (Ott et al., 1994), and the other to 2,3,7,8-tetrabrominated dioxin and furan (Zober et al., 1992), found dose-related increases of complements C3 or C4, whereas the Ranch Hands have continued to exhibit elevations in immunoglobulin A (IgA) (Roegner et al., 1991; Grubbs et al.,

1995). Other studies of groups with documented exposure to 2,3,7,8-TCDD have not examined complement components to any great extent or observed significant changes in IgA. Suggestions of immunological disturbances have been observed in a small group of exposed workers (Tonn et al., 1996) and in perinatally exposed children (ten Tusscher et al., 2003), providing support for a testable hypothesis to be evaluated in other exposed populations.

Comprehensive evaluation of immunologic status and function of the NIOSH (Halperin et al., 1998), Ranch Hand (Michalek et al., 1999b), and Hamburg chemical workers (Jung et al., 1998; Ernst et al., 1998) cohorts found no consistent differences between exposed and unexposed groups for lymphocyte subpopulations, response to mitogen stimulation, or rates of infection. However, recent data from the Seveso experience demonstrate subtle effects on immune function (Baccarelli et al., 2002).

More comprehensive evaluations of immunologic function with respect to exposure to 2,3,7,8-TCDD and related compounds are necessary to assess more definitively the relationships observed in nonhuman species. Longitudinal studies of the maturing human immune system may provide the greatest insight, particularly because animal studies have found significant results in immature animals, and human breast milk is a source of 2,3,7,8-TCDD and other related compounds. The studies of Dutch infants (ten Tusscher et al., 2003) described earlier provide an example of such a study design. Additional studies of highly exposed adults may also shed light on the effects of long-term chronic exposures through elevated body burdens. Therefore, there appears to be too little information to suggest definitively that 2,3,7,8-TCDD, at the levels observed, causes long-term adverse effects on the immune system in adult humans.

2.2.3.2. *Animal Findings*

Cumulative evidence from a number of studies indicates that the immune system of various animal species is a target for toxicity of TCDD and structurally related compounds, including other PCDDs, PCDFs, and PCBs. Both cell-mediated and humoral immune responses are suppressed following TCDD exposure, suggesting that there are multiple cellular targets within the immune system that are altered by TCDD. Evidence also suggests that the immune system is indirectly targeted by TCDD-induced changes in nonlymphoid tissues. TCDD exposure of experimental animals results in decreased host resistance following challenge with certain infectious agents, which likely result from TCDD-induced suppression of immunological functions.

The primary antibody response to the T cell-dependent antigen, sheep red blood cells (SRBCs), is the most sensitive immunological response that is consistently suppressed in mice exposed to TCDD and related compounds. The degree of immunosuppression is related to the

potency of the dioxin-like congeners. There is remarkable agreement among several different laboratories for the potency of a single acute dose of TCDD (i.e., suppression at a dose as low as 0.1 μg TCDD/kg with an average 50% immunosupressive dose [ID_{50}] value of approximately 0.7 μg TCDD/kg) to suppress this response in Ah-responsive mice. Results of studies that have compared the effects of acute exposure to individual PCDDs, PCDFs, and PCB congeners (which differ in their binding affinity for the AhR) on this response have provided critical evidence that certain dioxin-like congeners are also immunosuppressive. The degree of immunosuppression has been found to be related to potency of the dioxin-like congeners. Antibody responses to T cell-independent antigens such as trinitrophenyl-lipopolysaccharide and the cytotoxic T lymphocyte (CTL) response are also suppressed by a single acute exposure to TCDD, albeit at higher doses than those that suppress the SRBC response. Although a thorough and systematic evaluation of the immunotoxicity of TCDD-like congeners in different species and for different immunological endpoints has not been performed, it can be inferred from the available data that dioxin-like congeners are immunosuppressive.

Perinatal exposure of experimental animals to TCDD results in suppression of primarily T cell immune functions, with suppression persisting into adulthood. In mice, the effects on T cell functions appear to be related to the fact that perinatal TCDD exposure alters thymic precursor stem cells in the fetal liver and bone marrow and thymocyte differentiation in the thymus. These studies suggest that perinatal development is a critical and sensitive period for TCDD-induced immunotoxicity. Further efforts should be made to determine the consequences of perinatal exposure to TCDD and related compounds and mixtures on immune system integrity.

2.2.3.3. *Other Data Related to Immunologic Effects*

In addition to the TCDD-like congener results, studies using strains of mice that differ in the expression of the AhR have provided critical evidence to support a role for Ah-mediated immune suppression following exposure to dioxin-like compounds. Recent in vitro work also supports a role for Ah-mediated immune suppression. Other in vivo and in vitro data, however, suggest that non-Ah-mediated mechanisms may also play some role in immunotoxicity induced by dioxin-like compounds. However, more definitive evidence remains to be developed to support this latter view.

The immunosuppressive potency of individual dioxin-like compounds in mice is related to their structural similarity to TCDD. However, the immunotoxicity of TCDD and related congeners can be modified by co-exposure to nondioxin-like PCBs in simple binary or more complex mixtures, resulting in additive or antagonistic interactions. There is a need for the

generation of dose-response data of acute, subchronic, and chronic exposure to the individual congeners in a mixture and for the mixture itself in order to fully evaluate potential synergistic, additive, or antagonistic effects of environmentally relevant mixtures. A preliminary report demonstrating that the immunotoxicity of a food-like mixture of dioxins was well-predicted by the TEQ has been presented (Smialowicz et al., 1997).

Animal host resistance models that mimic human disease have been used to assess the effects of TCDD on altered host susceptibility. TCDD exposure increases susceptibility to challenge with bacteria, viruses, parasites, and tumors. Mortality is increased in TCDD-exposed mice challenged with certain bacteria. Increased parasitemia occurs in TCDD-exposed mice and rats challenged with parasitic infections. Low doses of TCDD also alter resistance to virus infections in rodents. Increased susceptibility to infectious agents is an important benchmark of immunosuppression; however, the role that TCDD plays in altering immune-mediated mechanisms important in murine resistance to infectious agents remains to be elucidated. Also, because little is known about the effects that dioxin-like congeners have on host resistance, more research is recommended in this area.

Studies in nonhuman primates exposed acutely, subchronically, or chronically to halogenated aromatic hydrocarbons (HAH) have revealed variable alterations in lymphocyte subpopulations, primarily T lymphocyte subsets. In three separate studies in which monkeys were exposed subchronically or chronically to PCBs, the antibody response to SRBC was consistently found to be suppressed. These results in nonhuman primates are important because they corroborate the extensive database of HAH-induced suppression of the antibody response to SRBC in mice and thereby provide credible evidence for immunosuppression by HAHs across species. In addition, these data indicate that the primary antibody response to this T cell-dependent antigen is the most consistent and sensitive indicator of HAH-induced immunosuppression.

The available database derived from well-controlled animal studies on TCDD immunotoxicity can be used for the establishment of NOELs. As the antibody response to SRBCs has been shown to be dose-dependently suppressed by TCDD and related dioxin-like compounds, this database is best suited for the development of dose-response modeling.

2.2.3.4. *Immunologic Effects Hazard Characterization*

Accidental or occupational exposure of humans to TCDD and/or related compounds variably affects a number of immunological parameters. Unfortunately, the evaluation of immune system integrity in humans exposed to dioxin-like compounds has provided data that are inconsistent across studies. The broad range of “normal” responses in humans due to the large

amount of variability inherent in such a heterogenous population, the limited number and sensitivity of tests performed, and poor exposure characterization of the cohorts in these studies compromise any conclusions about the ability of a given study to detect immune alterations. Consequently, there are insufficient clinical data from these studies to fully assess human sensitivity to TCDD exposure. Nevertheless, based on the results of the extensive animal work, the database is sufficient to indicate that immune effects could occur in the human population from exposure to TCDD and related compounds at some dose level. At present, it is EPA's scientific judgment that TCDD and related compounds should be regarded as nonspecific immunosuppressants and immunotoxicants until better data to inform this judgment are available.

It is interesting that a common thread in several human studies is the observed reduction in $CD4^+$ T helper cells, albeit generally within the "normal" range, in cohorts exposed to dioxin-like compounds. Even though these reductions may not translate into clinical effects, it is important to note that these cells play an important role in regulating immune responses and that their reduction in clinical diseases is associated with immunosuppression. It is also important to realize that those at the extremes of the population distribution may be at special risk of such alterations. Another important consideration is that a primary antibody response following immunization was not evaluated in any of the human studies. Because this immune parameter has been revealed to be the most sensitive in animal studies, it is recommended that TCDD and related compounds be judged immunosupressive and that this parameter be included in future studies of human populations exposed to TCDD and related compounds. It is also recommended that research focused on delineating the mechanism(s) underlying dioxin-induced immunotoxicity and immunosuppression continue.

2.2.4. Chloracne

Chloracne and associated dermatologic changes are widely recognized responses to TCDD and other dioxin-like compounds in humans. Along with the reproductive hormones discussed above and gamma glutamyl transferase (GGT) levels, which are discussed below, chloracne is one of the noncancer effects that has a strong positive association with exposure to TCDD in humans (see Part II, Chapter 7b, Section 7.13). Chloracne is a severe acne-like condition that develops within months of first exposure to high levels of dioxin and related compounds. For many individuals, the condition disappears after discontinuation of exposure, despite initial serum levels of dioxin in the thousands of parts per trillion; for others, it may remain for many years. The duration of persistent chloracne is on the order of 25 years, although

cases of chloracne persisting for more than 40 years have been noted (see Part II, Chapter 7b, Section 7.13).

In general, chloracne has been observed in most incidents where substantial dioxin exposure has occurred, particularly among TCP production workers and Seveso residents (see Part II, Chapter 7b). The amount of exposure necessary for development of chloracne has not been resolved, but studies suggest that high exposure (both high acute and long-term exposure) to 2,3,7,8-TCDD increases the likelihood of chloracne, as evidenced by chloracne in TCP production workers and Seveso residents who had documented high serum 2,3,7,8-TCDD levels (Beck et al., 1989; Fingerhut et al., 1991a; Mocarelli et al., 1991; Neuberger et al., 1991) or in individuals who had a work history with long duration of exposure to 2,3,7,8-TCDD-contaminated chemicals (Bond et al., 1989).

In earlier studies, chloracne was considered to be a "hallmark of dioxin intoxication" (Suskind, 1985). However, in only two studies were risk estimates calculated for chloracne. Both were studies of different cohorts of TCP production workers, one of which was employed in a West Virginia plant (Suskind and Hertzberg, 1984), the other in a plant in Michigan (Bond et al., 1989). Of the 203 West Virginia workers, 52.7% ($p<0.001$) were found to have clinical evidence of chloracne, and 86.3% reported a history of chloracne ($p<0.001$). None of the unexposed workers had clinical evidence or reported a history of chloracne. Among the Michigan workers, the relative risk for cases of chloracne was highest for individuals with the longest duration of exposure ($\geq$ 60 months; RR = 3.5, 95% CI = 2.3–5.1), those with the highest cumulative dose of TCDD (based on duration of assignment across and within 2,3,7,8-TCDD-contaminated areas in the plant) (RR = 8.0, 95% CI = 4.2–15.3), and those with the highest intensity of 2,3,7,8-TCDD exposure (RR = 71.5, 95% CI = 32.1–159.2).

Studies in multiple animal species have been effective in describing the relationship between 2,3,7,8-TCDD and chloracne, particularly in rhesus monkeys (McNulty, 1977; Allen et al., 1977; McConnell et al., 1978). Subsequent to exposure to 2,3,7,8-TCDD, monkeys developed chloracne and swelling of the meibomian glands, the modified sebaceous glands in the eyelid. The histologic changes in the meibomian glands are physiologically similar to those observed in human chloracne (Dunagin, 1984).

In summary, the evidence provided by the various studies convincingly supports what is already presumed—that chloracne is a common sequel of high levels of exposure to 2,3,7,8-TCDD and related compounds. More information is needed to determine the level and frequency of exposure to dioxin-like compounds needed to cause chloracne and whether personal susceptibility plays a role in the etiology. Finally, it is important to recall that the absence of chloracne does not imply lack of exposure (Mocarelli et al., 1991).

2.2.5. Diabetes

Diabetes mellitus is a heterogeneous disorder that is a consequence of alterations in the number or function of pancreatic beta cells responsible for insulin secretion and carbohydrate metabolism. Diabetes and fasting serum glucose levels were evaluated in more recent cross-sectional medical studies because of the apparently high prevalence of diabetes and abnormal glucose tolerance tests in one case report of 55 TCP workers (Pazderova-Vejlupkova et al., 1981). Recent epidemiology studies, as well as early case reports, have indicated a weak association between serum concentrations of dioxin and diabetes. This association was first noted in the early 1990s when a decrease in glucose tolerance was seen in the NIOSH cohort. This was followed by a report of an increase in diabetes in the Ranch Hand cohort (Michalek et al., 1999a; Longnecker and Michalek, 2000). An increase in diabetes in other occupational cohorts (Steenland et al., 1999; Vena et al., 1998) as well as in the Seveso population (Pesatori et al., 1998) has also been reported. There was not a significant increase in diabetes in the NIOSH mortality study, although 6 of the 10 most highly exposed workers did have diabetes (Calvert et al., 1999). However, mortality studies are limited in their ability to assess risk from diabetes mellitus because the prevalence of disease may not be available from death certificates.

A paper by Longnecker and Michalek (2000) found a pattern suggesting that low levels of dioxin may influence the prevalence of diabetes. However, these results did not show an exposure-response relationship. Because it is the only study of its type to have been published, additional population-based studies are warranted to validate its findings. A recent update of the Ranch Hand study shows a 47% excess of diabetes in the most heavily exposed group of veterans (Michalek et al., 1999a).

Most of the data suggest that the diabetes observed in the studies is Type II, or adult-onset diabetes, rather than insulin dependent, or Type I. Aging and obesity are the key risk factors for Type II diabetes. However, dioxins may shift the distribution of sensitivity, putting people at risk at younger ages or when they have less weight. Dioxin alters lipid metabolism in multiple species, including humans (Sweeney et al., 1997; Pohjanvirta and Tuomisto, 1994), and it also alters glucose uptake into both human and animal cells in culture (Enan and Matsumura, 1994; Olsen et al., 1994). Mechanistic studies have demonstrated that dioxin affects glucose transport (Enan and Matsumura, 1994), a property under the control of the hypoxia response pathway (Ouiddir et al., 1999). A key regulatory protein in this pathway is the partner of the AhR, Arnt (also known as HIF1-beta) (Gu et al., 2000; Taylor and Zhulin, 1999). Activation of the AhR by dioxin may compete with other pathways for Arnt, such as the hypoxia-inducible factor (HIF) pathway (Gradin et al., 1992). Dioxin has also been shown to downregulate the insulin growth factor receptor (Liu et al., 1992). These three issues—altered lipid metabolism, altered glucose

transport, and alterations in the insulin signaling pathway—all provide biological plausibility to the association of dioxins with diabetes.

A causal relationship between diabetes and dioxin has not been established, although both the toxicologic and epidemiological data are suggestive of a plausible association (Remillard and Bunce, 2002). Many questions have yet to be answered. For example, does diabetes alter the pharmacokinetics of dioxin? Diabetes is known to alter the metabolism of several drugs in humans (Matzke et al., 2000) and may also alter dioxin metabolism and kinetics. Because adult-onset diabetes is also associated with being overweight, and body composition has been shown to modify the apparent half-life of dioxin, could the rate of elimination of dioxins be lowered in people who have diabetes, causing them to have higher body burdens? This may be relevant to the background population, but it is hardly likely to be an explanation in highly exposed populations.

Key research needs are twofold. The first is to develop an animal model with which to study the association between dioxins and diabetes and glucose perturbation. Several rodent models for Type II diabetes exist and may be used. The second is to conduct population-based incidence studies that take into account dioxin levels as well as the many known factors associated with diabetes. Although diabetes may cause the underlying pathology leading to death, it is often not attributed as the cause of death and thus limits the utility of mortality studies.

2.2.6. Other Effects

2.2.6.1. *Elevated GGT*

As mentioned above, there appears to be a consistent pattern of increased GGT levels among individuals exposed to 2,3,7,8-TCDD-contaminated chemicals. Elevated levels of serum GGT were observed within a year after exposure in Seveso children (Caramaschi et al., 1981; Mocarelli et al., 1986) and 10 or more years after cessation of exposure among TCP and 2,4,5-T production workers (May, 1982; Martin, 1984; Moses et al., 1984; Calvert et al., 1992) and among Ranch Hands (Roegner et al., 1991; Grubbs et al., 1995). All of these groups had a high likelihood of substantial exposure to 2,3,7,8-TCDD. In addition, for those studies that evaluated dose-response relationships with 2,3,7,8-TCDD levels, the effect was observed only at the highest levels or categories of 2,3,7,8-TCDD and, in the NIOSH study, only in workers who reported drinking high levels of alcohol.

In contrast, although background levels of serum 2,3,7,8-TCDD suggested minimal exposure in Army Vietnam veterans, GGT was increased at borderline significance among Vietnam veterans as compared to non-Vietnam veterans (CDC Vietnam Experience Study,

1988). In addition, despite the increases observed in some studies of occupational cohorts, other studies of TCP production workers from West Virginia or Missouri residents measured but did not report elevations in GGT levels (Suskind and Hertzberg, 1984; Webb et al., 1989).

In clinical practice, GGT is often measured because it is elevated in almost all hepatobiliary diseases and is used as a marker for alcoholic intake (Guzelian, 1985). In individuals with hepatobiliary disease, elevations in GGT are usually accompanied by increases in other hepatic enzymes, for example, AST and ALT, and metabolites, for example, uro- and coproporphyrins. Significant increases in hepatic enzymes other than GGT and metabolic products were not observed in individuals whose GGT levels were elevated 10 or more years after exposure ended, suggesting that the effect may be GGT-specific. These data suggest that in the absence of increases in other hepatic enzymes, elevations in GGT are associated with exposure to 2,3,7,8-TCDD, particularly among individuals who were exposed to high levels.

The animal data with respect to 2,3,7,8-TCDD-related effects on GGT are sparse. Statistically significant changes in hepatic enzyme levels, particularly AST, ALT, and alkaline phosphatase, have been observed after exposure in rats and hamsters (Gasiewicz et al., 1980; Kociba et al., 1978; Olson et al., 1980). Only one study evaluated GGT levels (Kociba et al., 1978); moderate but statistically nonsignificant increases were noted in rats fed 0.10 μg/kg 2,3,7,8-TCDD daily for 2 years, and no increases were observed in control animals.

In summary, GGT is the only hepatic enzyme examined that was found in a number of studies to be chronically elevated in adults exposed to high levels of 2,3,7,8-TCDD. The consistency of the findings in a number of studies suggests that the elevation may reflect a true effect of exposure, but its clinical significance is unclear. Long-term pathological consequences of elevated GGT have not been illustrated by excess mortality from liver disorders or cancer or in excess morbidity in the available cross-sectional studies.

It must be recognized that the absence of an effect—for example, liver enzymes—in a cross-sectional study does not obviate the possibility that the enzyme levels may have increased concurrently with the exposure but declined after cessation. The apparently transient elevations in ALT levels among the Seveso children suggest that hepatic enzyme levels other than GGT may react in this manner to 2,3,7,8-TCDD exposure.

2.2.6.2. *Thyroid Function*

Many effects of 2,3,7,8-TCDD exposure in animals resemble signs of thyroid dysfunction or significant alterations of thyroid-related hormones. In the few human studies that have examined the relationship between 2,3,7,8-TCDD exposure and hormone concentrations in adults (CDC Vietnam Experience Study, 1988; Roegner et al., 1991; Grubbs et al., 1995;

Suskind and Hertzberg, 1984), the results are mostly equivocal. Cross-sectional analysis of the Ranch Hand cohort (Pavuk et al., 2003) found signs of elevated TSH means among the high TCDD exposure group in the 1985 and 1987 follow-ups, with an increasing trend across the decade 1982 - 1992, but no association with the occurrence of thyroid disease. Concentrations of thyroid binding globulin also appeared to be positively correlated with current levels of 2,3,7,8-TCDD in the BASF accident cohort (Ott et al., 1994). Little additional information on thyroid hormone levels has been reported for production workers and none for Seveso residents, two groups with documented high serum 2,3,7,8-TCDD levels.

Thyroid hormones play important roles in the developing nervous system in all vertebrate species, including humans—to the extent that all infants in the United States are tested for hypothyroidism shortly after birth. Several studies of nursing infants suggest that ingestion of breast milk with a higher dioxin TEQ may alter thyroid function (Pluim et al., 1993; Koopman-Esseboom et al., 1994c; Nagayama et al., 1997). These findings suggest a possible shift in the distribution of thyroid hormones, particularly T4, and point out the need for collection of longitudinal data to assess the potential for long-term effects associated with developmental exposures.

The exact processes that account for these observations in humans are unknown, but when put in perspective of animal responses, the following might apply: dioxin increases the metabolism and excretion of thyroid hormone, mainly T4, in the liver, and reduced T4 levels stimulate the pituitary to secrete more TSH, which enhances thyroid hormone production. Early in the disruption process, the body can overcompensate for the loss of T4, which may result in a small excess of circulating T4 to the increased TSH. In animals given higher doses of dioxin, the body is unable to maintain homeostasis, TSH levels remain elevated, and T4 levels decrease.

A plausible mode of action for thyroid effects is described in Section 2.2.1.3.

2.2.6.3. *Cardiovascular Disease*

Elevated cardiovascular disease has been noted in several occupational cohort studies (Steenland et al., 1999; Sweeney et al., 1997; Flesch-Janys et al., 1995) and in the Seveso (Pesatori et al., 1998) and the rice oil poisoning studies. This appears to be associated with ischemic heart disease and in some cases with hypertension. Recent data from the Ranch Hand study indicate that dioxin may be a possible risk factor for the development of essential hypertension (Grubbs et al., 1995). Elevated blood lipids have also been seen in several cohorts. The association of dioxins with heart disease in humans has biological plausibility, given the data in animals. First is the key role of hypoxia in heart disease and the potential for involvement of the activated AhR in blocking an hypoxic response (Gradin et al., 1996; Gu et al., 2000). Dioxin

has been shown to perturb lipid metabolism in multiple laboratory species (Pohjanvirta and Tuomisto, 1994). The heart—in fact the entire vascular system—is a clear target for the adverse effects of dioxin in fish and birds (Hornung et al., 1999; Cheung et al., 1981). Recent studies have demonstrated that the heart is also a target in mammals (Lund et al., 2003; NTP 2003a). In mammals, dioxin has been shown to disturb heart rhythms at high doses in guinea pigs (Gupta et al., 1973; Pohjanvirta and Tuomisto, 1994).

2.2.6.4. *Oxidative Stress*

Several investigators have hypothesized that some of the adverse effects of dioxin and related compounds may be associated with oxidative stress. Induction of CYP1A isoforms has been shown to be associated with oxidative DNA damage (Park et al., 1996). Altered metabolism of endogenous molecules such as estradiol can lead to the formation of quinones and redox cycling. This has been hypothesized to play a role in the enhanced sensitivity of female rats to dioxin-induced liver tumors (Tritscher et al., 1996). Lipid peroxidation, enhanced DNA single-strand breaks, and decreased membrane fluidity have been observed in liver as well as in extrahepatic tissues following exposure to high doses of TCDD (Stohs, 1990). A dose- and time-dependent increase in superoxide anion in peritoneal macrophages following exposure to TCDD (Alsharif et al., 1994). A recent report that low-dose (0.15 ng TCDD/kg/day) subchronic exposure can lead to oxidative changes in several tissues in mice (Slezak et al., 2000) suggests that this mechanism or mode of toxicity deserves further attention.

Table 2-1. Effects of TCDD and related compounds in different animal species

Effect	Humans	Monkey	Guinea pig	Rat	Mouse	Hamster	Cow	Rabbit	Chicken	Fish	Avian wildlife	Marine mammals	Mink
Presence of AhR	+	+	0	+	+	+	+	+	+	+	+	+	+
Binding of TCDD: AhR complex to the DRE (enhancer)	+		+	+	+	+	+	+	+	+			
Enzyme induction	+	+	+	+	+	+		+	+	+	+	+	+
Acute lethality	0	+	+	+	+	+	+	+	+	+	+	+	+
Wasting syndrome	+	+	+	+	+	+	+	+		+	+	+	+
Teratogenesis/fetal toxicity, mortality	+/-	+	+	+	+	+		+	+	+	+	+	+
Endocrine effects	+/-	+		+	+					+	+	+	+
Immunotoxicity	+/-	+	+	+	+	+	+		+	+		+	
Carcinogenicity	+/-			+	+	+				+			
Neurotoxicity	+	+		+	+				+				
Chloracnegenic effects	+	+			+		+	+		+			
Porphyria	+	0	0	+	+	0			+				
Hepatotoxicity	+	+	+/-	+	+	+/-	+	+	+	+	+	+	+
Edema		+	0	0	+	+			+	+			
Testicular atrophy		+	+	+	+								
Bone marrow hypoplasia		+	+		+/-				+				
Teeth	+	+		+									

+ = observed.
+/- = observed to limited extent, or +/- results.
0 = not observed.
Blank cells = no data.

Table 2-2. Some biochemical responses to TCDD

CYP1A1	Human chorionic gonadotrophin
CYP1A2	Interleukin-1beta
CYP1B1	Gastrin
GST Ya	TNF alpha
GST Yb	TGF-beta
GST Yc	EGF
UDP glucuronyl transferase	Fibrinogen
QR quinone reductase/ Nmo	Plastin
Aldehyde dehydrogenase	EGFR
Ornithine decarboxylase	c-erbA related hormone receptor
Malic enzyme	Estrogen receptor
Phospholipase A2	25Dx-putative progesterone receptor
60kDa microsomal esterase	MDR-1 multidrug resistance
Aminolevulinic acid synthetase	Aryl hydrocarbon binding protein
Choline kinase	c-fos
EctoATPase	c-jun
Prostaglandin synthetase -2 (COX-2)	Cystatin-like protein
Plasminogen activator inhibitor-2	MHC-Q1
Urokinase plasminogen activator	Protein kinase C
Nedd-4-like ubiquitin protein ligase	pp60 c-src protein kinase
PEPC kinase	p21 ras
Terminal transferase	p27/Kip1
Testosterone 7alpha hydroxylase	bcl-2

Note: This list is not a comprehensive list of all responses known to be affected by TCDD.

Source: Sutter et al., 1992; Lai et al., 1996.

Table 2-3. Summary of the combined cohort and selected industrial cohort studies with high exposure levels, as described by IARC (1997)[a]

Reference	All cancers			Lung cancer		
	Observed	SMR	95% CI	Observed	SMR	95% CI
International cohort						
Kogevinas et al. (1997)[b]	394	1.2	1.1–1.3	127	1.2	1.0–1.4
Industrial populations (high-exposure subcohorts)						
Fingerhut et al. (1991a)[c] (USA)	114	1.5	1.2–1.8	40	1.4	1.0–1.9
Becher et al. (1996)[d] (Germany)	105	[1.3]	[1.0–1.5]	33	[1.4]	[1.0–2.0]
Hooiveld et al. (1996)[e] (Netherlands)	51	1.5	1.1–1.9	14	1	0.5–1.7
Ott and Zober (1996b)[f] (BASF accident)	18	1.9	1.1–3.0	7	2.4	1.0–5.0
TOTAL	[288]	[1.4]	[1.2–1.6]	[94]	[1.4]	[1.1–1.7]
p value	<0.001			<0.01		

[a] Adapted from IARC; Table 38 (1997); non-Hodgkin's lymphoma, soft-tissue sarcoma, and gastrointestinal results not shown. TOTALs were calculated by the IARC Working Group.

[b] Men and woman > 20 years since first exposure. These data include the cohorts of Fingerhut et al. (1991a,b), Becher et al. (1996), Hooiveld et al. (1996a), the original IARC cohort (Saracci et al., 1991), and other cohorts.

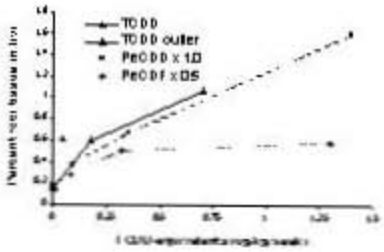
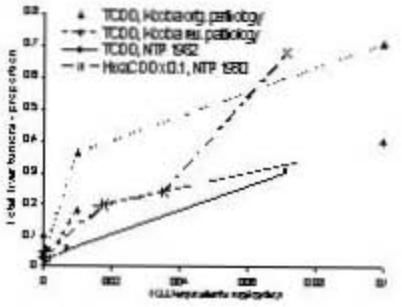
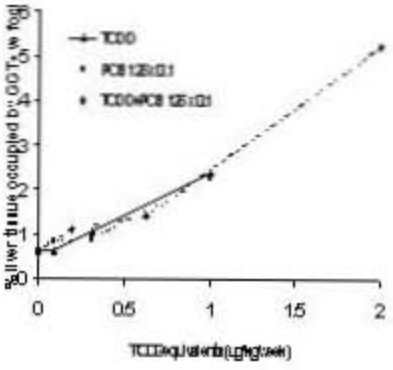
[c] Men ≥ 20 years latency and ≥ 1 year exposure.

[d] Men, cohorts I and II, summed (Boehringer-Ingelheim, Bayer-Uerdingen cohorts).

[e] Men and women, Factory A.

[f] Men, chloracne subgroup, ≥ 20 years latency. Data presented for lung cancer are all respiratory tract cancers combined.

Table 2-4. Tumor incidence and promotion data cited for the TEF-WHO$_{98}$ for principal congeners

Congener	TEF-WHO$_{98}$ tumor incidence/promotion citation[a]	TEF-WHO$_{98}$	% of adipose TEQ$_{DFP}$-WHO$_{98}$ tissue conc.[b]	Dose-response graphs: dose adjusted to reflect TEF multiplier
2,3,7,8-TCDD	TEF Standard	1	8	
1,2,3,7,8-PeCDD	Waern et al. (1991)	1	15	
2,3,4,7,8-PeCDF	Waern et al. (1991)	0.5	7	
1,2,3,6,7,8-HxCDD	NTP (1980); 1,2,3,6,7,8-HxCDD/ 1,2,3,7,8,9-HxCDD; 1:2 mixture; long-term bioassays, Osborne-Mendel rats in NTP studies, Sprague-Dawley rats in Kociba et al. (1978)	0.1	10	
1,2,3,7,8,9-HxCDD		0.1	2	
PCB 126	Hemming et al. (1995)	0.1	33	

[a] van den Berg et al., 2000. Hexa-CDD referenced to previous TEF reviews.
[b] See Part II, Chapter 4, Tables 4-46, 4-47

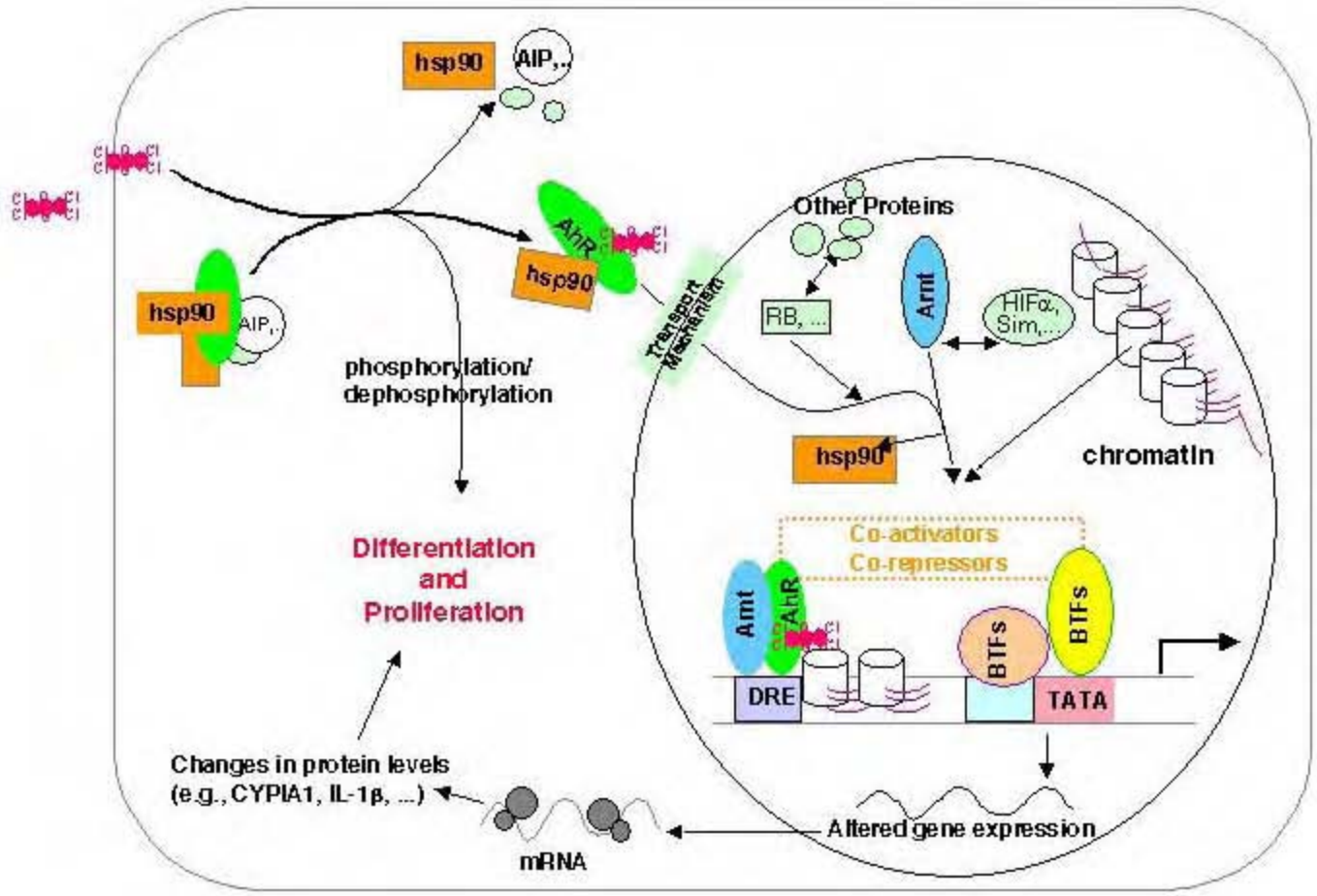


Figure 2-1. Cellular mechanism for AhR action. TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; AhR, aryl hydrocarbon receptor; AIP, associated immunophilin-like protein; hsp90, 90 kilodalton heat shock protein; p, sites of phosphorylization; Arnt, AhR nuclear translocator protein; RB, retinoblastoma protein; NF-kB, nuclear transcription factor; HIF, hypoxia inducible factor; DRE, dioxin-responsive element; BTFs, basal transcription factors; TATA, DNA recognition sequence.

3. MECHANISMS AND MODE OF DIOXIN ACTION

Mechanistic studies can reveal the biochemical pathways and types of biological and molecular events that contribute to dioxin's adverse effects (See Part II, Chapter 2, for a detailed discussion). For example, much evidence indicates that TCDD acts via an intracellular protein (the AhR), which functions as a ligand-dependent transcription factor in partnership with a second protein (Arnt). Therefore, from a mechanistic standpoint, TCDD's adverse effects appear likely to reflect alterations in gene expression that occur at an inappropriate time and/or for an inappropriately long time. Mechanistic studies also indicate that several other proteins contribute to TCDD's gene regulatory effects and that the response to TCDD probably involves a relatively complex interplay between multiple genetic and environmental factors. If TCDD operates through such a mechanism, as all evidence indicates, then there are certain constraints on the possible models that can plausibly account for TCDD's biological effects and, therefore, on the assumptions used during the risk assessment process (e.g., Poland, 1996; Limbird and Taylor, 1998).

Mechanistic knowledge of dioxin action may also be useful in other ways. For example, a further understanding of the ligand specificity and structure of the AhR will likely assist in the identification of other chemicals to which humans are exposed that may add to, synergize, or block the toxicity of TCDD. Knowledge of genetic polymorphisms that influence TCDD responsiveness may also allow the identification of individuals at greater risk from exposure to dioxin. In addition, knowledge of the biochemical pathways that are altered by TCDD may help identify novel targets for the development of drugs that can antagonize dioxin's adverse effects.

As described below, biochemical and genetic analyses of the mechanisms by which dioxin may modulate particular genes have revealed the outline of a novel regulatory system whereby a chemical signal can alter cellular regulatory processes. Future studies of dioxin action have the potential to provide additional insights into mechanisms of mammalian gene regulation that are of a broader interest. Additional perspectives on dioxin action can be found in several reviews (Birnbaum, 1994a, b; Schecter, 1994; Hankinson, 1995; Schmidt and Bradfield, 1996; Gasiewicz, 1997; Rowlands and Gustafsson, 1997; Denison et al., 1998; Hahn, 1998; Wilson and Safe, 1998; Schecter and Gasiewicz, 2003; Matsumura, 2003; Carlson and Perdew, 2002).

Knowledge of the mode(s) of action by which the broad class of chemicals known as dioxins act may facilitate the risk assessment process by contributing to the weight of the evidence for hazard characterization and by imposing bounds on the models used to describe possible responses of humans resulting from exposure to mixtures of these chemicals (see

Sections 2 and 5 of this document). The relatively extensive database on TCDD, as well as the more limited database on related compounds, has been reviewed, with emphasis on the role of the specific cellular receptor for TCDD and related compounds—the AhR—in the postulated mode(s) of action. This discussion focuses on summarizing the elements of the mode(s) of dioxin action that are relevant for understanding and characterizing dioxin risk for humans. These elements include:

- Similarities between humans and other animals with regard to receptor structure and function;

- The relationship between receptor binding and toxic effects; and

- The extent to which the purported mechanism(s) or mode(s) of action might contribute to the diversity of biological responses seen in animals and, to some extent, in humans.

In addition, this section identifies important and relevant knowledge gaps and uncertainties in the understanding of the mechanism(s) of dioxin action and indicates how these may affect the approach to risk characterization.

3.1. MODE VERSUS MECHANISM OF ACTION

In the context of revising its carcinogen risk assessment guidelines, EPA has proposed giving greater emphasis to use of all of the data in hazard characterization, dose-response characterization, exposure characterization, and risk characterization (U.S. EPA, 1996, 1999, 2003). One aid to the use of more information in risk assessment has been the definition of mode versus mechanism of action. Mechanism of action is defined as the detailed molecular description of key events in the induction of cancer or other health endpoints. Mode of action refers to the description of key events and processes, starting with interaction of an agent with the cell through functional and anatomical changes, resulting in cancer or other health endpoints.

Despite a desire to construct detailed biologically based toxicokinetic and toxicodynamic models to reduce uncertainty in characterizing risk, few examples have emerged. Use of a mode of action approach recognizes that, although all of the details may not have been worked out, prevailing scientific thought supports moving forward using a hypothesized mode of action supported by data. This approach is consistent with advice offered by the National Academy of

Sciences' National Research Council in its report entitled *Science and Judgment in Risk Assessment* (NAS/NRC, 1994).

Mode of action discussions help to provide answers to the questions: How does the chemical produce its effect? Are there mechanistic data to support this hypothesis? Have other modes of action been considered and rejected? In order to demonstrate that a particular mode of action is operative, it is generally necessary to outline the hypothesized sequence of events leading to effects, to identify key events that can be measured, to outline the information that is available to support the hypothesis, and to discuss those data that are inconsistent with the hypothesis or support an alternative hypothesis. Following this, the information is weighed to determine whether there is a causal relationship between key precursor events associated with the mode of action and cancer or other toxicological endpoint in animals, and ultimately whether this inference can be extended to humans.

3.2. GENERALIZED MODEL FOR DIOXIN ACTION

Dioxin and related compounds are generally recognized to be receptor-mediated toxicants. The generalized model has evolved over the years to appear as illustrated in Table 3-1 and Figure 2-1.

3.2.1. The Receptor Concept

One of the fundamental concepts that influences our approach to risk assessment of dioxin and related compounds is the receptor concept. The idea that a drug, hormone, neurotransmitter, or other chemical produces a physiological response by interacting with a specific cellular target molecule, that is, a "receptor," evolved from several observations. First, many chemicals elicit responses that are restricted to specific tissues. This observation implies that the responsive tissue (e.g., the adrenal cortex) contains a "receptive" component whose presence is required for the physiologic effect (e.g., cortisol secretion). Second, many chemicals are quite potent. For example, picomolar to nanomolar concentrations of numerous hormones and growth factors elicit biological effects. This observation suggests that the target cell contains a site(s) to which the particular chemical binds with high affinity. Third, stereoisomers of some chemicals (e.g., catecholamines, opioids) differ by orders of magnitude in their ability to produce the same biological response. This observation indicates that the molecular shape of the chemical strongly influences its biological activity. This, in turn, implies that the binding site on or in the target cell also has a specific, three-dimensional configuration. Together, these types of observations support the prediction that the biological responses to some chemicals involve

stereospecific, high-affinity binding of the chemicals to specific receptor sites located on or in the target cell. Many of these characteristics have been noted for TCDD and related compounds.

The availability of compounds of high specific radioactivity has permitted quantitative analyses of their binding to cellular components in vitro. To qualify as a potential receptor, a binding site for a given chemical must satisfy several criteria: (1) the binding site must be saturable, that is, the number of binding sites per cell should be limited; (2) the binding should be reversible; (3) the binding affinity measured in vitro should be consistent with the potency of the chemical observed in vivo; (4) if the biological response exhibits stereospecificity, so should the in vitro binding; (5) for a series of structurally related chemicals, the rank order for binding affinity should correlate with the rank order for biological potency; and (6) tissues that respond to the chemical should contain binding sites with the appropriate properties.

The binding of a chemical ("ligand") to its specific receptor is assumed to obey the law of mass action; that is, it is a bimolecular, reversible interaction. The concentration of the liganded, or occupied, receptor [RL] is a function of both the ligand concentration [L] and the receptor concentration [R] as shown in equation 3-1:

$$[L] + [R] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [RL] \qquad (3\text{-}1)$$

Inherent in this relationship is the fact that the fractional occupancy (i.e., $[RL]/[R_t]$) is a function of ligand concentration [L] and the apparent equilibrium dissociation constant K_D, which is a measure of the binding affinity of the ligand for the receptor, that is, $[RL]/[R_t] = [L]/(K_D + [L])$, where $K_D = [L]\,[R_t]/[LR] = k_2/k_1$. Therefore, the relationship between receptor occupancy and ligand concentration is hyperbolic. At low ligand concentrations (where $[L] << K_D$), a small increase in [L] produces an approximately linear increase in fractional receptor occupancy. At high ligand concentration (where $[L] >> K_D$), the fractional occupancy of the receptor is already very close to 1, that is, almost all receptor sites are occupied. Therefore, a small increase in [L] is likely to produce only a slight increase in receptor occupancy. These issues are discussed in regard to TCDD binding to the AhR and dose-response in Part II, Chapter 8.

Ligand binding constitutes only one aspect of the receptor concept. By definition, a receptor mediates a response, and the functional consequences of the ligand-receptor binding represent an essential aspect of the receptor concept. Receptor theory attempts to quantitatively relate ligand binding to biological responses. The classic "occupancy" model of Clark (1933)

postulated that (1) the magnitude of the biological response is directly proportional to the fraction of receptors occupied, and (2) the response is maximal when all receptors are occupied. However, analyses of numerous receptor-mediated effects indicate that the relationship between receptor occupancy and biological effect is not as straightforward as Clark envisioned.

In certain cases, no response occurs even when there is some receptor occupancy. This suggests that there may be a threshold phenomenon that reflects the biological "inertia" of the response (Ariens et al., 1960). In other cases, a maximal response occurs well before all receptors are occupied, a phenomenon that reflects receptor "reserve" (Stephenson, 1956). Therefore, one cannot simply assume that the relationship between fractional receptor occupancy and biological response is linear. Furthermore, for a ligand (such as TCDD) that elicits multiple receptor-mediated effects, one cannot assume that the binding-response relationship for a simple effect (such as enzyme induction) will necessarily be identical to that for a different and more complex effect (such as cancer).

The cascades of events leading to different complex responses (e.g., altered immune response to pathogens or development of cancer) are likely to be different, and other rate-limiting events likely influence the final biological outcome, resulting in different dose-response curves. Thus, even though ligand binding to the same receptor is the initial event leading to a spectrum of biological responses, ligand-binding data may not always mimic the dose-effect relationship observed for particular responses.

Another level of complexity is added when one considers different chemical ligands that bind to the same receptor. Relative potencies are determined by two properties of the ligand: affinity for the receptor and capacity to confer a particular response in the receptor (e.g., a particular conformational change), also called efficacy (Stephenson, 1956). Ligands with different affinities and the same degree of efficacy would be expected to produce parallel dose-response curves with the same maximal response within a particular model system. However, ligands of the same affinity with different efficacies may result in dose-response curves that are not parallel or that differ in maximal response. These issues relate particularly to Ah receptor ligands that are not "dioxins," where different efficacies or an inability to elicit the suite of dioxin-like responses compound differences in binding affinity for the Ah receptor. This complicates the use of the toxic equivalency approach, particularly for extrapolation purposes beyond the closely related congener groups. As described previously, this argues strongly for the use of all available information in setting TEFs and highlights the important role that scientific judgment plays in addressing uncertainty in the face of incomplete mechanistic understanding.

3.2.2. A Framework to Evaluate Mode of Action

In its revised proposed guidelines for carcinogen risk assessment (U.S. EPA, 1999, 2003), EPA recommends the use of a structured approach to evaluating mode of action. This approach is similar to and builds upon an approach developed within the WHO/IPCS Harmonization Project (WHO, 2000). Fundamentally, the approach uses a modification of the "Hill Criteria" (Hill, 1965), which have been used in the field of epidemiology for many years to examine causality between associations of exposures and effects. The framework calls for a summary description of the postulated mode of action, followed by the identification of key events that are thought to be part of the mode of action. These key events are then evaluated as to strength, consistency, and specificity of association with the endpoint under discussion. Dose-response relationships between the precursor key events are evaluated and temporal relationships are examined to be sure that "precursor" events actually precede the induction of the endpoint. Finally, biological plausibility and coherence of the data with the biology are examined and discussed. All of these "criteria" are evaluated and conclusions are drawn with regard to postulated mode of action.

In the case of dioxin and related compounds, elements of such an approach are found for a number of effects, including cancer, in Part II. Application of the framework to dioxin and related compounds may now proceed in a step-wise fashion to evaluate the association between the chemical or complex mixture and clearly adverse effects. The approach can be applied sequentially to early events, for example, receptor binding and intermediate events such as enzyme induction or endocrine impacts. Additional data will be required to extend the framework to most effects, but several have data that would support a framework analysis, a number of which are discussed below.

3.2.3. Mechanistic Information and Mode of Action—Implications for Risk Assessment

A substantial body of evidence from investigations using experimental animals indicates that the AhR mediates the biological effects of TCDD. The key role of the AhR in the effects of dioxin and related compounds is substantiated by four lines of research: (1) structure/activity relationships, (2) responsive versus nonresponsive mouse strains, (3) mutant cell lines, and (4) the development of transgenic mice in which the gene for the AhR has been "knocked out" (Birnbaum, 1994a; Fernandez-Salguero et al., 1996; Lahvis and Bradfield, 1998). Dioxin appears not to cause effects in the AhR knockout mouse (Fernandez-Salguero et al., 1996; Lahvis and Bradfield, 1998; Peters et al., 1999).

It is clear that the AhR is necessary, but not sufficient, for essentially all of the well-studied responses to dioxin. The AhR functions as a ligand-activated transcription factor, controlling the expression of specific genes via interaction with defined nucleotide sequences in the promoter regions. In order to control transcription, the TCDD-AhR complex interacts with another protein, Arnt, to bind to the dioxin response element. This complex is also bound by other nuclear coactivators and/or corepressors to bind to the transcriptional complex and initiate transcription (Gu et al., 2000). However, Arnt has many other partners that control hypoxia response, neuronal differentiation, morphological branching, etc. (Gu et al., 2000).

It is possible that there are other mechanisms that impact how dioxin initiates its toxic effects, apart from its direct transcriptional activation of drug metabolizing genes. It may be that the adverse effects of dioxin may result from competition of the ligand-activated AhR with other Arnt partners (Gradin et al., 1996). The AhR, Arnt, and Arnt partners are all members of the Per-Arnt-Sim (PAS) family of basic helix-loop-helix proteins that function as nuclear regulatory proteins (Gu et al., 2000). The PAS proteins are highly conserved, with homologous proteins being present in prokaryotes. They play key roles in circadian rhythms and development. The embryolethality of Arnt knockout mice, as well as the reduced fertility and viability of the AhR knockout mice (Abbott et al., 1999), point to a key role of these proteins in normal physiology.

Another potential mechanism by which TCDD can cause effects involves the protein/protein interactions of the AhR. When not bound to a ligand, the AhR exists in a multimeric protein complex that involves two molecules of heat shock protein 90 as well as other proteins, including AIP/XAP2/ara9, ara3, ara6, src, rel, and Rb (Carver et al., 1998; Enan and Matsumura, 1996; Puga et al., 2000b). AIP/XAP2/ara9 is a 37 kilodalton protein that is related to known immunophilins and is involved in the control of signal transduction processes. C-src has been shown to be associated with the AhR in several tissues and is a tyrosine kinase (Enan and Matsumura, 1996). Dioxin has been shown to cause a rapid increase in phosphorylation upon exposure. Recent studies have shown that rel, which is a key component of the NF-kappaB complex that controls apoptosis, binds to the AhR complex (Tian et al., 1999; Puga et al., 2000c). Similarly, several investigators have demonstrated an association between the AhR and the retinoblastoma protein; this has been shown to affect cell cycling (Puga et al., 2000b).

Thus, the AhR may act as a negative regulator of key regulator molecules involved in phosphorylation, cell cycling, and apoptosis in its unliganded state. Upon binding of TCDD, these other proteins are now able to exert their effects. In addition, dioxin may act by competing for Arnt, thus blocking key roles of other PAS regulatory proteins. Both of these mechanisms for the effects of dioxin are in addition to the direct role of the ligand-bound form of the receptor in

control of transcription via the well-studied mechanism of binding to a dioxin-response element in DNA.

Although studies using human tissues are much less extensive, it appears reasonable to assume that dioxin's mode of action to produce effects in humans includes receptor-mediated key events. Studies using human organs and cells in culture are consistent with this hypothesis. A receptor-based mode of action would predict that, except in cases where the concentration of TCDD is already high (i.e., [TCDD]~K_D), incremental exposure to TCDD will lead to some increase in the fraction of AhRs occupied. However, it cannot be assumed that an increase in receptor occupancy will necessarily elicit a proportional increase in all biological response(s), because numerous molecular events (e.g., cofactors, other transcription factors, genes) that contribute to the biological endpoint are integrated into the overall response. That is, the final biological response should be considered as an integration of a series of dose-response curves, with each curve dependent on the molecular dosimetry for each particular step.

Dose-response relationships that will be specific for each endpoint must be considered when using mathematical models to estimate the risk associated with exposure to TCDD. It remains a challenge to develop models that incorporate all the complexities associated with each biological response. Furthermore, the parameters for each mathematical model may apply only to a single biological response within a given tissue and species.

Given TCDD's widespread distribution, its persistence, and its accumulation within the food chain, it is likely that most humans are exposed to some level of dioxin; thus, the population at potential risk is large and genetically heterogeneous. By analogy with the findings in inbred mice, polymorphisms in the AhR probably exist in humans. Therefore, a concentration of TCDD that elicits a particular response in one individual may not do so in another. For example, studies of humans exposed to dioxin following an industrial accident at Seveso, Italy, failed to reveal a simple and direct relationship between blood TCDD levels and the development of chloracne (Mocarelli et al., 1991). These differences in responsiveness to TCDD may reflect genetic variation either in the AhR or in some other component of the dioxin-responsive pathway. Therefore, analyses of human polymorphisms in the AhR and Arnt genes have the potential to identify genotypes associated with higher (or lower) sensitivities to dioxin-related effects. Such molecular genetic information may be useful in the future for accurately predicting the health risks posed by dioxin to humans.

Complex responses (such as cancer) probably involve multiple events and multiple genes. For example, a homozygous recessive mutation at the *hr* (hairless) locus is required for TCDD's action as a chloracnegen and tumor promoter in mouse skin (Poland et al., 1982). Thus, the *hr*

locus influences the susceptibility of a particular tissue (in this case, skin) to a specific effect of dioxin (tumor promotion). An analogous relationship may exist for the effects of TCDD in other tissues. For example, TCDD may produce porphyria cutanea tarda only in individuals who have inherited uroporphyrinogen decarboxylase deficiency (Doss et al., 1984). Such findings suggest that, for some adverse effects of TCDD, the population at risk may be limited to individuals who have a particular genetic predisposition.

Other factors can influence an organism's susceptibility to TCDD. For example, female rats are more prone to TCDD-induced liver neoplasms than are males; this phenomenon is related to the hormonal status of the animals (Lucier et al., 1991). In addition, hydrocortisone and TCDD synergize in producing cleft palate in mice (Abbott et al., 1992). Retinoic acid and TCDD produce a similar synergistic teratogenic effect (Couture et al., 1990). These findings indicate that, in some cases, TCDD acts in combination with hormones or other chemicals to produce adverse effects. Such phenomena might also occur in humans. If so, the difficulty in assessing risk is increased, given the diversity among humans in hormonal status, lifestyle (e.g., smoking, diet), and chemical exposure.

Dioxin's action as a tumor promoter and developmental toxicant presumably reflects its ability to alter cell proliferation and differentiation processes. There are several plausible mechanisms by which this could occur. First, TCDD might activate a gene (or genes) that is directly involved in tissue proliferation. Second, TCDD-induced changes in hormone metabolism may lead to tissue proliferation (or lack thereof) and altered differentiation secondary to altered secretion of a trophic hormone. Third, TCDD-induced changes in the expression of growth factor or hormone receptors may alter the sensitivity of a tissue to proliferative stimuli. Fourth, TCDD-induced toxicity may lead to cell death, followed by regenerative proliferation. These mechanisms likely differ among tissues and period of development, and they may be modulated by different genetic and environmental factors.

The parallels between animal and human data relating to dioxin's tumor-promotion potential can assist in informing determinations of human risk, recognizing that the complexity of these intracellular processes limits our current mechanistic understanding. Using a weight-of-evidence approach, the Agency considers the cancer promotion data from in vitro and in vivo animal studies to be relevant and informative to humans. Although the specific mechanism(s) by which dioxin causes cancer remains to be established (as, indeed, for cancer in general), the intracellular factors and mechanistic pathways involved in dioxin's cancer-promotion mode of action all have parallels between animals and humans. No qualitative differences have been

reported to indicate that humans should be considered fundamentally different from the multiple animal species in which bioassays have demonstrated dioxin-induced neoplasia. Notably:

- the intracellular molecular protein, DNA, and RNA factors and mechanisms postulated in dioxin cancer promotion are common to animals and humans, reflecting intracellular functions that have been preserved phylogenetically over millions of years. These factors include the AhR, Arnt heterodimerization, cellular growth and differentiation functions, dioxin responsive elements, DNA transcription mechanisms, and oxidative enzyme induction; and,

- similar dioxin-induced toxic outcomes are evident between animals and humans across a variety of endpoints, progressing from enzyme induction, altered intracellular regulatory proteins, dermal lesions, and liver function and porphyria through to in vitro neoplastic cell promotion and clonal expansion following viral or chemical induction (in addition to the epidemiological cancer results following occupational exposures).

As detailed in Part II, Chapter 2 (mechanism of action), the mode of action parallels between humans and animals can be traced through dioxin's impacts at the subcellular level, as follows:

AhR binding: The AhR has been phylogenetically retained over hundreds of millions of years of evolution in humans and animals (Hahn, 1998) and is highly expressed in developing tissues (Abbott et al., 1995), pointing to a fundamental role in cellular growth, differentiation and/or endogenous/xenobiotic metabolism. Species-specific AhR molecular structures reveal them to be members of a family of transcription-activating proteins that exhibit a basic helix-loop-helix (bHLH) DNA binding motif, PAS domain for dimerization and ligand binding, and a C-terminal transactivation domain related to transcription induction and associated with a variety of toxic endpoints.

Notable similarities exist in the AhR across animal taxa, particularly at the bHLH and PAS sites (Fujii-Kuriyama et al., 1995), with human AhR being structurally most closely related to that of the guinea pig (75% base homology) and other sensitive animal strains (Korkalainen et al., 2001). Dioxin-resistant strains of rats and hamsters exhibit mutations in the AhR and/or increased homology differences, particularly in the C-terminal transactivation domain and Q-rich

subdomain (Korkalainen et al., 2001). Human AhR binding affinities vary ~20-fold (Kd ~ 0.3–38.8 nM) (Okey et al. 1997), encompassing the range from sensitive C57BL/6 mice (0.27 nM) to relatively resistant DBA/2 mice (1.5 nM) (Ema et al., 1994). Evidence suggests that within species, the AhR binding affinity correlates with biochemical effects and toxicity (Birnbaum et al., 1990, Poland and Glover, 1980), whereas between species, relative AhR binding affinities do not determine dioxin sensitivity because multiple downstream events intercede (DeVito and Birnbaum, 1995). Differences in conformational changes in the AhR following ligand binding are also likely to impact toxicity (Henry and Gasiewicz, 2003).

TCDD-AhR binding to Arnt: Following ligand binding, the TCDD-Arnt complex translocates to the nucleus, where it heterodimerizes (joins) with the bHLH-PAS transcription partner protein, Arnt. Arnt has been phylogenetically retained over evolutionary time in both humans and animals in several related forms and is essential for fetal survival. Arnt molecular weights vary across species from 85 kDa for the mouse, 87 kDa for humans, and 88 kDa for the rat (Pohjanvirta et al., 1999). The Arnt protein also dimerizes with other receptor/transcription pathways in the cell nucleus, indicating its importance and fundamental role in regulating DNA transcription (Schmidt and Bradfield, 1996; Zaher et al., 1998; Ge and Elferink, 1998; Tian et al., 1999).

Cross-talk among intracellular regulatory proteins: As noted, cancer is inherently a loss of the regulation of normal cell growth, differentiation, and death (apoptosis) that is locked into the genetic coding through clonal expansion. Central to the control of cell cycling and programmed cell death are numerous regulatory proteins (e.g., EGF, HIF-1α, TNF-α, TGF-β_1, NF-κB, RB), whose functional roles, although being rapidly elucidated, remain uncertain. These regulatory proteins are expressed in humans and animals and can be impacted by dioxin exposure, as in the role of EGF in dioxin-induced cleft palate in mice (Bryant et al., 2001). The Arnt protein is a common co-transcription factor for many bHLH-PAS regulatory proteins in addition to its role in the TCDD-AhR transcription pathway. The potential exists, therefore, for prolonged, inappropriate TCDD-AhR induction to impact multiple Arnt-related functions in the nucleus, thereby altering other regulatory pathways.

Competition for the Arnt protein has been demonstrated regarding the hypoxia inducible factor 1 (HIF-1α) pathway following dioxin administration and Arnt cross-talk (Gradin et al., 1996; Nie et al., 2001). In addition, dioxin-induced clonal expansion in human and animal cell cultures has resulted in fixed changes to the intranuclear expression of plasminogen activation

inhibitor (PAI-2), tumor necrosis factor alpha (TNF-α), and transforming growth factor β_1 (TGF-β_1), although it remains to be determined whether these changes were cause or effect of the dioxin-promoted clonal expansion (Yang et al., 1999).

Dioxin response elements (DREs): In the well-studied pathway of cytochrome mixed function oxidase induction (e.g., CYP1A1, 1A2), the ligand-AhR-Arnt heterodimer binds 1:1 to DREs upstream of the DNA gene battery transcription site (Denison et al., 1989). This mechanism is common to the mouse (six DREs) (Lusska et al. 1993), the rat (three DREs), and humans (two DREs) (Swanson and Bradfield, 1993), and is based on the 3'A-CGCAC5' DNA sequence. Subsequent to DRE binding, the C-terminal transactivation domain of the AhR alters histone proteins and causes unwinding of the chromatin, exposing the dioxin promoter and aryl hydrocarbon hydroxylase (AHH) gene battery to constitutively expressed DNA transcription proteins (Whitlock et al., 1996).

Enzyme induction: At least seven enzyme genes, and likely more, are included in the AhR-Arnt induced gene battery: three oxidative P450 cytochromes (CYP1A1, 1A2 ,1B1) and four non-P450 enzymes responsive to reactive oxygenated metabolites and oxidative stress (for example, a quinone oxidoreductase, aldehyde dehydrogenase, glucuronosyltransferase, and glutathione transferase [Nebert et al., 2000; Zhang et al., 1998]). These enzymes are expressed in humans and animals. Similar EC_{50}s were reported for CYP1A1 induction in lymphocytes in mice (1.3 nM) and humans (1.8nM) (Clark et al., 1992). However, substantial interspecies differences have been noted between cultured human and mouse embryonic palatal cells regarding CYP1A1 induction and morphological effects. Paralleling a ~200-fold lower sensitivity for morphological and cellular effects on embryonic palatal tissue, human cell cultures expressed ~350-fold fewer receptors and exhibited ~1500-fold lower dioxin-induced CYP1A1 m-RNA induction than mice (Abbott et al., 1999). Notably, though, effects on human and rat embryonic palatal shelf tissue occur at similar in vitro concentrations as compared to the much higher sensitivity shown in mice, suggesting that mice may exhibit a particular sensitivity to effects on palatal differentiation (Abbott and Birnbaum, 1990, 1991; Couture et al., 1990).

For CYP1A2 there is a ~40-fold variability in protein and enzyme activity levels in the human population (Eaton et al., 1995; Nebert et al., 1996). The importance of CYP1A2 to dioxin toxicity in rodents has been demonstrated in knockout mice, where dioxin-induced porphyrin changes did not occur in the absence of CYP1A2, and hepatic toxicity was substantially reduced

(Smith et al., 2001). This is likely due to the lack of hepatic sequestration in the absence of CYP1A2 (Diliberto et al., 1999).

Recent human epidemiological data have reported long-term hepatic enzyme and porphyrin ratio changes many years after industrial dioxin exposure (Neuberger et al., 1999). The prolonged up-regulation of mixed-function oxidase (MFO) enzymes has been postulated to impact the carcinogenic potential of xenobiotics that are metabolically activated, such as the PAHs. Indeed, carcinogenicity from PAHs is absent in AhR-knockout mice, presumably from lack of induction of the mixed-function oxidases. In a related mechanistic postulate, emphasis has been placed on the existence of both MFOs (CYP1A1, 1A2) and detoxifying/scavenging phase II transferase enzymes in the dioxin-induced gene battery, suggesting an evolutionary mechanism that creates reactive oxidative products through the MFOs (possibly as a result of endogenous ligand metabolism) yet provides a protective mechanism for mitigating the resulting oxidative stress through the phase II transferase enzymes. Abnormal regulation of this mechanism could cause oxidative stress that is related both to DNA damage and cell cycling/apoptosis regulation (Nebert et al., 2000).

Toxic effects and clonal proliferation: A spectrum of toxic effects has been demonstrated in both animals and humans following dioxin exposure, including developmental impacts, hormonal changes, skin lesions, and liver damage (DeVito et al., 1995). Dioxin has also been demonstrated to promote neoplastic changes and clonal expansion in human and animal cell cultures following viral induction. Exposure of normal human keratinocytes in vitro leads to accelerated differentiation, increased cell proliferation, and decreased senescence in differentiating cells (Ray and Swanson, 2003). These changes were accompanied by decreased levels of a number of cell regulatory proteins, including p53, supporting the concept that dioxin may exert its tumor promoting effects, in part, through this mechanism.

In Yang et al. (1992), human epidermal keratinocytes immortalized by adenovirus 12 - simian virus 40 exposure (SV40) underwent neoplastic transformation after 2 weeks of dioxin exposure in vitro at $\geq$ 0.1 nM, exhibiting increased saturation density, colony formation on soft agar, and squamous cell carcinoma when inoculated into athymic nude mice. These phenomena did not occur in the absence of SV40 virus induction or in control cell lines, including the immortalized cell culture. Both the neoplastic cell transformation and AHH induction in the untransformed cells were dose dependent. Follow-up analyses demonstrated alterations in growth regulatory gene expression (PAI-2, TNF-α, and TGF-β_1) that became fixed in the genome following successive division in TCDD-damaged cells (Yang et al., 1999).

Conversely, under certain circumstances, exposure to TCDD may elicit beneficial effects in selected tissue or cells. For example, TCDD protects against the subsequent carcinogenic effects of PAHs in mouse skin, possibly reflecting induction of detoxifying enzymes (Cohen et al., 1979; DiGiovanni et al., 1980). In other situations, TCDD-induced changes in estrogen metabolism may alter the growth of hormone-dependent tumor cells, producing a potential anticarcinogenic effect (Spink et al., 1990; Gierthy et al., 1993). However, several recent studies in mice indicate that the AhR has an important role in the genetic damage and carcinogenesis caused by components in tobacco smoke, such as BaP, through its ability to regulate CYP1A1 gene induction (Dertinger et al., 1998; Shimizu et al., 2000). TCDD's biological effects likely reflect a complicated interplay between genetic and environmental factors. These issues complicate the risk assessment process for dioxin.

Thus, it is clear that the robust database on mode(s) of dioxin action related to biochemical effects and to clearly adverse effects supports an understanding of dioxin's impact on biological and cellular processes. This database is among the best available for xenobiotic chemicals. The short-comings described above will stimulate additional research to further elucidate details in this understanding of the impact of dioxins, but they should not detract from the recognition that, among the data available to aid hazard characterization and risk assessment, these are remarkably consistent and useful findings.

Table 3-1. Early molecular events in response to dioxin[a]

Diffusion into the cell
Binding to the AhR protein
Impacts on cytoplasmic phosphorylation
Dissociation from hsp90
Active translocation from cytoplasm to nucleus
Association with Arnt protein
Competition for Arnt with other nuclear cofactors
Conversion of liganded receptor to the DNA-binding form
Binding of liganded receptor heteromer to enhancer DNA
Enhancer activation
Altered DNA configuration
Histone modification
Recruitment of additional proteins
Nucleosome disruption
Increased accessibility of transcriptional promoter
Binding of transcription factors to promoter
Enhanced mRNA and protein synthesis

[a] These events are discussed in detail in Part II, Chapter 2.

4. EXPOSURE CHARACTERIZATION

This section summarizes key findings developed in the exposure portion of the Agency's dioxin reassessment. These findings are developed in the companion document entitled *Part I: Estimating Exposure to Dioxin-Like Compounds*, which is divided into three volumes: (1) Sources of Dioxin in the United States, (2) Properties, Environmental Levels, and Background Exposures, and (3) Site-Specific Assessment Procedures. Readers are encouraged to examine the more detailed companion document for further information on the topics covered here and to see complete literature citations. The characterization discussion provides cross-references to help readers find the relevant portions of the companion document.

This discussion is organized as follows: (1) sources, (2) fate, (3) environmental media and food concentrations, (4) background exposures, (5) potentially highly exposed populations, and (6) trends. The key findings are presented in italics.

4.1. SOURCES (Cross-reference: Part I, Volume 1: Sources of Dioxin-Like Compounds in the United States)

CDD/CDFs have never been intentionally produced other than on a laboratory-scale basis for use in scientific analysis. Rather, they have been generated as unintended by-products in trace quantities in various combustion, industrial, and biological processes. PCBs, on the other hand, were commercially produced in large quantities, but they are no longer commercially produced in the United States. EPA has classified sources of dioxin-like compounds into five broad categories:

1. *Combustion Sources.* CDD/CDFs are formed in most combustion systems, which can include waste incineration (such as municipal solid waste, sewage sludge, medical waste, and hazardous wastes), burning of various fuels (such as coal, wood, and petroleum products), other high temperature sources (such as cement kilns), and poorly or uncontrolled combustion sources (such as forest fires, building fires, and open burning of wastes). Some evidence exists that very small amounts of dioxin-like PCBs are produced during combustion, but they appear to be a small fraction of the total TEQs emitted.

2. *Metals Smelting, Refining, and Processing Sources.* CDD/CDFs can be formed during various types of primary and secondary metals operations, including iron ore sintering, steel production, and scrap metal recovery.

3. *Chemical Manufacturing.* CDD/CDFs can be formed as by-products from the manufacture of chlorine-bleached wood pulp, chlorinated phenols (e.g., pentachlorophenol, or PCP), PCBs, phenoxy herbicides (e.g., 2,4,5-T), and chlorinated aliphatic compounds (e.g., ethylene dichloride).

4. *Biological and Photochemical Processes.* Recent studies suggest that CDD/CDFs can be formed under certain environmental conditions (e.g., composting) from the action of microorganisms on chlorinated phenolic compounds. Similarly, CDD/CDFs have been reported to be formed during photolysis of highly chlorinated phenols.

5. *Reservoir Sources.* Reservoirs are materials or places that contain previously formed CDD/CDFs or dioxin-like PCBs and have the potential for redistribution and circulation of these compounds into the environment. Potential reservoirs include soils, sediments, biota, water, and some anthropogenic materials. Reservoirs become sources when they have releases to the circulating environment.

The development of national estimates of annual environmental releases to air, water, and land is complicated by the fact that only a few facilities in most industrial sectors have been evaluated for CDD/CDF emissions. Thus, an extrapolation is needed to estimate national emissions. The extrapolation method involves deriving an estimate of emissions per unit of activity (i.e., an emission factor) at the tested facilities and multiplying this by the total activity level in the untested facilities.

In order to convey the level of uncertainty in both the measure of activity and the emission factor, EPA developed a qualitative confidence rating scheme. The confidence rating scheme, presented in Table 4-1, uses qualitative criteria to assign a high, medium, or low confidence rating to the emission factor and activity level for those source categories for which emission estimates can be reliably quantified. The overall "confidence rating" assigned to a quantified emission estimate was determined by the confidence ratings assigned to the corresponding "activity level" and "emission factor." If the lowest rating assigned to either the activity level or the emission factor terms is "high," then the category rating assigned to the

emission estimate is high (also referred to as "A"). If the lowest rating assigned to either the activity level or emission factor terms is "medium," then the category rating assigned to the emission estimate is medium (also referred to as "B"). If the lowest rating assigned to either the activity level or emission factor terms is "low," then the category rating assigned to the emission estimate is low (also referred to as "C").

For many source categories, either the emission factor information or the activity level information were inadequate to support development of reliable quantitative release estimates for one or more media. For some of these source categories, sufficient information was available to make preliminary estimates of environmental releases of CDD/CDFs or dioxin-like PCBs; however, the confidence in the activity level estimates or emission factor estimates was so low that the estimates cannot be included in the sum of quantified emissions from sources with confidence ratings of A, B, or C. These estimates were given an overall confidence class rating of D. For other sources, some information exists suggesting that they may release dioxin-like compounds; however, the available data were judged to be insufficient for developing any quantitative emission estimate. These estimates were given an overall confidence class rating of E.

4.1.1. Inventory of Releases

This dioxin reassessment has produced an "inventory" of sources of environmental releases of dioxin-like compounds for the United States (Table 4-2). The inventory was developed by considering all sources identified in the published technical and scientific literature and by the incorporation of results from numerous individual emissions test reports of individual industrial and combustion source facilities. In order to be representative of the United States, data generated from U.S. sources of information were always given first priority for developing emission estimates. Data from other countries were used for making estimates in only a few source categories where foreign technologies were judged similar to those found in the United States and the U.S. data were judged to be inadequate. The inventory is limited to sources whose releases can be reliably quantified (i.e., those with confidence ratings of A, B, or C, as defined above). As discussed below, this document does provide preliminary estimates of releases from Class D sources, but they are presented separately from the inventory.

The inventory presents the environmental releases in terms of two reference years: 1987 and 1995. The year 1987 was selected primarily because little empirical data existed for making source-specific emission estimates prior to this time; 1995 represents the latest year that could reasonably be addressed within the timetable for producing the rest of this document. EPA

expects to conduct periodic revisions and updates to the source inventory in the future to track changes in environmental releases over time.

Figure 4-1 displays the emission estimates to air for sources included in the inventory and shows how the emission factors and activity levels were combined to generate emission estimates. Figure 4-2 compares the annual mean I-TEQ emission estimates to air for the two reference years (1987 and 1995).

The following conclusions are made for sources of dioxin-like compounds included in the inventory:

- *EPA's best estimates of releases of CDD/CDFs to air, water, and land from reasonably quantifiable sources were approximately 3300 g TEQ_{DF}-WHO_{98} (3000 g I-TEQ) in 1995 and 14,000 g TEQ_{DF}-WHO_{98} (12,800 g I-TEQ) in 1987.* This finding is derived directly from Table 4-2.

- *The inventory indicates that, between 1987 and 1995, there was approximately a 76% decrease in total environmental releases of CDDs/CDFs from known sources in the United States.* EPA is currently evaluating source releases for the year 2000. Preliminary indications support the observation of a continued reduction in total environmental releases from 1995 levels. The inventory updated for the year 2000 will undergo scientific peer review.

- *The environmental releases of CDD/CDFs in the United States occur from a wide variety of sources, but they are dominated by releases to the air from combustion sources.* The current (1995) inventory indicates that emissions from combustion sources are more than an order of magnitude greater than emissions from the sum of emissions from all other categories. Approximately 70% of all quantifiable environmental releases were contributed by air emissions from just three source categories in 1995: municipal waste incinerators (representing 38% of total environmental releases); backyard burning of refuse in barrels (19%); and medical waste incinerators (14%).

- *The decrease in estimated releases of CDD/CDFs between 1987 and 1995 (approximately 76%) was due primarily to reductions in air emissions from municipal and medical waste incinerators, and further reductions are anticipated.*

For both categories, these emission reductions have occurred from a combination of improved combustion and emission controls and from the closing of a number of facilities. EPA's regulatory programs estimate that full compliance with recently promulgated regulations should result in further reductions in emissions from the 1995 levels of more than 1800 I-TEQ. These reductions will occur in the following source types: municipal waste combustors, medical waste incinerators, and various facilities that burn hazardous waste (see Part I, Volume 1, for further details about these reductions). No federal regulations are in place or currently under development for limiting dioxin emissions from backyard burning of refuse in barrels. A number of states have general restrictions on the practice of backyard trash burning.

- *Insufficient data are available to comprehensively estimate point source releases of dioxin-like compounds to water.* Sound estimates of releases to water are available only for chlorine bleached pulp and paper mills (356 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} for 1987 and 20 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} for 1995) and the manufacture of ethylene dichloride (EDC)/vinyl chloride monomer (VCM) (< 1 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995). Other releases to water bodies that cannot be quantified on the basis of existing data include effluents from publicly owned treatment works (POTW) and most industrial/commercial sources. EPA's Office of Water estimates that when full compliance with limitations on effluent discharges of CDD/CDF from chlorine bleached pulp and paper mills is achieved, annual emissions will be reduced to 5 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98}.

- *Based on the available information, the inventory includes only a limited set of activities that result in direct environmental releases to land.* Total releases to land quantified in the national inventory are estimated at 110 g TEQ_{DF}-WHO_{98} in 1995 and are principally from municipal wastewater treatment sludge (76.6 g) and the use of 2,4-D (28.9 g). Not included in the inventory's definition of an environmental release is the disposal of sludge and ashes into approved landfills.

- *Significant amounts of dioxin-like compounds produced annually are not considered environmental releases and, therefore, are not included in the national inventory.* Examples include dioxin-like compounds generated internal to a process but destroyed before release, waste streams that are disposed of in approved landfills and

are therefore outside the definition of annual environmental releases, and products that contain dioxin-like compounds but for which environmental releases, if any, cannot be estimated.

The procedures and results of the U.S. inventory may have underestimated releases from contemporary sources. A number of investigators have suggested that national inventories may underestimate emissions because of the possibility of unknown sources. This claim has been supported with mass balance analyses that suggest that deposition exceeds emissions (Rappe, 1991; Harrad and Jones, 1992; Bruzy and Hites, 1995); however, the uncertainty, in both the emissions and deposition estimates for the United States prevents the use of this approach for reliably evaluating the issue.

A variety of other arguments indicate that the inventory could underestimate emissions of dioxin-like compounds:

- A number of sources lacked sufficient data to include in the inventory but there were limited evidence indicating that these sources can emit CDD/CDFs. These sources are listed in Tables 4-3 and 4-4 and include various components of the metals industries, such as electric arc furnaces and foundries and uncontrolled or minimally controlled combustion practices (e.g., accidental fires at landfills).

- The possibility remains that truly unknown sources exist. Many of the sources that are well-accepted today were discovered only in the past 10 years. For example, CDD/CDFs were found unexpectedly in the wastewater effluent from bleached pulp and paper mills in the mid 1980s. Ore sintering is now listed as one of the leading sources of CDD/CDF emissions in Germany, but it was not recognized as a source until the early 1990s.

4.1.2. General Source Observations

For any given time period, releases from both contemporary formation sources and reservoir sources determine the overall amount of the dioxin-like compounds that are being released to the open and circulating environment. Because existing information is incomplete with regard to quantifying contributions from contemporary and reservoir sources, it is not currently possible to estimate the total magnitude of release for dioxin-like compounds from all

sources into the U.S. environment. For example, in terms of 1995 releases from reasonably quantifiable sources, this document estimates releases of 3300 g TEQ_{DF}-WHO_{98} (3000 g I-TEQ_{DF}) for contemporary formation sources and 2900 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} for reservoir sources.

In addition, there remain a number of unquantifiable and poorly quantified sources. No quantitative release estimates can be made for agricultural burning or for most CDD/CDF reservoirs or for any dioxin-like PCB reservoirs. The preliminary 1995 estimate of releases from poorly characterized contemporary formation sources is 1400 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98}. The preliminary release estimates for contemporary formation sources and reservoir sources are presented in Table 4-2. Table 4-3 lists all the sources that have been reported to release dioxin-like compounds but cannot be characterized on even a preliminary basis.

Additional observations and conclusions about all sources of dioxin-like compounds are summarized below:

- *The contribution of dioxin-like compounds to waterways from nonpoint source reservoirs is likely to be greater than the contribution from point sources.* Current data are only sufficient to support preliminary estimates of nonpoint source contributions of dioxin-like compounds to water (i.e., from urban storm water runoff and rural soil erosion). These estimates suggest that, on a nationwide basis, total nonpoint releases are significantly larger than point source releases.

- *Current emissions of CDD/CDFs to the U.S. environment result principally from anthropogenic activities.* Evidence that supports this finding includes matches in time of rise of environmental levels with time when general industrial activity began rising rapidly (see trend discussion in Part I, Volume 2, Chapter 6), the lack of any identified large natural sources, and observations of higher CDD/CDF body burdens in industrialized versus less industrialized countries (see discussion on human tissue levels in Part I, Volume 2, Chapter 4).

- *Although chlorine is an essential component for the formation of CDD/CDFs in combustion systems, the empirical evidence indicates that for commercial-scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of CDD/CDF stack emissions.* Important factors that can affect the rate of CDD/CDF formation include the overall combustion efficiency, post-combustion flue gas

temperatures and residence times, and the availability of surface catalytic sites to support CDD/CDF synthesis. Data from bench-, pilot- and commercial-scale combustors indicate that CDD/CDF formation can occur by a number of mechanisms. Some of these data, primarily from laboratory and pilot-scale combustors, have shown direct correlation between chlorine content in fuels and rates of CDD/CDF formation. Other data, primarily from commercial-scale combustors, show little relation between availability of chlorine in feeds and rates of CDD/CDF formation.

- The conclusion that chlorine in feed is not a strong determinant of CDD/CDF emissions applies to the overall population of commercial-scale combustors. For any individual commercial-scale combustor, circumstances may exist in which changes in chlorine content of feed could affect CDD/CDF emissions. For uncontrolled combustion, such as open burning of household waste, the chlorine content of the waste may play a more significant role in rates of CDD/CDF formation and release than is observed at commercial-scale combustors. The full discussion on this issue is presented in Part I, Volume 1, Chapter 2.

- *Dioxins are present in some ball clays, but insufficient data are available to estimate whether environmental releases occur during mining and use.* Recent studies in the United States and Europe have measured dioxins (principally CDDs) in some ball clays and other related clays. As discussed in Part I, Volume 1, Chapter 13, it is likely that the dioxin present in ball clay is of a natural origin. Ball clay is principally used in the manufacture of ceramics, which involves firing the clay in high-temperature kilns. This activity may cause some portion of the CDDs contained in the clay to be released into the air, but emission tests have not yet been conducted that would allow characterizing these releases.

- *Data are available to estimate the amounts of CDD/CDFs contained in only a limited number of commercial products.* No systematic survey has been conducted to determine levels of dioxin-like compounds in commercial products. The available data do, however, allow estimates to be made of the amounts of dioxin-like compounds in bleached pulp (40 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995), POTW sludge used in fertilizers (3.5 g I-TEQ_{DF} or 2.6 g TEQ_{DF}-WHO_{98} in 1995), pentachlorophenol-treated wood (8400 g I-TEQ_{DF} or 4800 g TEQ_{DF}-WHO_{98} in 1995),

dioxazine dyes and pigments (< 1 g I-TEQ_{DF} or TEQ_{DF}-WHO_{98} in 1995), and 2,4-D (18.4 g I-TEQ_{DF} or 28.9 g TEQ_{DF}-WHO_{98} in 1995).

- *No significant release of newly formed dioxin-like PCBs is occurring in the United States.* Unlike CDD/CDFs, PCBs were intentionally manufactured in the United States in large quantities from 1929 until production ceased in 1977. Although it has been demonstrated that small quantities of coplanar PCBs can be produced during waste combustion, no strong evidence exists that the dioxin-like PCBs make a significant contribution to TEQ releases during combustion. The occurrences of dioxin-like PCBs in the U.S. environment most likely reflect past releases associated with PCB production, use, and disposal. Further support for this finding is based on observations of reductions since the 1980s in PCBs in Great Lakes sediment and other areas.

- *It is unlikely that the emission rates of CDD/CDFs from known sources correlate proportionally with general population exposures.* Although the inventory shows the relative contribution of various sources to total emissions, it cannot be assumed that these sources make the same relative contributions to human exposure. It is quite possible that the major sources of dioxin in food (see the discussion in Part I, Volume 2, Chapter 2, indicating that diet is the dominant exposure pathway for humans) may not be those sources that represent the largest fractions of current total emissions in the United States. It is important to consider the geographic locations of sources relative to the areas from which much of the beef, pork, milk, and fish come. That is, many of the agricultural areas that produce dietary animal fats are not located near or directly downwind of the major sources of dioxin and related compounds.

- *The contribution of reservoir sources to human exposure may be significant.* Several factors support this finding:
  1. Because the magnitude of releases from current sources of newly formed PCBs are most likely negligible, human exposure to the dioxin-like PCBs is thought to be derived almost completely from reservoir sources. Key pathways involve releases from both soils and sediments to both aquatic and terrestrial food chains. As discussed in Part I, Volume 2, Chapter 4, one-third of general population

TEQ_{DFP} exposure is due to PCBs. Thus, at least one-third of the overall risk from dioxin-like compounds comes from reservoir sources.

2. CDD/CDF releases from soil via soil erosion and runoff to waterways may be significant. These releases appear to be greater than releases to water from the primary sources included in the inventory. CDD/CDFs in waterways can bioaccumulate in fish, leading to human exposure via their consumption. As discussed in Part I, Volume 2, Chapter 4, fish consumption makes up about one-fifth of the total general population CDD/CDF TEQ exposure. This suggests that a significant portion of the CDD/CDF TEQ exposure could be due to releases from the soil reservoir. It is not known, however, how much of the soil erosion and runoff represents recently deposited CDD/CDFs from primary sources or longer-term accumulation. Much of the eroded soil comes from tilled agricultural lands, which would include a mix of CDD/CDFs from various deposition times. The age of CDD/CDFs in urban runoff is less clear.

3. Potentially, soil reservoirs could have vapor and particulate releases that deposit on plants and enter the terrestrial food chain. The magnitude of this contribution, however, is unknown.

Collectively, these three factors suggest that reservoirs are a significant source of current background TEQ exposure, perhaps contributing half or more of the total.

4.2. ENVIRONMENTAL FATE (Cross-reference: Part I, Volume 2, Chapter 2)

The estimates of environmental releases are presented above in terms of TEQs. This is done for convenience in presenting summary information and to facilitate comparisons across sources. For purposes of environmental fate modeling, however, it is important to use the individual CDD/CDF and PCB congeners values rather than TEQs because the physical/chemical properties of individual dioxin congeners vary and will behave differently in the environment. For example, the relative mix of congeners released from a stack cannot be assumed to remain constant during transport through the atmosphere and deposition to various media. The full congener-specific release rates for most sources are given in an electronic database that is available as a companion to this document (U.S. EPA, 1998) Database of Sources of Environmental Releases of Dioxin-Like Compounds in the United States. EPA/600/P-98/002Ab.

In Part I, Volume 3, site-specific procedures are provided for estimating the impact of emissions on local populations, and this section emphasizes that congener specific emission values should be used in modeling their environmental fate. Finally, it is important to recognize that this document does not use source release estimates to generate background population intake/risk estimates; rather, these estimates are derived primarily from food levels and consumption rates.

Dioxin-like compounds are widely distributed in the environment as a result of a number of physical and biological processes. The dioxin-like compounds are essentially insoluble in water, they are generally classified as semivolatile, and they tend to bioaccumulate in animals. Some evidence has shown that these compounds can degrade in the environment, but in general they are considered to be very persistent and relatively immobile in soils and sediments. These compounds are transported through the atmosphere as vapors or attached to airborne particulates and can be deposited on soils, plants, or other surfaces (by wet or dry deposition). The dioxin-like compounds enter water bodies primarily via direct deposition from the atmosphere or by surface runoff and erosion. From soils, these compounds can reenter the atmosphere as either resuspended soil particles or vapors. In water, they can be resuspended into the water column from sediments, they can be volatilized out of the surface waters into the atmosphere, or, they can become buried in deeper sediments. Immobile sediments appear to serve as permanent sinks for the dioxin-like compounds. Although anthropogenic materials (such as PCP) are not always considered an environmental compartment, dioxin-like compounds are also found in such materials, and from there they have the potential to be released into the broader environment.

Atmospheric transport and deposition of the dioxin-like compounds are a primary means of their dispersal throughout the environment. The dioxin-like compounds have been measured in wet and dry deposition in most locations, including remote areas. Numerous studies have shown that they are commonly found in soils throughout the world. Industrialized countries tend to show similar elevated concentrations in soil, and detectable levels have been found in nonindustrialized countries. The only satisfactory explanation available for this distribution is air transport and deposition. Finally, by analogy these compounds would be expected to behave similarly to other compounds that have similar properties, and this postulated mechanism of global distribution is becoming widely accepted for a variety of persistent organic compounds.

The two primary pathways for the dioxin-like compounds to enter the ecological food chains and human diet are air-to-plant-to-animal and water/sediment-to-fish. Vegetation receives these compounds via atmospheric deposition in the vapor and particle phases. The compounds are retained on plant surfaces and bioaccumulated in the fatty tissues of animals that

feed on these plants. Vapor phase transfers onto vegetation have been experimentally shown to dominate the air-to-plant pathway for the dioxin-like compounds, particularly for the lower chlorinated congeners. In the aquatic food chain, dioxins enter water systems via direct discharge or deposition and runoff from watersheds. Fish accumulate these compounds through their direct contact with water, suspended particles, and bottom sediments and through their consumption of aquatic organisms.

Although these two pathways are thought to normally dominate contribution to the commercial food supply, others can also be important. Elevated dioxin levels in cattle resulting from animal contact with PCP-treated wood have been documented by the U.S. Department of Agriculture. Animal feed contamination episodes have led to elevations of dioxins in poultry in the United States, milk in Germany, and meat/dairy products in Belgium (see Part I, Volume 2, Chapter 5).

4.3. ENVIRONMENTAL MEDIA AND FOOD CONCENTRATIONS (Cross-reference: Part I, Volume 2, Chapter 3)

Background levels of dioxin-like compounds in various environmental media, including food, are presented in Table 4-4 in terms of means, variability, and sample sizes used to support the estimates. Estimates for background levels of dioxin-like compounds in environmental media are based on a variety of studies conducted at different locations in North America. Of the studies available for this compilation, only those conducted in locations representing "background" were selected. The amount and representativeness of the data vary, but in general they were derived from studies that were not designed to estimate national background means. The environmental media concentrations were similar to those in studies from Western Europe. These data are the best available for comparisons with site-specific values. Because of the limited number of locations examined, it is not known whether these estimates adequately capture the full national variability. As new data are collected, these ranges are likely to be expanded and refined. The limited data on dioxin-like PCBs in environmental media are summarized in Part I, Volume 2, Chapter 3.

Estimates for levels of dioxin-like compounds in food are based on data from a variety of studies conducted in North America. Beef, pork, and poultry estimates were derived from statistically based national surveys. Milk estimates were derived from a survey of a nationwide milk sampling network. Dairy estimates were derived from milk fat concentrations, coupled with appropriate assumptions for the amount of milk fat in dairy products. The background egg concentrations were based on an analysis of 15 egg samples collected from retail stores in eight

states (CA, OH, GA, NY, PA, OR, MN, WS; two samples per state except one in OR), where each sample was a composite of 24 individual eggs (i.e., 15 samples represented 360 eggs). The fish data, as discussed below, were derived from multiple studies, with samples collected both directly from water bodies and from retail outlets. All fish concentrations were expressed on the basis of fresh weight in edible tissue. As with other environmental media, food levels found in the United States were similar to levels found in Europe.

The procedure to evaluate background fish exposures emphasizes the use of both species-specific consumption rates and species-specific concentrations. EPA's national bioaccumulation study (U.S. EPA, 1992b) provides some species-specific information on freshwater/estuarine fish caught in the wild at various locations in the United States. Additional species-specific data on store-bought fish are available from studies conducted by the U.S. Food and Drug Administration (FDA) during the mid to latter 1990s (Jensen and Bolger, 2000; Jensen et al., 2000). An important aspect of the FDA studies is that they include data on store-bought catfish, tuna, shellfish, and salmon, which are some of the most highly consumed species. Accordingly, the data used to characterize CDD/CDF fish levels are much improved over previous estimates, with more than 300 individual samples and good representation of the most highly consumed species. However, the levels of dioxins in fish remain more uncertain than those in the other foods.

The compilation of data from different studies still lacks the geographic coverage and statistical power of the other food surveys. The EPA and FDA studies did not address dioxin-like PCBs; rather, these are based on a much smaller data set derived from the open literature. Also, the estimates of dioxin intake resulting from fish consumption do not include consumption of fish oils. Currently, insufficient data are available to support estimates of dioxin intake from direct fish oil consumption.

The general population dioxin intake calculations used in this document are a function of both consumption rate and dioxin concentration in food. The concentration data used in this document were measured in raw foods; therefore, if cooking significantly alters the dioxin concentration in consumed portions it must be accounted for in estimating dioxin intake.

This issue has been examined in a number of studies that measured the effects of cooking on the levels of CDDs, CDFs, and PCBs in foods (see Part I, Volume 2, Chapter 3). These studies have a range of results, depending on food type and cooking method. Most of the cooking experiments suggested that cooking reduces the total amount of dioxins in food but causes relatively little change in its concentration.

Although some cooking experiments have shown increases and others have shown decreases in dioxin concentrations, the relative prevalence of these impacts have not been

established. Therefore, given that most experiments show little change and others show change in both directions, the most reasonable assumption that can be made from the existing data is that dioxin concentration in uncooked food is a reasonable surrogate for dioxin concentration in cooked food. Although cooking in general does not reduce dioxin concentration in food, some specific food preparation practices can be adopted that can reduce dioxin intake by significantly reducing overall animal fat consumption. For example, carefully trimming fat from meat, removing skin from chicken and fish, and avoiding cooking in animal fats should reduce both animal fat and dioxin intake.

Some evidence from Europe suggests that during the 1990s a decline occurred in concentrations of dioxins and furans in food products, particularly dairy products (see Part I, Volume 2, Chapter 6). For example, the United Kingdom's Ministry of Agriculture, Fisheries, and Food collected milk samples in 1990 and again from similar locations in 1995. In 1990, the I-TEQ_{DF} ranged from 1.1 to 3.3 ppt, whereas the 1995 I-TEQ_{DF} ranged from 0.7 to 1.4. In Germany, a sampling of 120 dairy products in 1994 found I-TEQ_{DF} concentrations that were 25% lower than those in a similar sampling program in 1990. Liem et al. (2000) reports on a European cooperative study coordinated by the National Institute of Public Health and the Environment in the Netherlands and the Swedish National Food Administration. Ten countries supplied data on food concentrations, food consumption patterns, and other data used to evaluate exposure to dioxins in Europe. Some of the data suggested reductions in concentrations over time, but the available information was insufficient to draw general conclusions.

No systematic study of temporal trends in dioxin levels in food has been conducted in the United States. Although not statistically based, one U.S. study examined dioxin levels in 14 preserved food samples from various decades in the 20th century (Winters et al., 1998). It was found that meat samples of the 1950s through the 1970s had concentrations that were two-three times higher for the CDD/CDF TEQs and about 10 times higher for the PCB TEQs, as compared to current meat concentrations.

The food data and associated exposure estimates presented here reflect a mid-1990's time frame. New studies underway now or recently completed could be used in future updates to this report to make exposure estimates for a new reference year, such as 2000. The following studies on dioxin levels in food were not completed in time to be included in this document and should be considered in future updates:

- The milk levels used in Tables 4-4 and 4-6 are based on a study by Lorber et al. (1998) where milk samples were collected in 1996. A very similar milk survey was

conducted by Schaum et al. (2003) involving the collection and analysis of TEQ_{DFP} in cow milk samples from 45 dairy plants in July of 2000 and again in January 2001. This study reported TEQ_{DFP} levels in whole milk which were about half the levels found by Lorber et al. (1998). Follow-up work by Schuda et al. (2004), which addressed CDD/Fs only, allowed estimation of 2000/2001 TEQ_{DF} milk levels on a lipid basis. This approach showed similar TEQ_{DF} levels in milk lipid, or perhaps a slight decrease, when comparing CDD/F TEQs in the two sampling times (0.71 pg TEQDF/g lipid in 2000/2001 compared to 0.82 pg TEQDF/g lipid in 1996).

- USDA is currently conducting a nationwide survey of dioxin levels in beef, pork and poultry. Samples were collected in 2002 and 2003 and data analysis is now underway. The survey design and data analysis are structured in a similar way to the earlier USDA surveys used in this report and should allow for trend analysis.

- The Institute of Medicine of the National Academies published a review of dioxin levels in foods in 2003 (Institute of Medicine of the National Academies, 2003). This document presents policy options for reducing dietary exposure to dioxins in food and related research recommendations. Appendix B of the Institute of Medicine's report summarizes FDA's Total Diet Survey of dioxin levels in food collected in 2001. A wide variety of foods were sampled including dairy products, eggs, meats, fish, fruits, vegetables and fats/oils.

The food consumption rates used here are based primarily on USDA's 1994-1996 Continuing Survey of Food Intakes by Individuals. As new USDA survey data come available, these should be incorporated into future updates of this report.

4.4. BACKGROUND EXPOSURES (Cross-reference: Part I, Volume 2, Chapter 4)

4.4.1. Tissue Levels

The average CDD/CDF/PCB tissue level for the general adult U.S. population appears to be declining, and the best estimate of current (late 1990s) levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis).

The tissue samples collected in North America in the late 1980s and early 1990s showed an average TEQ_{DFP}-WHO_{98} level of about 55 pg/g lipid. This finding is supported by a number of studies—all conducted in North America—that measured dioxin levels in adipose, blood, and

human milk. However, the number of participants in most of these studies was relatively small and they were not statistically selected in ways that ensure their representativeness of the general U.S. adult population. One study, the 1987 National Human Adipose Tissue Survey, involved more than 800 individuals and provided broad geographic coverage, but it did not address coplanar PCBs. Similar tissue levels of these compounds have been measured in Europe and Japan during similar time periods.

Because dioxin levels in the environment have been declining since the 1970s (see the trends discussion in Part I, Volume 2, Chapter 6), it is reasonable to expect that levels in food, human intake, and, ultimately, human tissue have also declined over this period. The changes in tissue levels are likely to lag the decline seen in environmental levels, and the changes in tissue levels cannot be assumed to occur proportionally with declines in environmental levels.

CDC (2000) summarizes levels of CDDs, CDFs, and PCBs in human blood collected between 1995 to 1997 from 316 U.S. residents (ages 20–70 years). The individuals sampled had no known exposures to dioxin other than normal background. Although the samples in this data set were not collected in a manner that can be considered statistically representative of the national population and they lack wide geographic coverage, they are judged to provide a better indication of current tissue levels in the United States than the earlier data.

PCBs 105, 118, and 156 are missing from the blood data for the comparison populations reported by CDC (2000). These congeners account for 62% of the total PCB TEQ estimated in the early 1990s. Assuming that the missing congeners from the CDC study data contribute in the same proportion to the total PCB TEQ as in earlier data, they would increase the estimate of current body burdens by another 3.3 pg TEQ/g lipid, for a total PCB TEQ of 5.3 pg/g lipid and a total of 25.4 pg TEQ_{DFP}-WHO_{98}/g lipid (i.e., the TEQ_{DF}-WHO_{98} concentration was 20.1 pg/g lipid, and the TEQ_{P}-WHO_{98} concentration was estimated at 5.3 pg/g lipid). A summary of the CDC (2000) data is shown in Table 4-5.

A portion of the CDC blood data were plotted as a function of age. This plot, shown in Figure 4-3, indicates that blood levels generally increase with age, as does the variability in blood levels.

The calculation of a current tissue level of 25.4 pg/g lipid TEQ_{DFP}-WHO_{98} is further supported by the observation that this mean tissue level is consistent with the best estimate of current adult intake, 66 pg TEQ_{DFP}-WHO_{98}/d. Using this intake in a one-compartment, steady-state pharmacokinetic model yields a tissue level estimate of about 11.3 pg TEQ_{DFP}/g lipid (assumes TEQ_{DFP} has an effective half-life of 7.1 years, 80% of ingested dioxin is absorbed into the body, and lipid weight is 25% of the adult assumed body weight of 70 kg, or 17.5 kg).

Because intake rates appear to have declined in recent years, and steady-state is not likely to have been achieved, it is reasonable to observe higher measured tissue levels, such as the 25.4 pg TEQ/g lipid, than those predicted by the model.

Characterizing national background levels of dioxins in tissues is uncertain because the current data cannot be considered statistically representative of the general population. It is also complicated by the fact that tissue levels are a function of both age and birth year. Because intake levels have varied over time, the accumulation of dioxins in a person who turned 50 years old in 1990 is different than that in a person who turned 50 in 2000. As discussed in Part I, Volume 2, Chapter 6, exposure to dioxin-like compounds peaked during the 1960s, with declining exposures since then. Therefore, a person born in 1910 will see a rise in body levels that peaks at 50 to 70 years old. At the other end of the spectrum, a person born in 1970 will experience a higher body concentration very early in life, with declining levels in later years.

A pharmacokinetic (PK) modeling framework was developed to study trends in population body burdens of CDDs/CDFs throughout the 20th century and into the 21st century (Lorber, 2002). It was assumed that individuals within a population were exposed to doses rising from 0.50 pg WHO_{98}-TEQ_{DF}/kg-day during the 1940s to about 6.5 pg WHO_{98}-TEQ_{DF}/kg-day by the late 1960s, down to 1.0 pg WHO_{98}-TEQ_{DF}/kg-day by 1980, and finally to 0.50 pg WHO_{98}-TEQ_{DF}/kg-day by 2000, remaining constant at that level into the 21st century. It was found that a modeled population tissue level distribution will vary, depending on the year the modeled population is sampled. The results of this analysis are presented in Figure 4-4, which shows modeled population tissue level distributions for four years. An "age trend" is seen in the figure for modeled populations sampled in 1985 and 1995, as was seen in the CDC monitoring study of actual blood measurements of WHO_{98}-TEQ_{DFP} (see Fig. 4-3). Figure 4-4 also suggests that this age trend will disappear in the 21st century and that the CDD/CDF tissue level will drop below 10 ppt TEQ_{DF}-WHO_{98} lipid basis by 2030.

Monitoring studies which are currently underway should help determine whether the decline in body burdens has been continuing into the 21st century, as suggested by modeling. Results from the National Health and Nutrition Examination Survey of 1999-2000 (NHANES 1999-2000) were recently made available (CDC, 2003). NHANES 1999-2000 included data on dioxin-like compounds in the blood of 1921 sampled individuals, aged 12 and higher, and sampled from numerous locations around the country. These compounds included the 17 dioxin and furan congeners, as well as PCB congeners 126, 77, 169, and 81.

The current estimate of background body burden is based on 6 different studies totaling 316 individuals around the country which measured concentrations of these compounds in

populations characterized as "background" (CDC, 2000). Often these populations were selected the "background" population for studies which targeted other potentially exposed populations. The dates of these surveys, as noted above, were from about 1995 to 1997. In addition to being more recent, the NHANES 1999-2000 sampled population was much larger, but perhaps most importantly, NHANES was statistically designed to be representative of U.S. background after several years of data collection while the merged population from the 6 studies was not.

However, the amount of blood serum available for individual measurements in NHANES 1999-2000 was too small to be able to detect and characterize current levels of dioxin like compounds in the population. A large majority of the measurements were nondetects. For this reason, an effort is underway to pool remaining, available individual samples from NHANES and measure them for dioxin-like compounds, which would provide an updated measure of average concentrations of these compounds in the blood of U.S. citizens (ages 12 and greater, circa 1999-2000, and with all other delimiters relevant to the pooled samples, of course).

4.4.2. Intake Estimates

Adult daily intakes of CDD/CDFs and dioxin-like PCBs are estimated to average 43 and 23 pg TEQ_{DFP}-WHO_{98}/day, respectively, for a total intake of 66 pg/day TEQ_{DFP}-WHO_{98}. Daily intake is estimated by combining exposure media concentrations (food, soil, and air) with contact rates (ingestion, inhalation). Table 4-6 summarizes the media concentrations, contact rates, and resulting intake estimates.

The intake estimate is supported by an extensive database on food consumption rates and estimates of dioxin-like compounds in food (as discussed above). PK modeling provides further support for the intake estimates. Applying a simple steady-state PK model to an adult average blood level of 25 ppt TEQ_{DFP}-WHO_{98} (on a lipid basis) yields a daily intake of 146 pg TEQ_{DFP}-WHO_{98}/day (assumes TEQ_{DFP} has an effective half-life of 7.1 years, 80% of ingested dioxin is absorbed into the body, and lipid weight is 25% of the adult assumed body weight of 70 kg, or 17.5 kg). This PK-modeled CDD/CDF/PCB intake estimate is about 2.2 times higher than the direct intake estimate of 66 pg TEQ_{DFP}-WHO_{98}/day. This difference is to be expected with this application of a simple steady-state PK model to current average adipose tissue concentrations. Current adult tissue levels reflect intakes from past exposure levels, which are thought to be higher than current levels (Lorber, 2002; also in Part I, Volume 2, Chapter 6). Because the direction and magnitude of the difference in intake estimates between the two approaches are understood, the PK-derived value is judged supportive of the pathway-derived estimate. It

should be recognized, however, that the pathway-derived value will underestimate exposure if it has failed to capture all the significant exposure pathways.

4.4.3. Variability in Intake Levels

CDD/CDF and dioxin-like PCB intakes for the general population may extend to levels at least three times higher than the mean. Variability in general population exposure is primarily the result of the differences in dietary choices that individuals make. These are differences in both quantity and types of food consumed. An increased background exposure can result from either a diet that favors consumption of foods high in dioxin content or a diet that is disproportionately high in overall consumption of animal fats.

The best data available to determine the variability of total fat consumption come from several analyses of the Bogalusa Heart Study (Cresanta et al., 1988; Nicklas et al., 1993, 1995, Nicklas, 1995; Frank et al., 1986). These data show that the 95th percentile of total fat consumption is about twice the mean and the 99th percentile is approximately three times the mean. For a diet that has a broad distribution of animal fats (as does the typical U.S. diet), this same distribution can be assumed for dioxin intake.

Although body burden data cannot be assumed to be perfectly representative of current intakes (because they reflect past exposures as well as current ones), they also provide some support for this finding, based on the observation that the 95th percentile blood level in the CDC (2000) study was almost twice the mean level.

Intakes of CDDs/CDFs and dioxin-like PCBs are more than three times higher for a young child than for an adult, on a body-weight basis. This figure is based on combining age-specific food consumption rate and average food concentrations, as was done above for adult intake estimates (see Table 4-7).

Only 4 of the 17 toxic CDD/CDF congeners and 1 of the 11 toxic PCBs account for most of the toxicity in human tissue concentrations: 2,3,7,8-TCDD, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-HxCDD, and 2,3,4,7,8-PCDF and PCB 126. This finding is derived directly from the data described earlier on human tissue levels and is supported by intake estimations that indicate that these congeners are also the primary contributors to dietary dose. These five compounds make up about 80% of the total TEQ_{DFP}-WHO_{98} tissue level.

4.5. POTENTIALLY HIGHLY EXPOSED POPULATIONS OR DEVELOPMENTAL STAGES (Cross-reference: Part I, Volume 2, Chapter 5)

As discussed earlier, background exposures to dioxin-like compounds may extend to levels at least three times higher than the mean. This upper range is assumed to result from the normal variability of diet and human behaviors. Exposures from local elevated sources or exposures resulting from unique diets would be in addition to this background variability. Such elevated exposures may occur in small segments of the population, such as individuals living near discrete local sources. Nursing infants represent a special case: for a limited portion of their lives, these individuals may have elevated exposures on a body-weight basis when compared with nonnursing infants and adults.

Dioxin contamination incidents involving the commercial food supply have occurred in the United States and in other countries. For example, in the United States, contaminated ball clay was used as an anticaking agent in soybean meal, which resulted in elevated dioxin levels in some poultry and catfish. This incident, which occurred in 1998, involved a small faction of the national poultry production, and the use of contaminated ball clay has since been eliminated. Elevated dioxin levels have also been observed in a few beef and dairy animals, where the contamination was associated with contact with pentachlorophenol-treated wood. Evidence of this kind of elevated exposure was not detected in the national beef survey. Consequently, its occurrence is likely to be low, but it has not been determined.

These incidents may have led to small increases in dioxin exposure to the general population. However, it is unlikely that they have led to disproportionate exposures to populations living near where they occurred because in the United States meat and dairy products are highly distributed on a national scale. If contamination events were to occur in foods that are predominantly distributed on a local or regional scale, then such events could lead to more highly exposed local populations (see Part I, Volume 2, Chapter 5).

Elevated exposures associated with the workplace or with industrial accidents have also been documented. U.S. workers in certain segments of the chemical industry had elevated levels of TCDD exposure, with some tissue measurements in the thousands of part per trillion TCDD. There is no clear evidence that elevated exposures are currently occurring among U.S. workers. Documented examples of past exposures for other groups include certain Air Force personnel exposed to Agent Orange during the Vietnam War and people exposed as a result of industrial accidents in Europe and Asia.

Consumption of breast milk by nursing infants leads to higher levels of exposure and higher body burdens of dioxins during early years of life as compared with those of nonnursing infants (Part I, Volume 2, Chapter 5).

Kreuzer et al. (1997) and Abraham et al. (1994, 1995, 1998, 2000) compared dioxin levels in infants who were breast-fed with those who were formula-fed. All the studies showed elevations in the concentrations of dioxins in the breast-fed infants. Collectively, these studies included more than 100 infants, and they found that blood levels in infants aged 4-12 months were generally higher than 20 pg TEQ_{DF}-WHO_{98}/g lipid in nursing infants and lower than 5 pg TEQ_{DF}-WHO_{98}/g lipid in formula fed infants. Limited data suggest a similar difference for dioxin-like PCBs. Abraham et al. (1995) reported that at 11 months a breast-fed infant had a concentration of 31.4 pg TEQ_{P}-WHO_{98}/g lipid, compared to 2.5 pg TEQ_{P}-WHO_{98}/g lipid for the formula-fed infant.

U.S. dioxin intakes from nursing were calculated using time-dependent values for breast milk concentrations, consumption rates, and body weights. These calculations estimated an intake immediately after birth of 242 pg TEQ_{DFP}-WHO_{98}/kg/day. This level dropped to 18 pg TEQ_{DFP}-WHO_{98}/kg/day after 12 months of nursing. The average intake over 1-year of nursing was calculated to be 87 pg TEQ_{DFP}-WHO_{98}/kg/day. The cumulative intake for a 1 year nursing scenario represented about 13% of the total lifetime cumulative intake (see Lorber and Phillips, 2002, and Part I, Volume 2, Chapter 5, for details on these calculations).

CDC (1997) reported that in 1995, 55% of all babies experienced some breast-feeding, with about half of those breast-feeding beyond 5 months. The average duration of breast-feeding was 28.7 weeks. In a policy statement, the American Academy of Pediatrics (1997) stated that exclusive breast feeding provides ideal nutrition and is sufficient to support optimal growth and development for 6 months after birth. It recommended that breast-feeding continue for at least 12 months and thereafter for as long as mutually desired.

To better evaluate the impact of nursing on infants, changes in body burden were calculated using a one-compartment, first-order pharmacokinetic model (Lorber and Phillips, 2002). First, the model was validated using data from Abraham et al. (1998). Dioxin and furan concentrations for six mother/infant pairs were provided, including two breast milk measurements while the mother was feeding her infant and a blood measurement for the infant at about 1 year. These mothers' milk concentrations were used as the independent source term for the model, and the infant blood concentrations served as dependent model prediction. Other required parameters included the infant's body weight and lipid fraction over time (assigned average male and female infant values), absorption fraction (assigned a constant value of 0.80),

and, most importantly, an assumption of a rapid dissipation rate of TEQs in the infant (half-life < 1 year) during the early months of life. This dissipation rate was developed by Kreuzer et al. (1997), and it contrasts the more typical 7-year half-life found in adults for TCDD.

The average observed infant concentration was 24 pg TEQ_{DF}-WHO_{98}/g lipid, compared to a predicted concentration of 26 pg TEQ_{DF}-WHO_{98}/g lipid. The observed high and low concentrations were 5 and 44 pg TEQ_{DF}-WHO_{98}/g lipid, compared to predicted high and low concentrations in these infants of 10 and 36 pg TEQ_{DF}-WHO_{98}/g lipid. When the model was rerun at a higher TEQ dissipation rate of 7 years, the average predicted concentration rose to 39 pg TEQ_{DF}-WHO_{98}/g lipid. This demonstrated the appropriateness and importance of the assignment of a rapid dissipation rate of TEQs in infants.

This framework was used to evaluate various nursing scenarios: formula only and 6 weeks, 6 months, 1 year, and 2 years nursing. These scenarios reasonably capture the range of current nursing practices. This modeling effort required using the intake assumptions described earlier—242 pg TEQ_{DFP}-WHO_{98}/kg/day at birth and an average of 87 pg TEQ_{DFP}-WHO_{98}/kg/day over a year of breast-feeding—and other parameters noted above including the fraction of the oral dose that is absorbed into the body, changes in body weight over time, and changes in body fat fraction over time. For the infant, the half-life was less than 1 year, and during adulthood the half-life increased as the fraction of body fat increased. The longer half-life during the later years of life was based on a model presented in Michalek et al. (1996). The complete set of input values is listed in Lorber and Phillips (2002) as well as in Part I, Volume 2, Chapter 5.

The modeling results in terms of changes in lipid concentrations and body burdens as a function of age are shown in Figure 4-5**.** Some key observations include:

- For the 6-month, 1-year, and 2-year nursing scenarios, lipid concentrations peaked at around 9 weeks at 44 ppt TEQ_{DFP}-WHO_{98}. For the formula-fed infants they peaked at less than 10 ppt after the first year.

- In all four scenarios, the lipid concentrations merged at about 10 years of age at a concentration of about 13 ppt TEQ_{DFP}-WHO_{98}. Lipid and body burdens declined slightly from age 10 to about age 20 and then rose gradually through adulthood. This rise was due to the increase in half-life with age. At age 70, the modeled lipid and body burden concentrations were 13 ppt TEQ_{DFP}-WHO_{98} lipid and 5 ppt TEQ_{DFP}-WHO_{98} whole body weight.

- Breast-feeding leads to higher total lifetime exposures to TEQs as compared to formula feeding. Using an AUC approach, 70-year cumulative lifetime exposures were evaluated. The results suggest that breast-feeding added between 3% (for the 6-week breast-feeding scenario) and 18% (for the 2-year scenario) more accumulated exposure to TEQs as compared to formula-feeding.

The above analysis indicates that the average annual infant intake resulting from 1 year of nursing, 87 pg TEQ_{DFP}-WHO_{98}/kg/day, significantly exceeds the currently estimated adult intake of 1 pg TEQ_{DFP}-WHO_{98}/kg/day. The impact of nursing on infant body burdens, however, is much less, that is, infant body burdens will not exceed adult body burdens by 87 times. Rather, the modeling suggests that peak infant body burdens are only about two times the current adult body burdens (44 vs. 25 pg TEQ_{DFP}-WHO_{98}/g lipid). The reduced impact on body burden levels in nursing infants (relative to the intake) is due to the rapidly expanding infant body weight and lipid volume, and the faster elimination rate in infants. Body burden levels in nursing infants should decline in the future if, as discussed earlier, general population exposures decline.

Consumption of fish, meat, or dairy products containing elevated levels of dioxins and dioxin-like PCBs can lead to elevated exposures in comparison with the general population. The above discussion identified the general population distribution as extending up to roughly three times the mean. Most people will have exposures within this range even if they have unusual diets in terms of meat and dairy products. This is because (1) most people eat food from multiple sources, which tends to average out the contamination levels, and (2) meat and dairy products have similar dioxin levels, so substitution of one type of meat for another should not have a great impact on total exposure. Clearly, elevated exposures are possible in unusual situations, such as when an individual consumes large quantities of meat or dairy products that have significantly increased dioxin levels.

Elevated exposures resulting from fish consumption can occur in different situations. Concentrations in freshwater fish are significantly greater than in meat and dairy products; therefore, individuals who consume large quantities of freshwater fish at background contamination levels may have intakes higher than the general population distribution. A simple scenario was devised to evaluate this hypothesis. Through a review of the literature, EPA (U.S. EPA, 1997) concluded that a range of consumption of 59 to 170 g/day describes subsistence fish consumption behavior. These consumption rates were adopted to characterize the range of exposures in this scenario. Further, it is assumed that freshwater fish is the primary source of protein, that is, no meat or eggs are consumed. Assuming that all other exposure pathways stay

the same and using background exposure media concentrations, adult daily intake in this subsistence fisher scenario is calculated to range from 2.2 to 5.7 pg TEQ_{DFP}-WHO_{98}/kg-day. These intakes are about two to six times higher than the adult general population mean daily intake of 0.93 pg TEQ_{DFP}-WHO_{98}/kg-day. If subsistence fishers obtain their fish from areas where the concentration of dioxin-like chemicals in the fish is elevated, their exposure could be higher. Although this scenario appears reasonable, no clearly supportive data could be found to confirm that such highly exposed subpopulations exist in the United States.

One study that measured dioxin-like compounds in the blood of sport fishers in the Great Lakes area showed elevations over mean background but within the range of normal variability. However, another study that measured 90 PCB congeners (seven of which were dioxin-like PCBs, although PCB 126 was not measured) in the blood of sport fishers who consume high amounts of fish caught from Lake Michigan (> 26 pounds of sport fish per year) did find significant elevations of PCBs in their blood as compared to a control population (individuals consuming < 6 pounds of sport fish per year). The average total concentration of PCBs in the blood of the sport fishers was more than three times higher than that of the control population. Similarly, elevated levels of coplanar PCBs have been measured in the blood of fishers on the north shore of the Gulf of the St. Lawrence River who consume large amounts of seafood. Elevated CDD/CDF levels in human blood have been measured in Baltic fishermen. For further details on these studies see Part I, Volume 2, Chapter 5.

High exposures to dioxin-like compounds as a result of consuming meat and dairy products would most likely occur in situations where individuals consume large quantities of these foods and the level of these compounds is elevated. Most people eat meat and dairy products from multiple sources, and even if large quantities are consumed they are not likely to have unusually high exposures. Individuals who raise their own livestock for basic subsistence have the potential for higher exposures if local levels of dioxin-like compounds are high. One study in the United States showed elevated levels in chicken eggs near a contaminated soil site. European studies at several sites have shown elevated CDD/CDF levels in milk and other animal products near combustion sources, and some of these studies have also documented elevations in the levels of dioxin-like compounds in blood from families who consume their own home products.

Table 4-1. Confidence rating scheme

Confidence category	Confidence rating	Activity level estimate	Emission factor estimate
Categories/media for which emissions can be reasonably quantified			
A	High	Derived from comprehensive survey	Derived from comprehensive survey
B	Medium	Based on estimates of average plant activity level and number of plants or limited survey	Derived from testing at a limited but reasonable number of facilities believed to be representative of source category
C	Low	Based on data judged possibly nonrepresentative.	Derived from testing at only a few, possibly nonrepresentative facilities or from similar source categories
Categories/media for which emissions cannot be reasonably quantified			
D	Preliminary estimate	Based on extremely limited data, judged to be clearly nonrepresentative.	Based on extremely limited data, judged to be clearly nonrepresentative.
E	Not quantified	No data.	(1) Argument based on theory but no data (2) Data indicating dioxin formation but not in a form that allows developing an emission factor

Table 4-2. Inventory of environmental releases (grams/year) of TEQ_{DF}-WHO_{98} in the United States

Emission source category	Confidence rating[a] reference year 1995				Confidence rating[a] reference year 1987		
	A	B	C	D	A	B	C
Releases (g TEQ/yr) to air							
Waste incineration							
Municipal waste incineration		1250				8877	
Hazardous waste incineration		5.8				5	
Boilers/industrial furnaces			0.39				0.78
Medical waste/pathological incineration			488				2590
Crematoria			9.1[b]				5.5[b]
Sewage sludge incineration		14.8				6.1	
Tire combustion			0.11				0.11
Pulp and paper mill sludge incinerators[c]							
Power/energy generation							
Vehicle fuel combustion							
- leaded[d]			2				37.5
- unleaded			5.6				3.6
- diesel			33.5				27.8
Wood combustion							
- residential			62.8[b]				89.6[b]
- industrial		27.6				26.4	
Coal combustion							
- utility boilers		60.1				50.8	
- residential				30			
- commercial/Industrial				40			
Oil combustion							
- industrial/utility			10.7				17.8
- residential				6			
Other high temperature sources							
Cement kilns (hazardous waste burning)			156.1				117.8
Lightweight aggregate kilns burning hazardous waste			3.3[b]				2.4[b]
Cement kilns (nonhazardous waste burning)			17.8				13.7
Petroleum refining catalyst regeneration			2.21				2.24

Table 4-2. Inventory of environmental releases (grams/year) of TEQ_{DF}-WHO_{98} in the United States (continued)

Emission source category	Confidence rating[a] reference year 1995				Confidence rating[a] reference year 1987		
	A	B	C	D	A	B	C
Releases (g TEQ/yr) to air (continued)							
Other high temperature sources (continued)							
Cigarette combustion			0.8				1
Carbon reactivation furnaces			0.08[b]				0.06[b]
Kraft recovery boilers		2.3				2	
Combustion of landfill gas				7			
Biogas combustion				< 1			
Minimally controlled or uncontrolled combustion[e]							
Backyard barrel burning[f]			628				604
Landfill fires				1000			
Accidental fires (structural)				< 20			
Accidental fires (vehicles)				30			
Forest and brush fires				200			
Metallurgical processes							
Ferrous metal smelting/refining							
- sintering plants		28					32.7
- electric arc furnaces				40			
- foundries				20			
Nonferrous metal smelting/refining							
- primary copper		< 0.5[b]				< 0.5[b]	
- secondary aluminum			29.1				16.3
- secondary copper			271				983
- secondary lead		1.72				1.29	
- primary magnesium				15			
Coke production				7			
Drum and barrel reclamation			0.08				0.08
Chemical manufacturing/processing sources							
Ethylene dichloride/vinyl chloride		11.2[b]					
TOTAL RELEASES TO AIR[g]	3125				13515		

Table 4-2. Inventory of environmental releases (grams/year) of TEQ_{DF}-WHO_{98} in the United States (continued)

Emission source category	Confidence rating[a] reference year 1995				Confidence rating[a] reference year 1987		
	A	B	C	D	A	B	C
Releases (g TEQ/yr) to water							
Chemical manufacturing/ processing sources Bleached chemical wood pulp and paper mills	19.5				356		
POTW (municipal) wastewater				10			
Ethylene dichloride/vinyl chloride		0.43[b]					
Reservoir sources Urban runoff to surface water				190			
Rural soil erosion to surface water				2700			
TOTAL RELEASES TO WATER[g]	19.93				356		
Releases (g TEQ/yr) to land							
Chemical manufacturing/ processing sources Bleached chemical wood pulp and paper mill sludge	1.4				14.1		
Ethylene dichloride/vinyl chloride		0.73[b]					
Municipal wastewater treatment sludge	76.6				76.6		
Commercially marketed sewage sludge	2.6				2.6		
2,4-Dichlorophenoxy acetic acid	28.9				33.4		
TOTAL RELEASES TO LAND[g]	110.23				126.7		
OVERALL RELEASES (g/yr) TO THE OPEN AND CIRCULATING ENVIRONMENT	**3255 (SUM OF COLUMNS A, B, C)**				**13,998 (SUM OF COLUMNS A, B, C)**		

[a] The most reliable estimates of environmental releases are those sources within Categories A, B, and C, which are defined as:

A = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **High Confidence** in the **Emission Factor** and **High Confidence** in **Activity Level**.

Table 4-2. Inventory of environmental releases (grams/year) of TEQ_{DF}-WHO_{98} in the United States (continued)

B = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Medium Confidence** in the **Emission Factor** and at least **Medium Confidence** in **Activity Level**.

C = Characterization of the Source Category judged to be **Adequate for Quantitative Estimation** with **Low Confidence** in either the **Emission Factor** and/or the **Activity Level**.

D = **Preliminary Indication** of the Potential Magnitude of I-TEQ_{DF} Emissions from "Unquantified" (i.e., Category D) Sources in Reference Year 1995. **Based on extremely limited data, judged to be clearly nonrepresentative**.

[b] Congener-specific emissions data were not available; the I-TEQ estimate was used as a surrogate for the TEQ_{DF}-WHO_{98} emissions estimate.

[c] Included within estimate for Wood Combustion - industrial.

[d] Leaded fuel production and the manufacture of motor vehicle engines requiring leaded fuel for highway use have been prohibited in the United States. (See Section 4.1 for details.)

[e] This refers to conventional pollutant control, not dioxin emissions control. Very few of the sources listed in this inventory control specifically for CDD/CDF emissions.

[f] This term refers to the burning of residential waste in barrels.

[g] TOTAL reflects only the total of the estimates made in this report.

Table 4-3. Sources that are currently unquantifiable (Category E)[a]

Category	Unquantified sources
Combustion sources	Uncontrolled combustion of PCBs Agricultural burning
Metal smelting and refining	Primary aluminum Primary nickel
Chemical manufacturing	Mono- to tetrachlorophenols Pentachlorophenol Chlorobenzenes Chlorobiphenyls (leaks/spills) Dioxazine dyes and pigments 2,4-Dichlorophenoxy acetic acid Tall oil-based liquid soaps
Biological and photochemical processes	Composting
Reservoir sources	Air Sediments Water Biota PCP-treated wood

[a] There exist no or insufficient data characterizing environmental releases from these sources. Therefore, it is currently not possible to arrive at an estimate of annual environmental releases.

Table 4-4. Summary of North American CDD/CDF and PCB TEQ-WHO_{98} levels in environmental media and food[a]

Media	CDD/CDFs[b]	PCBs[b]
Urban soil, ppt	n= 270 9.3 ± 10.2 Range = 2–21	n = 99 2.3
Rural soil, ppt	n = 354 2.7 Range = 0.11–5.7	n = 62 0.59
Sediment, ppt	n=11 5.3 ± 5.8 Range = <1–20	n = 11 0.53 ± 0.69
Urban air, pg/m^3	n=106 0.12 ± 0.094 Range = 0.03–0.2	n=53 0.0009
Rural air, pg/m^3	n=60 0.013 Range = 0.004–0.02	n=53 0.00071
Freshwater fish and shellfish, ppt[c]	n=222 1.0 (NA[d])	n = 1 composite of 10 samples plus 6 composites 1.2[e] (NA[d])
Marine fish and shellfish, ppt[c]	n=158 0.26 (NA[d])	n = 1 composite of 13 samples plus 5 composites 0.25 (NA[d])
Water, ppq	n=236 0.00056 ± 0.00079 (NA[d])	NA[d]
Milk, ppt (Note: each composite for CDD/F/PCB comprised of 40+ U.S. regional samples)	n=8 composites 0.018[e]	n = 8 composites 0.0088[e]
Dairy, ppt[f]	n = 8 composites 0.12[e]	n = 8 composites 0.058[e]
Eggs, ppt (Note: each composite for CDD/F data comprised of 24 eggs)	n=15 composites 0.081[e]	n = 18 plus 6 composites 0.10[e] (NA[d])

Table 4-4. Summary of North American CDD/CDF and PCB TEQ-WHO_{98} levels in environmental media and food (continued)

Media	CDD/CDFs[b]	PCBs[b]
Beef ppt	n=63 0.18 ± 0.11 Range = 0.11–0.95	n = 63 0.084
Pork, ppt	n=78 0.28 ± 0.28 Range = 0.15–1.8	n = 78 0.012
Poultry, ppt	n=78 0.068 ± 0.070 Range = 0.03–0.43	n = 78 0.026
Vegetable fats, ppt	n=30 0.056 ± 0.24[g] (NA[d])	n = 5 composites 0.037[e]

[a] Whole-weight basis; concentrations provided in parenthesis for food products are calculated at ND = 0.
[b] Values are the arithmetic mean TEQs and standard deviations. Nondetects were set to one-half the limit of detection, except for soil and CDD/CDFs in vegetable fats for which nondetects were set to zero.
[c] The TEQ_{df} fish concentrations reported here are species-specific ingestion rate weighted averages.
[d] NA = not available; congener-specific PCB data and data to calculate TEQ concentrations at ND = 0 are limited.
[e] Standard deviations could not be calculated due to limitations associated with the data (i.e., composite analyses).
[f] TEQ calculated by setting nondetects to zero.
[g] Dairy concentration calculated from milk lipid concentrations and then assuming a fat fraction for dairy.

Table 4-5. Background serum levels in the United States 1995–1997

Value	TEQ_{DFP}-WHO_{98} (pg/g lipid)	2,3,7,8-TCDD (pg/g lipid)
Median	18.7	1.9
Mean	22.1[a]	2.1
95th Percentile	38.8	4.2

[a] After adjusting to account for missing PCBs, the mean is 25.4 pg/g lipid.

Source: CDC, 2000

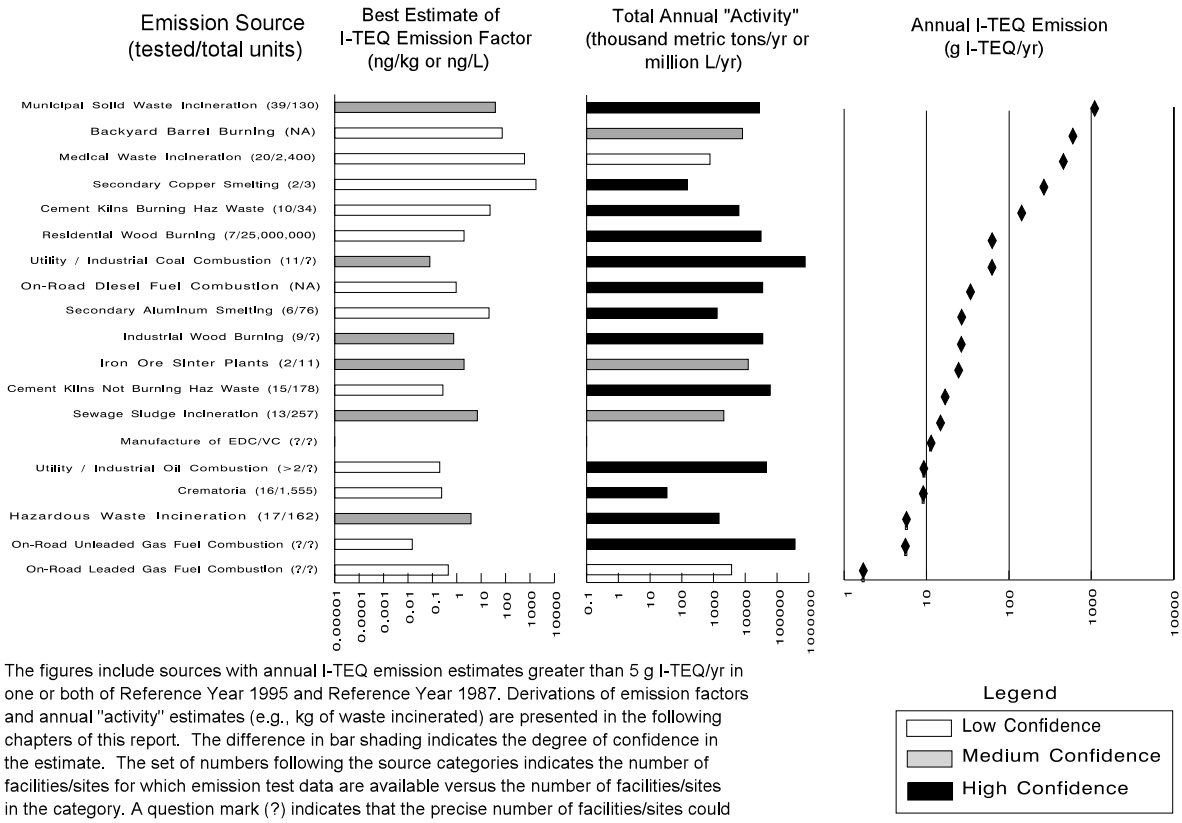
Table 4-6. Adult contact rates and background intakes of dioxin-like compounds

Exposure route	Contact rate	Dioxins and furans		Dioxin-like PCBS		Total
		Concentration TEQ_{DF}-WHO_{98}	Intake (pg TEQ_{DF}-WHO_{98}/kg-d)	Concentration TEQ_{P}-WHO_{98}	Intake (pg TEQ_{P}-WHO_{98}/kg-d)	Intake (pg TEQ_{DFP}-WHO_{98} /kg-d)
Soil ingestion	50 mg/d	9.3 pg/g	0.0066	2.3 ppt	0.0016	0.0082
Soil dermal	12 g/d	9.3 pg/g	0.0016	2.3 ppt	0.00039	0.002
Freshwater fish and shellfish[a]	5.9 g/d	1.0 pg/g	0.084	1.2 pg/g	0.1	0.18
Marine fish and shellfish[a]	9.6 g/d	0.26 pg/g	0.036	0.25 pg/g	0.034	0.07
Inhalation	13.3 m^3/d	0.12 pg/m^3	0.023	NA	NA	0.023
Milk	175 g/d	0.018 pg/g	0.045	0.0088 pg/g	0.022	0.067
Dairy	55 g/d	0.12 pg/g	0.094	0.058 pg/g	0.046	0.14
Eggs	0.24 g/kg-d	0.081 pg/g	0.019	0.10 pg/g	0.024	0.043
Beef	0.67 g/kg-d	0.18 pg/g	0.13	0.084 pg/g	0.06	0.19
Pork	0.22 g/kg-d	0.28 pg/g	0.062	0.012 pg/g	0.0026	0.065
Poultry	0.5 g/kg-d	0.068 pg/g	0.034	0.026 pg/g	0.013	0.047
Other meats	0.35 g/kg-d	0.18 ppt	0.062	0.041 pg/g	0.014	0.076
Vegetable fat	17 g/d	0.056 pg/g	0.014	0.037 pg/g	0.009	0.023
Water	1.4 L/d	0.0005 pg/L	0.000011	NA	NA	0.000011
Total			**0.61 (43 pg/d)**		**0.33 (23 pg/d)**	**0.94 (66 pg/d)**

[a] The TEQ_{df} fish concentrations reported here are species-specific ingestion rate weighted averages.

Table 4-7. Variability in average daily toxic equivalent (TEQ) intake as a function of age

Age range	Intake, mass basis pg TEQ_{DFP}-WHO_{98}/d	Intake, body weight basis pg TEQ_{DFP}-WHO_{98}/kg-d
1–5 years	50	3.3
6–11 years	54	1.8
12–19 years	61	1.1
Adult	66	0.9



The figures include sources with annual I-TEQ emission estimates greater than 5 g I-TEQ/yr in one or both of Reference Year 1995 and Reference Year 1987. Derivations of emission factors and annual "activity" estimates (e.g., kg of waste incinerated) are presented in the following chapters of this report. The difference in bar shading indicates the degree of confidence in the estimate. The set of numbers following the source categories indicates the number of facilities/sites for which emission test data are available versus the number of facilities/sites in the category. A question mark (?) indicates that the precise number of facilities/sites could not be estimated.

Figure 4-1. Estimated CDD/CDF I-TEQ emissions to air from combustion sources in the United States, 1995.

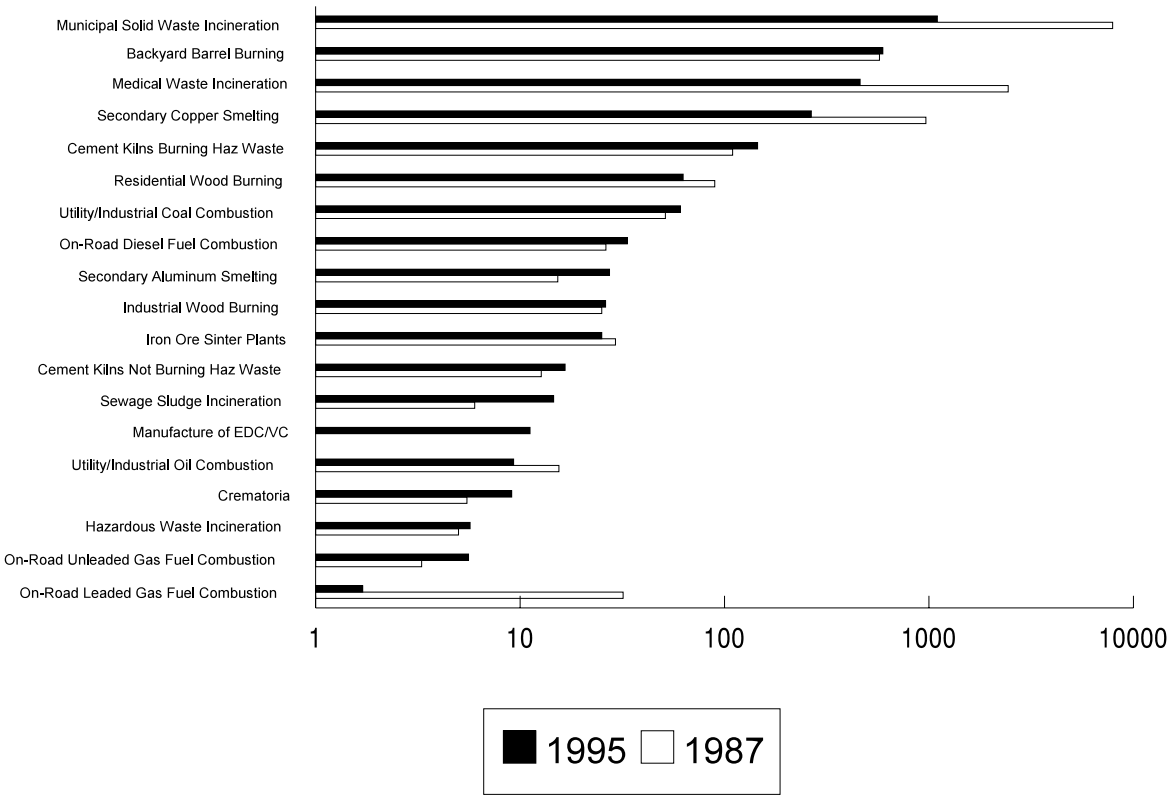


Figure 4-2. Comparison of estimates of annual I-TEQ emissions to air (grams I-TEQ/yr) for reference years 1987 and 1995.

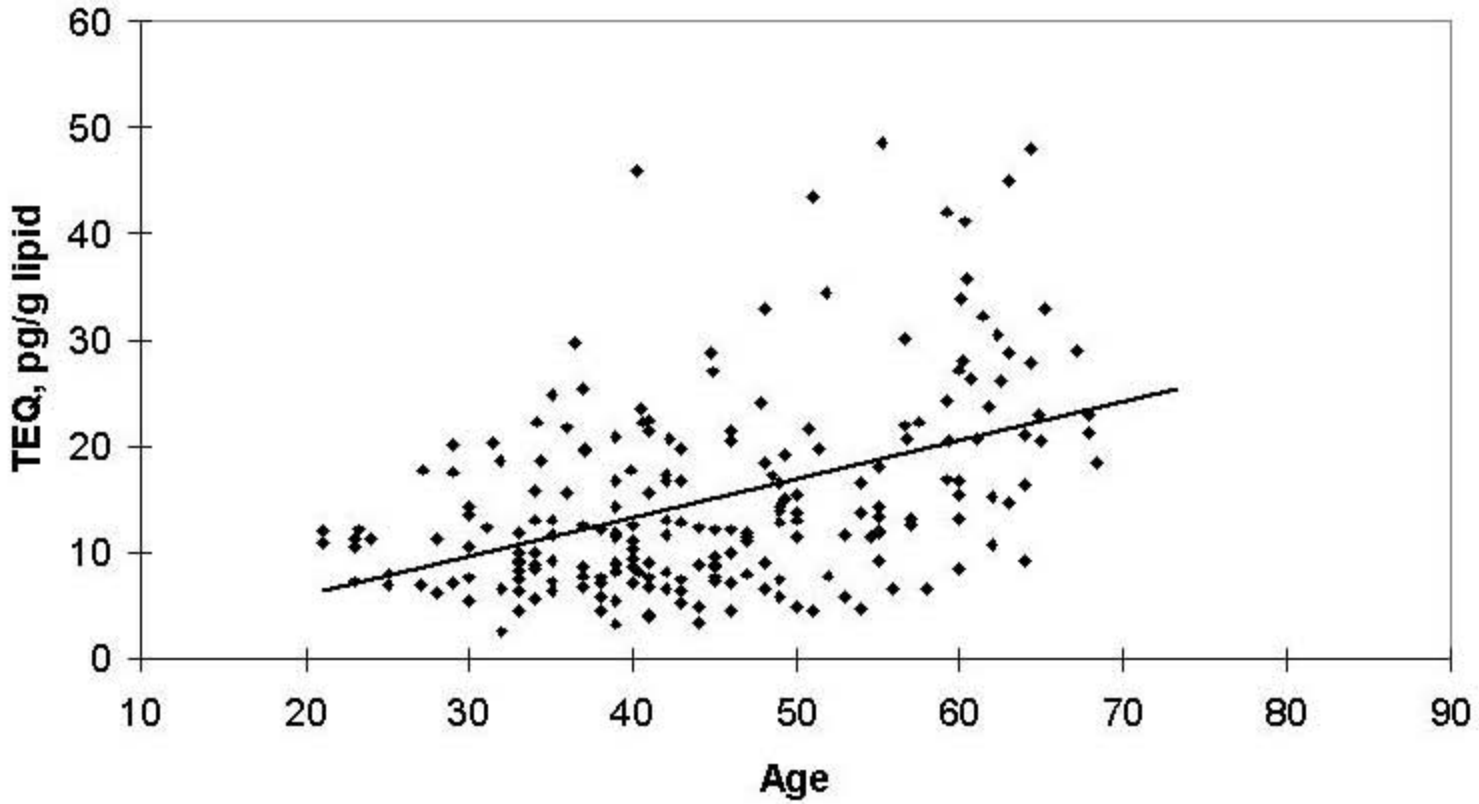


Figure 4-3. Blood levels (I-TEQ for CDD/CDF + WHO_{94}) versus age of a subset of participants in the CDC (2000).

Source: ATSDR, 1999b

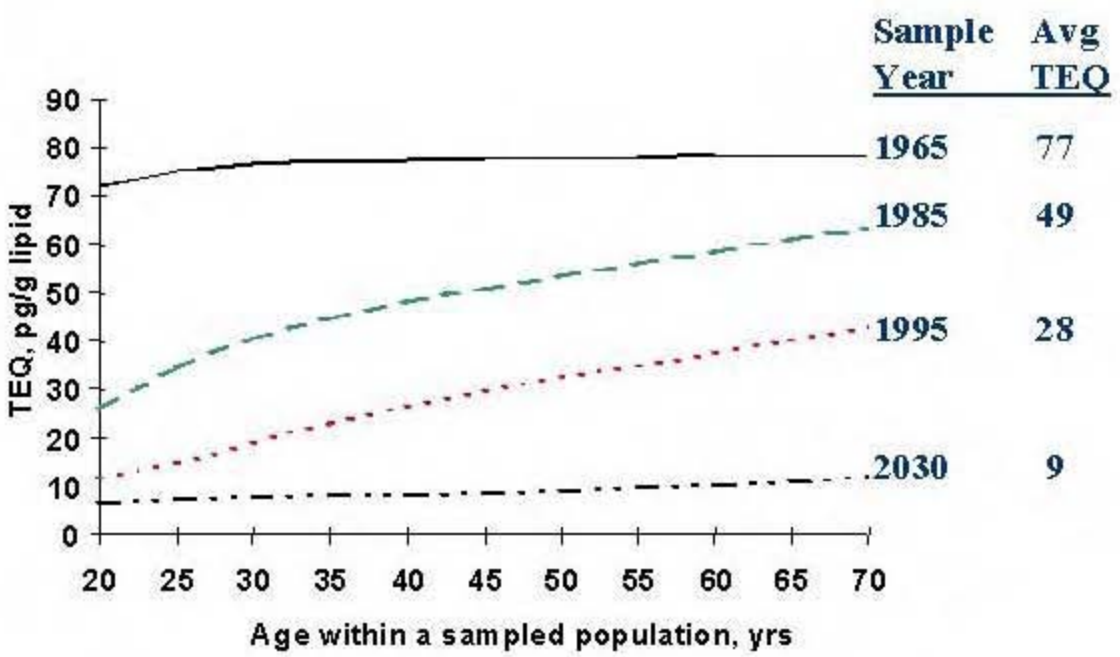
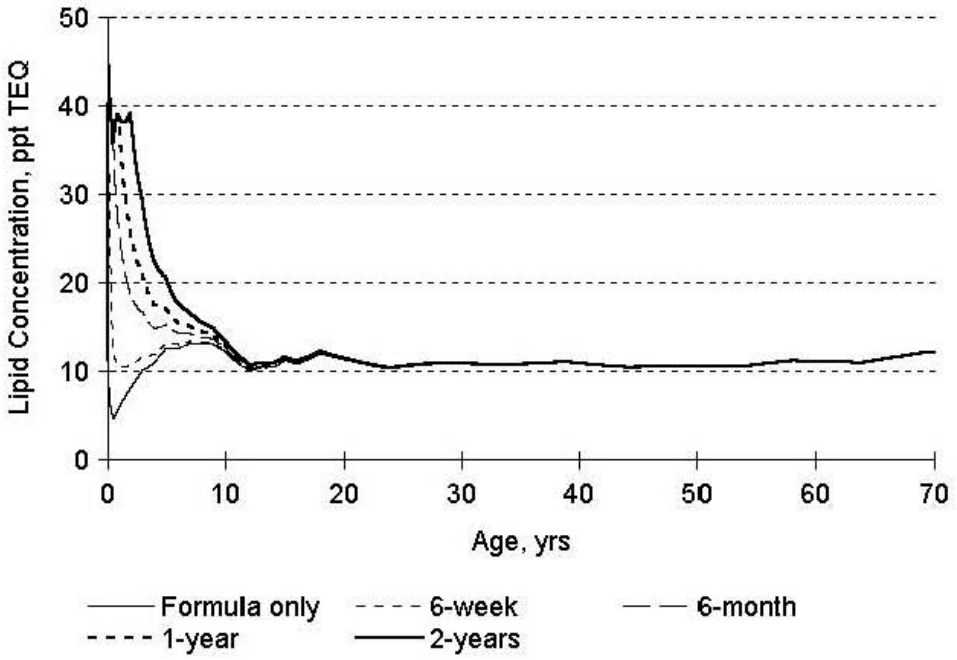


Figure 4-4. Predicted distributions and average TEQ_{DF} - WHO_{98} concentrations within an adult population for four years: 1965, 1985, 1995, and 2030. (CDD/CDFs only, not PCBs).

Source: Adapted from Lorber, 2002

(A)



(B)

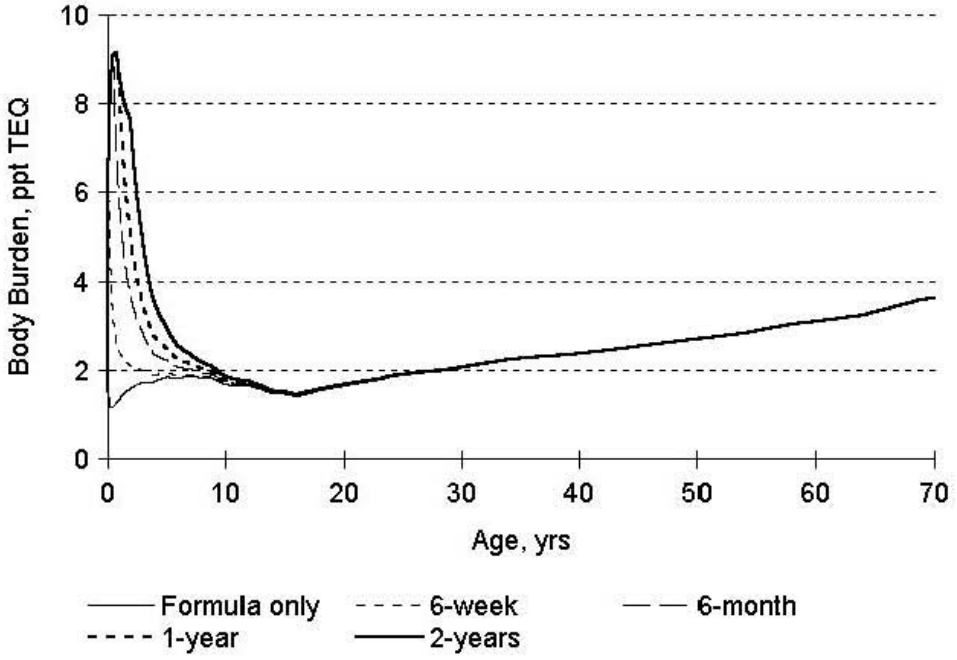


Figure 4-5. Demonstration of the model for evaluating impacts on lipid concentrations (A) and body burdens (B) of infants resulting from various nursing scenarios during a lifetime.

5. DOSE-RESPONSE CHARACTERIZATION

Previous sections of this integrated summary focused on characterizing the hazards of and exposure to dioxin-like compounds. In order to bring these issues together and provide an adequate characterization of risk, the relationships of exposure to dose and, ultimately, to response must be evaluated. Key questions to be asked include: (1) What can be said about the shape of the dose-response function in the observable range and what does this imply about dose-response in the range of environmental exposures? and (2) What is a reasonable limit (critical dose or point of departure [POD]) at the lower end of the observable range and what risk is associated with this exposure? In addition, one can address the issue of extrapolation beyond the range of the data in light of the answers to the above questions. Although extrapolation of risks beyond the range of observation in animals and/or humans is an inherently uncertain enterprise, it is recognized as an essential component of the risk assessment process (NAS/NRC, 1983). The level of uncertainty is dependent on the nature (amount and scope) of the available data and on the validity of the models that have been used to characterize dose-response. These form the bases for scientific inference regarding individual or population risk beyond the range of current observation (NAS/NRC, 1983, 1994).

Dose-response analysis can be implemented in a variety of ways in risk assessment, depending on the extent and quality of the available data. At the basic level, dose-response information comes from a comparison of doses or levels at which there are no observed adverse effects with those at which the lowest adverse effect is observed. Such an analysis can be enhanced through the application of mathematical models to interpolate between empirically measured data points (plus incorporating their statistical variability), with the option for extrapolation below these data points subject to model shape assumptions when going beyond the range of known data. One such form of modeling is the benchmark dose (BMD) analysis, where a mathematical model is used to calculate the dose necessary to elicit a predetermined response rate (e.g., an effective dose [ED] for a 1% response: ED_{01}). Ultimately, the development and use of physiologically-based pharmacokinetic PBPK models and biologically-based dose response models goes beyond the mathematical replication of data points by linking the model to relevant and measurable biological parameters in the species of interest, and potentially between species (Kim et al., 2002).

These dose-response concepts are developed in Part II, Chapter 8, where the body of literature concerning dose-response relationships for TCDD is presented. Among other things, this chapter addresses the important concept of selecting an appropriate metric for cross-species

scaling of dose and presents the results of empirical modeling for many of the available data sets on TCDD exposures in humans and in animals. Although not all human observations or animal experiments on TCDD are amenable to this level of dose-response modeling, more than 200 data sets were evaluated for shape, leading to an effective dose value expressed as a percent response being presented for each endpoint being evaluated.

The analysis of dose-response relationships for TCDD, considered within the context of toxic equivalency, mechanism of action, and background human exposures, helps elucidate the common ground and the boundaries of the science and science policy components inherent in this risk characterization for the broader family of dioxin-like compounds. For instance, the dose-response relationships provide a basis to infer a POD for extrapolation for cancer and noncancer risk for a complex mixture of dioxin-like congeners given the assumption of toxic equivalency as discussed in Part II, Chapter 9, Section 9.6. Similarly, these relationships provide insight into the shape of the dose-response at the POD, which can help inform choices for extrapolation models for both TCDD and total TEQ. Dose-response modeling also provides a perspective on the relationship between the level at which effects are seen in experimental systems or epidemiologic studies and background exposures and body burdens for dioxin and related compounds.

In evaluating the dose-response relationships for TCDD as a basis for assessing this family of compounds, both empirical dose-response modeling approaches and mode of action based approaches have been developed and applied (see Part II, Chapter 8, Section 8.3 and 8.4; Portier et al., 1996; Kim et al., 2003). Empirical models have advantages and disadvantages relative to more ambitious mechanism-based models. Empirical models provide a simple mathematical model that adequately describes the pattern of response for a particular data set; they can also provide the means for hypothesis testing and interpolation between data points. In addition, they can provide qualitative insights into underlying mechanisms. However, the major disadvantage of empirical models is their inability to quantitatively link data sets in a mechanistically meaningful manner. On the other hand, mechanism-based modeling can be a powerful tool for understanding and combining information on complex biological systems. Use of a truly mechanism-based approach can, in theory, enable more reliable and scientifically sound extrapolations to lower doses and between species. However, any scientific uncertainty about the mechanisms that the models describe is inevitably reflected in uncertainty about the predictions of the models.

PBPK models have been validated in the observable response range for numerous compounds in both animals and humans. The development of PBPK models for disposition of

TCDD in animals has proceeded through multiple levels of refinement, with newer models showing increasing levels of complexity by incorporating data for disposition of TCDD and its molecular actions with the AhR and other proteins, as well as numerous physiological parameters (Part II, Chapter 1). These models have provided insights into key determinants of TCDD disposition in treated animals. Development of such models continues and the current generation of dioxin PBPK models are being submitted for publication (DeVito et al., personal communication). Pharmacokinetic models have been extended to generate predictions for early biochemical consequences of tissue dosimetry of TCDD, such as induction of CYP1A1, and are being developed to address the impacts of enzyme induction (e.g., CYP1A2) on TCDD storage and half-life. It is anticipated that these enhanced PBPK models will improve the understanding of early phase human distributional and half-life kinetic data. However, extension of these models to more complex responses is more uncertain at this time, particularly regarding selection of the appropriate tissue metric to link to the effect(s) under consideration. Differences in interpretation of the mechanism of action embodied in these pharmacodynamic models lead to varying estimates of dose-dependent behavior for similar responses. The shape of the dose-response curves governing extrapolation to low doses are determined by these hypotheses and assumptions.

At this time, the knowledge of the mechanism of action of dioxin, receptor theory, and the available dose-response data do not firmly establish a scientific basis for replacing a linear procedure for estimating cancer potency. Consideration of this same information indicates that the use of different procedures to estimate the risk of exposure for cancer and noncancer endpoints may not be appropriate. Both the cancer and noncancer effects of dioxin appear to result from qualitatively similar modes of action. Initial steps in the process of toxicity are the same, and many early events appear to be shared. Thus, the inherent potential for low dose significance of either type of effect (cancer or noncancer) should be considered equal and evaluated accordingly. In the observable range around 1% excess response, the quantitative differences are relatively small. Below this response, the different mechanisms can diverge rapidly. The use of predicted biochemical responses as dose metrics for toxic responses is considered a potentially useful application of these models. However, greater understanding of the linkages between these biochemical effects and toxic responses is needed to reduce the potentially large uncertainty associated with these predictions.

5.1. DOSE METRIC(S)

One of the most difficult issues in risk assessment is determining the dose metric to use for animal-to-human extrapolations. An appropriate animal-to-human extrapolation of tissue dose is required to provide significant insight into differences in sensitivity among species. As noted in Section 1.3, the most appropriate dose metric should reflect both the magnitude and frequency of exposure, and it should be clearly related to the toxic endpoint of concern by a well-defined mechanism. However, this is often difficult, because human exposures with observable responses may be very different from highly controlled exposures in animal experiments. In addition, comparable exposures may be followed by very different pharmacokinetics (absorption, distribution, metabolism and/or elimination) in animals and humans. Finally, the sequelae of exposure in the form of a variety of responses related to age, organ, and species sensitivity complicate the choice of a common dose metric. Despite these complexities, relatively simple default approaches, including body surface or body weight scaling of daily exposures, have often been recommended (U.S. EPA, 1992a, 1996; ATSDR, 1999).

As discussed in Section 1.3, dose can be expressed in a number of ways. For TCDD and other dioxin-like compounds, attention has focused on the consideration of dose expressed as daily intake (ng/kg/day), body burden (ng/kg), or AUC (DeVito et al., 1995; Aylward et al., 1996). The concept of physiological time (lifetime of an animal) complicates the extrapolation, as the appropriate scaling factor is uncertain for toxic endpoints. Because body burden incorporates differences between species in TCDD half-life (these differences are large between rodent species and humans [see Part II, Chapter 8, Table 8.2]), this dose metric appears to be the most practical for many effects of this class of compounds (DeVito et al., 1995).

Average lifetime body burden is best suited for steady-state conditions, with difficulties arising when this dose metric is applied to the evaluation of acute exposures, such as those occurring in the 1976 accidental exposure in Seveso, Italy (Bertazzi and di Domenico, 1994). In cases such as this one, increased body burden associated with the acute exposure event is expected to decline (half-life for TCDD is approximately 7 years) until it begins to approach a steady-state level associated with the much smaller daily background intake. In general, daily excursions in human exposure are relatively small and have minor impact on average body burden. Instead, PBPK models suggest that human body burdens increase over time and begin to approach steady-state after approximately 25 years with typical background doses. Occupational exposures represent the middle ground where daily excursions during the working years can significantly exceed daily background intakes for a number of years, resulting in elevated body burdens.

The relationship between occupational exposures and body burden and between body burden and AUC are demonstrated in Figure 5-1. This figure graphs two hypothetical body burden scenarios during the 70-year lifespan of an individual. The first is a continuation to 70 years of age of the background body burden scenario discussed—with caveats and assumptions— in Part I, Volume 3, Chapter 5. In this scenario, an infant is breast-fed for 6 months by a mother who has a background dioxin body burden level and is subsequently exposed to the average current level of dioxin in the food supply (1 pg/kg/day). This background scenario leads to a 70 year lifetime area under the curve (AUC) of 184 ng/kg*Y, equivalent to a lifetime average body burden (LABB) of 2.6 ng/kg (~184/70 years).

In the second scenario, the same individual incurs an additional occupational exposure between 20 and 30 years of age of 100 pg/kg/day—100 times background—which then ceases. The buildup of dioxin body burden is evident in the peak level and shark fin appearance. AUC in this occupational scenario is 3911 ng/kg*Y, and LABB is 55.9 ng/kg. Note that in the occupational scenario the AUC and LABB are only 21 times background.

Table 5-1 and Figure 5-2 summarize literature on average levels of dioxin TEQs in the background human population and peak levels in commonly cited epidemiological cohorts. Table 5-1 collates data on tissue lipid levels (ppt lipid adjusted) in populations, principally from serum, and tabulates either current levels for the background population or back-calculated peak levels for the exposed cohorts. Figure 5-2 graphs the estimated range and central tendency of the total TEQ_{DFP} body burden (ng/kg whole body), combining the range of measured 2,3,7,8-TCDD values with the estimate of the background non-2,3,7,8-TCDD TEQ level from the U.S. population in the late 1980s/early 1990s. TEQ levels are calculated for PCDD, PCDF, and PCBs, based on TEQ_{DFP}-WHO_{98} values, and assume a constant 25% body fat ratio when converting from serum lipid ppt to ng/kg body burden. Total TEQ values for the Hamburg cohort women were calculated by the authors, but did not include a dioxin-like PCB contribution. Seveso values reported by Needham et al. (1999) are based on stored serum samples from subjects undergoing medical examinations contemporaneous with the exposure and were not back-calculated. Additional information consistent with Figure 5-2 has recently been published (Eskenazi et al., 2004) that demonstrate similar Seveso Zones A and B initial levels, with an important further measurement of background 2,3,7,8-TCDD (20.2 ppt serum lipid) and other congener TEQ contributions (80.2 ppt) in the unexposed background population (non-ABR women) in this time period.

As discussed earlier, using background total body burden (TEQ_{DFP}-WHO_{98}) as a point of comparison, these often-termed "highly exposed" populations have peak body burdens that are

relatively close to general population backgrounds at the time. When compared with background body burdens of the late 1980s, many of the median values and some of the mean values fall within a range of one order of magnitude (factor of 10) and all fall within a range of two orders of magnitude (factor of 100). General population backgrounds at the time are likely to have been higher than present background body burdens.

One uncertainty in comparing peak body burdens is the use of a first-order elimination rate with an overall half-life of 7.1 years. Recent evidence suggests that the elimination of TCDD may be dependent on the level of exposure, in addition to an early distributional or sequestration phase. Populations with high exposures may have half-lives significantly less than 7.1 years. Relatively rapid early elimination was noted in two highly exposed Austrian women (initial half-lives of ~1.5 and 2.9 years; Geusau et al., 2002). Supportive data are also available through an analysis of the Seveso populations (Michalek et al., 2002). In this analysis, a period of fast elimination within the first 0.27 years after the exposure in Seveso was observed, followed by a period of slower elimination between 3 and 16.35 years from exposure. The mean TCDD half-life in the first 0.27 years after exposure in the Seveso cohort was 0.34 years in males (n=6) and 0.43 years in females (n=10). From 3 years onward in the Seveso cohort, the half-life in males was 6.9 years (n=9) and 9.6 years in females (n=13). For Ranch Handers, the half-life was 7.5 years (n=97) between 9 and 33 years after exposure. This analysis indicates that dioxin body burdens and elimination kinetics may be more complex at higher doses than represented by a single first-order half-life, including issues of tissue distribution and dose-dependent elimination. This is consistent with the limited data available in rodents that also indicates a dose-dependent elimination.

There are a number of physiologically-based pharmacokinetic models of TCDD in both experimental animals and humans. Several of the rodent models assume that the elimination rate of TCDD is a constant (Wang et al., 1997; 2000; Emond et al., 2004). One model by Anderson et al. (1993) has a dose dependent doubling of the elimination rate which is dependent upon Ah receptor occupancy. Kohn et al. (1993; 1996) has the elimination rate increasing in proportion to body weight and includes an increased elimination of TCDD from the liver at high doses due to hepatocyte cell death. The Carrier et al. (1995a, b) model describes a dose-dependent elimination of TCDD and other dioxins due to a dose-dependent hepatic sequestration of these chemicals. While these models use different approaches, they all provide reasonable fits to the available experimental data.

Attempts to develop pharmacokinetic models for TCDD in humans have also resulted in a variety of mathematical descriptions of the elimination rate. Maruyama et al. (2002, 2003)

have assumed that the elimination rate is constant. Van der Molen et al. (1998; 2000) multiply a constant elimination rate by the ratio of liver fat/body fat. This results in an overall change in the elimination of TCDD based on body composition and body weight. Gentry et al. (2003) and Clewell et al. (2004) describe the elimination of TCDD in proportion to hepatic CYP1A2 expression. Aylward et al. (2004) modified the Carrier et al. (1995a, b) model to include an elimination of dioxins directly into the large intestine based on lipid partitioning. This model provided reasonable fits to data from Seveso patients as well as three Austrian patients. Finally, Michalek et al. (2002) used a classical pharmacokinetic approach to describe the Seveso data. This work suggests that there is an early distribution phase that results in a rapid loss of TCDD from the blood (half-life of 0.37 years) followed by a prolonged terminal elimination phase (half-life approximately 6.9 years).

Hence, there are a number of pharmacokinetic models available that describe the absorption, distribution and elimination of TCDD in animals and humans. While these models provide reasonable fits to the available data, they employ a wide range of descriptions of the elimination of TCDD. Some assume first order elimination, while others assume dose-dependent pharmacokinetics. Others suggest that body composition significantly influences the elimination of dioxins. Presently, it is difficult to determine which of these model structures provides the most accurate description of the pharmacokinetics of TCDD and other dioxins.

Advances in understanding the dose-dependency of the pharmacokinetics of TCDD and related chemicals will improve our ability to describe the relationship between exposure, dose and response. The development of more accurate models may affect both exposure group assignment in epidemiology studies and the calculation of dose-response curves, although the magnitude and direction of these postulated impacts remains to be quantified. Estimates of back-calculated doses are important because the ability to detect effects in epidemiologic studies is dependent on a sufficient difference between control and exposed populations. Using published first-order back-calculation procedures, the relatively small difference (< 10–100-fold) in body burden between exposed and controls in the dioxin epidemiology studies makes exposure characterization in the studies a particularly serious issue. This point also strengthens the importance of measured blood or tissue levels in the epidemiologic analyses, despite the uncertainties associated with calculations extending the distribution of measured values to the entire cohort and assumptions involved in back-calculations.

As a bounding exercise on the impact of half-lives on back-extrapolated exposure estimates, EPA has compared the impacts of varying half-life values on back-calculated peak and AUC results. This scenario is constructed by calculating the peak body burden 20 years prior to a

terminal level for various half-lives versus a 7.1 year fixed half-life, assuming first order kinetics ($C_t = C_0e^{-rt}$). A constant dosing regimen is then constructed to simulate an occupational exposure that would achieve these same peak body burdens following 10 years exposure, maintaining the same half-life as in the 20 year follow-up. For each half-life value, a different dose level is necessary and was mathematically derived to reach the required peak level after ten years occupational exposure.

In this occupational scenario, peak and AUC ratios ($AUC_{variable\ half\text{-}life}/AUC_{7.1years}$) varied in a non-linear manner depending on the input half-life. Half-life values of 4 years and longer had low, single digit numerical impacts on the peak and AUC ratios compared to the 7.1 year half-life results (e.g., at a 4 year half-life, the ratio for the peak value = 4.6, the AUC ratio = 3.8; at a 5 year half-life, the ratio for peak = 2.3, AUC = 2). At half-lives below 4 years, peak and AUC ratios rose dramatically to approximately 1 and 2 orders of magnitude for 3 and 2 year half-lives, respectively. The terminal body burden did not influence the ratio because the mathematical function remained constant. More complex PBPK models, where half-life varies with body burden, are under development and will be more influenced by the terminal body burden for each individual. This bounding exercise suggests that impacts on back-calculated peak and AUC values may become significant if the models predict prolonged periods with half-lives of less than 4 years.

5.1.1. Calculations of Effective Dose

Comparisons across multiple endpoints, multiple species, and multiple experimental protocols are too complicated to be made on the basis of the full dose-response curve. As discussed above, comparisons of this sort can be made by either choosing a given exposure and comparing the responses or choosing a particular response level and comparing the associated exposures. In the analyses contained in Chapter 8, Section 8.3, and elsewhere in the reassessment, emphasis is placed on comparing responses using estimated exposures associated with a given level of excess response or risk. To avoid large extrapolations, this common level of excess risk was chosen such that for most studies the estimated exposure is in or near the range of the exposures seen in the studies being compared, with extra weight given to the human data. A common metric for comparison is the effective dose, which is the dose resulting in an excess response over background in the studied population. This excess response rate can be calculated as a fraction of the minimum to maximum response (e.g., 1% increase in risk). Alternatively, for continuous data the dose can be calculated as the amount necessary to move an additional percentage of distribution of the response past a predetermined "effect" level. EPA

has suggested this approach in calculating BMDs (Allen et al., 1994) and in its proposed approaches to quantifying cancer risk (U.S. EPA, 1996, 1999, 2003).

Although effective dose evaluation at the 10% response level (ED_{10} or lower bound on ED_{10} [LED_{10}]) is somewhat the norm, given the power of most chronic toxicology studies to detect an effect, this level is actually higher than those typically observed in the exposed groups in studies of TCDD impacts on humans. To illustrate, lung cancer mortality has a background lifetime risk of approximately 4% (smokers and nonsmokers combined), so that even a relative risk of 2.0 (two times the background lifetime risk) represents approximately a 4%, or 4 in 100, increased lifetime risk (see Chapter 8 for a comprehensive elaboration of formulae). On the basis of this observation, and recognizing that many of the TCDD-induced endpoints studied in the laboratory include 1% effect levels in the experimental range, Chapter 8 presents effective doses of 1%, or $ED_{01,}$ and 10%, or ED_{10}, values.

The use of effective dose values below 10% is consistent with the Agency's guidance on the use of mode of action in assessing risk, as described in the proposed carcinogen risk assessment guidelines (U.S. EPA, 1996, 1999, 2003) and in the evaluation framework discussed in Section 3.3, in that the observed range for many "key events" for TCDD extends down to or near the 1% response level. Determining the dose at which key events for dioxin toxicity begin to be seen in a heterogeneous human population provides important information for decisions regarding risk and safety.

5.2. EMPIRICAL MODELING OF INDIVIDUAL DATA SETS

As described in Chapter 8, Section 8.3, empirical models have advantages and disadvantages relative to more ambitious mechanism-based models. Empirical models provide a simple mathematical model that adequately describes the pattern of response for a particular data set and that can also provide the means for hypothesis testing and interpolation between data points. In addition, they can provide qualitative insights into underlying mechanisms. However, the major disadvantage is their inability to quantitatively link data sets in a mechanistically meaningful manner.

Data available for a number of biochemical and toxicological effects of TCDD and for its mechanism of action indicate that there is good qualitative concordance between responses in laboratory animals and humans (see Table 2-1). In addition, as described below, human data on exposure and cancer response appear to be qualitatively consistent with animal-based risk estimates derived from carcinogenicity bioassays. These and other data presented throughout this reassessment would suggest that animal models are generally an appropriate basis for estimating

human responses to dioxin-like compounds. Nevertheless, there are clearly differences in exposures and responses between animals and humans, and recognition of these is essential when using animal data to estimate human risk. The level of confidence in any prediction of human risk depends on the degree to which the prediction is based on an accurate description of these interspecies extrapolation factors. See Chapter 8, Section 8.3, for a further discussion of this point.

Almost all dioxin research data are consistent with the hypothesis that the binding of TCDD to the AhR is the first step in a series of biochemical, cellular, and tissue changes that ultimately lead to toxic responses observed in both experimental animals and humans (see Part II, Chapter 2, Section 2.3). Therefore, an analysis of dose-response data and models should use, whenever possible, information on the quantitative relationships among ligand (i.e., TCDD) concentration, receptor occupancy, and biological response. However, it is clear that multiple dose-response relationships are possible when considering ligand receptor-mediated events. For example, dose-response relationships for relatively simple responses, such as enzyme induction, may not accurately predict dose-response relationships for complex responses such as developmental effects and cancer.

Cell- or tissue-specific factors may determine the quantitative relationship between receptor occupancy and the ultimate response. Indeed, for TCDD there are much experimental data from studies using animal and human tissues to indicate that this is the case. This serves as a note of caution, as empirical data on TCDD are interpreted in the broader context of complex exposures to mixtures of dioxin-like compounds as well as to nondioxin-like toxicants.

As for other chemical mechanisms where high biological potency is directed through the specific and high-affinity interaction between chemical and critical cellular target, the supposition of a response threshold for receptor-mediated effects is a subject for scientific debate. The basis of this controversy has been summarized by Sewall and Lucier (1995).

Based on classic receptor theory, the occupancy assumption states that the magnitude of biological response is proportional to the occupancy of receptors by drug molecules. The "typical" dose-response curve for such a receptor-mediated response is sigmoidal when plotted on a semilog graph or hyperbolic if plotted on an arithmetic plot. Implicit in this relationship is low-dose linearity (0–10% fractional response) through the origin. Although the law of mass action predicts that a single molecule of ligand can interact with a receptor, thereby inducing a response, it is also widely held that there must be some dose that is so low that receptor occupancy is trivial and, thus, no perceptible response is obtainable.

Therefore, the same receptor occupancy assumption of the classic receptor theory is interpreted by different parties as support for and against the existence of a threshold. It has been stated that the occupancy assumption cannot be accepted or rejected on experimental or theoretical grounds (Goldstein et al., 1974). To determine the relevance of receptor interaction for TCDD-mediated responses, one must consider (1) alternatives as well as limitations of the occupancy theory, (2) molecular factors contributing to measured endpoints, (3) limitations of experimental methods, (4) contribution of measured effect to a relevant biological/toxic endpoint, and (5) background exposure.

Throughout this reassessment, each of these considerations has been explored within the current context of the understanding of the mechanism of action of TCDD, of the methods for analysis of dose-response for cancer and noncancer endpoints, and of the available data sets of TCDD dose and effect for several rodent species, as well as humans who were occupationally exposed to TCDD at levels exceeding the exposure of the general population.

5.2.1. Cancer

As discussed in Section 2.2.1.4, TCDD is characterized as carcinogenic to humans when using a weight-of-evidence approach, and is a carcinogen in all species and strains of laboratory animals tested. The epidemiological database for TCDD, described in detail in Part II, Chapter 7a, suggests that exposure may be associated with increases in all cancers combined and respiratory cancer and with the possibility of elevated risks at other sites. Although there are sufficient data in animal cancer studies to model dose-response for a number of tumor sites, as with many chemicals it is generally difficult to find human data with sufficient information to model dose-response relationships. For TCDD, three studies of human occupational exposure have sufficient information to perform a quantitative dose-response analysis: Becher et al. (1998) (the Hamburg cohort); Ott and Zober (1996) (the BASF cohort); and Steenland et al. (2001) (the NIOSH cohort).

The all-cancer mortality ED_{01}/LED_{01} results from these three studies are detailed in Part II, Chapter 8, Section 8.3, and tabulated and graphed in Table 5-2, along with the bioassay results for liver cancer in female Sprague-Dawley rats (Kociba et al., 1978). Table 5-2 includes only the results and mathematical formulae that were published by the primary authors in the peer-reviewed literature. These calculations and formulae were chosen because they are based on the full primary data set and not on secondary analyses using summary results. In order to graph results for the occupational cohort studies, the central points for data ranges were requested from,

and kindly provided by, the authors (Drs. Steenland, Zober and Becher) and are included in the table.

Slightly different approaches are used for modeling cancer in humans than are used for modeling in animal studies. The modeling approach used in the analysis of the human epidemiology data for all cancers combined and lung cancer involves applying the estimated human body burden-to-cancer response and estimating parameters in a mathematical risk model for each data set. For the three occupational cohort studies, exposure subgroups were defined by the authors using measured and then back-extrapolated TCDD levels in a subset of workers to inform exposure calculations for the remainder of the cohort. None of the studies sampled TCDD blood serum levels for more than a fraction of its cohort, and these samples were generally taken decades after the last known exposure. In each study, serum fat or body fat levels of TCDD were back-calculated using a first-order model. The assumed half-life of TCDD used in the model varied from study to study.

Steenland et al. and Becher et al. used the measured and back-extrapolated TCDD concentrations to refine and quantitate job exposure matrices, which were then used to estimate dioxin cumulative dose for each member of their entire cohort. Ott and Zober (1996a) used regression procedures with data on time spent at various occupational tasks to estimate TCDD levels for all members of the cohort. The cohorts were then divided into exposure groups on the basis of the estimated TCDD levels. As noted, central measures of the ranges from the primary data were provided to the Agency by the authors, removing the need to estimate this parameter from the upper and lower range points in the literature.

Risk outcomes in these cohorts were expressed as standardized mortality ratios (SMRs) or rate ratios. SMRs are calculated by comparing the cancer rates in the subcohorts to the age- and gender-matched general community in that time period. SMR results are usually expressed as a ratio, with SMR = 100 set as the community, or expected, cancer death rate. Rate ratios are calculated from within cohort data using the lowest exposed group as the control value for both dose and risk. Although the lowest exposed group is defined to have a risk equal to unity (rate ratio = 1), this low group may not, in fact, have an SMR equal to the general community (it could be either lower or higher).

The three occupational cohort studies provide best fit dose-response models within the range of their data. These models and the resulting formulae allow for the calculation of ED_{01}/LED_{01} values, from which a linear extrapolation can be performed, consistent with the EPA's draft cancer guidelines. There are several assumptions and uncertainties involved in modeling these data, including extrapolation of dosage (both in back-calculation and in

elimination kinetics), the type of extrapolation model employed, and whether the origin point should be fixed (i.e., SMR = 100) or allowed to float.

Based on the model formulae using the full data set as provided in the primary literature (Steenland et al., 2001; Ott and Zober, 1996; Becher et al., 1998; detailed in Chapter 8), the calculated ED_{01} central estimates for all cancers combined range from 1.4 to 62 ng TCDD/kg LABB (Table 5-3). The lower bounds on these doses (based on a modeled 95% CI) range from 0.71 ng TCDD/kg to 30.5 ng TCDD/kg (not available for models published by Becher et al., 1998, due to the absence of statistical parameter measures). A parallel measure of unit excess risk per one part per trillion TCDD body burden above background (assumed 5 ppt) is also tabulated. These values are strongly dependent on the study chosen and the model used, and it must be recognized that the risks posed to some members of the population from TCDD may be zero, depending on the model chosen to extrapolate results below the range of observation. Male and female values do not match because of differences in the input variable of background lifetime all-cancer mortality risk.

Analysis of model results indicates that the power model applied to the Steenland et al. (2001) data leads to unreasonably high risks at low exposure levels, based on calculations of the attributable risk that this model would predict from background dioxin levels in the general population. This result is due to the very steep slope of this power curve at low environmental levels. The steep dose-response curve also makes the power model very sensitive to the background dose that is incorporated into the calculations and the location of the calculation point on the dose-response curve. Exclusion of the Steenland et al. power model reduces the ED_{01} range to 6–62 ng TCDD/kg LABB and the LED_{01} range to 11.5–31 ng TCDD/kg LABB (lower confidence values were unavailable for the Becher et al. 1998 data). For the purposes of this assessment, the piecewise linear formula published by Steenland et al. (2001) is the preferred model from this data set.

These epidemiologically derived ED_{01} values are summarized in Table 5-4 (additional details in Part II, Chapter 8), along with the resulting cancer slope factors. The results of the Kociba et al. (1978) cancer bioassay are also included in Table 5-4 for comparison purposes, using the Goodman and Sauer (1992) revision to the liver tumor pathology results. Dose-response modeling for this bioassay used the EPA Benchmark Dose software and multistage model to calculate the ED_{01}/LED_{01}. The similarity between the cancer bioassay ED_{01} results in rodents (Kociba et al. 1978) and the human epidemiology results is noteworthy when the exposure metric is based on lifetime average body burden (LABB). LABB is calculated as the AUC divided by lifetime years, and it equilibrates tissue doses across species.

The epidemiological data and dose-response models have stimulated considerable contemporary interest and statistical analysis, particularly the option of performing a pooled or meta-analysis on the entire occupational cohort data set. In reviewing this literature, care should be taken to note which published analyses form the basis for the statistical tests, the recent provision of data-derived central dose estimates for the ranges given in the literature (courtesy of the primary authors), and the availability of more detailed primary dose-response literature (Steenland et al., 2001; Becher et al., 1998), which supercede studies used previously (Aylward et al., 1996; Flesch-Janys et al., 1998). For instance, the dose-response pattern for the NIOSH cohort summary data, as published by Aylward et al. (1996), demonstrates a different high dose point from the more recent and detailed analysis of the full dataset, as published by Steenland et al. (2001).

Starr (2001, 2003) reviewed meta-analysis data and results that were included in the external review draft of the EPA dioxin reassessment, and the analysis performed by Crump et al. (2003; see below). The draft EPA meta-analysis was based on summary results published by Aylward et al. (1996; NIOSH), Ott and Zober (1996; BASF), and Flesch-Janys et al. (1998). Exposure range midpoints were either obtained from the original publication (Aylward et al., 1996) or were based on a log-normal fit to the data ranges to estimate the midpoint (for Ott and Zober, 1996; Flesch-Janys et al., 1998). On the basis of these earlier data sets and the application of a linear model, Starr concluded that the assumption of a fixed origin at an SMR = 100 should be rejected on statistical grounds. Although a significantly increased cancer risk was evident in these cohorts, the overall results using an unconstrained linear model (not fixed to the SMR = 100 point) were concluded to be consistent with the null hypothesis of no dose-response relationship between TCDD and the cancer rate.

In a subsequent dioxin meta-analysis performed as part of the Joint European Commission on Food Additives, Crump et al. (2003) performed similar and expanded statistical analyses on a more recent data set using data-derived central estimates of exposure levels for Ott and Zober (1996; Hamburg cohort) and from Steenland et al. (2001; NIOSH cohort). Fitting a linear model to the data again indicated that the baseline SMR = 100 assumption could be rejected, based on statistical tests.

Goodness of fit trend tests for this linear model were statistically significant both with the background SMR set equal to 100 and with the background SMR estimated (p=0.01). A further series of trend tests were performed by successively removing the highest cumulative exposure to determine the lowest exposure for which there remained statistically significant evidence for an effect. This progressive analysis of the data was considered by Crump et al. to provide a more

robust test for trends than a linear goodness of fit test. The analysis demonstrated an increase in total cancer at cumulative TEQ serum levels that would result from a lifetime average intake of 7 pg TEQ/kg body weight/day (assuming 50% uptake, $t_{1/2}$ 7.6 years, 25% body fat), with no trend for increase at 6 pg/kg/day.

The pooled analysis of the Ott and Zober (1996), Flesch-Janys et al. (1998), and Steenland et al. (2001) data yielded ED_{01} estimates of 51 ng/kg body burden (baseline SMR fixed at 100) and 91 ng/kg body burden (baseline SMR estimated), corresponding to ED_{01} daily intake estimates of 25 and 45 (95% CI = 21–324) pg/kg/day, respectively, above current background TCDD-TEQ for all cancers combined (calculated using the half-life and absorption assumptions in Crump et al.). These results are consistent with the range of ED_{01}s in Part II, Chapter 8, and Tables 5-3 and 5-4. On the basis of their results and comparison to other published analyses, Crump et al. (2003) concluded that they could not see a clear choice between their ED_{01} estimate of 45 pg/kg/day and the Steenland et al. (2001) estimate of 7.7 pg/kg/day, citing advantages to each study.

The choice of model is central to the above statistical analyses of the individual studies and the meta-analysis. The epidemiological data are not sufficient to mandate the selection of any particular model shape. The published literature includes power, linear, piecewise linear, and multiplicative models (see Table 5-2). The EPA's draft carcinogen risk assessment guidelines (U.S. EPA, 1999) propose applying a standard curve-fitting procedure within the range of the data (e.g., Benchmark Dose software), recognizing that more elaborate models will be appropriate for more complex information and that, ultimately, biologically based pharmacokinetic models would be preferred.

The curve-fitting procedure is used to determine a POD, generally at the 10% response level, but where more sensitive data are available, a lower point for linear extrapolation can be used to improve the assessment (e.g., 1% response for dioxin, ED_{01}). Extrapolation from the POD to lower doses is conducted using a straight line drawn from the POD to the origin—zero incremental dose, zero incremental response—to give a probability of extra risk. The linear default is selected on the basis of the agent's mode of action when the linear model cannot be rejected and there is insufficient evidence to support an assumption of nonlinearity. Additional important uncertainties in the human epidemiological data are discussed in Part II, Chapter 8, Section 8.3, and include the representativeness and precision of the dose estimates that were used, the choice of half-life and whether it is dose dependent, and potential interactions between TCDD and smoking or other toxicants.

For the animal data, both empirical and mechanistic models have been applied to examine cancer dose-response. Portier et al. (1984) used a simple multistage model of carcinogenesis with up to two mutation stages affected by exposure to model the five tumor types observed to be increased in the 2-year feed study by Kociba et al. (1978) (Sprague-Dawley rats) and the eight tumor types observed to be increased in the 2-year gavage cancer study conducted by NTP (1982a) (Osborne-Mendel rats and $B6C3F_1$ mice). The findings from this analysis, which examined cancer dose-response within the range of observation, are presented in Part II, Chapter 8, Table 8.3., which is reproduced with slight modifications as Table 5-5. All but one of the estimated ED_{01}s are above the lowest dose used in the experiment (approximately 1 ng TCDD/kg/day in both studies) and are thus interpolations rather than extrapolations. The exception, liver cancer in female rats from the Kociba study, is very near the lowest dose used in this study and is only a small extrapolation (from 1 ng TCDD/kg/day to 0.77 ng TCDD/kg/day). Steady-state body burden calculations were also used to derive doses for comparison across species. Absorption was assumed to be 50% for the Kociba et al. (feed experiment) and 100% for the NTP study (gavage experiment).

The shapes of the dose-response curves as determined by Portier et al. (1984) are also presented in Table 5-5. The predominant shape of the dose-response curve in the experimental region for these animal cancer results is linear. This does not imply that a nonlinear model such as the quadratic or cubic—or for that matter a "J-shaped" model—would not fit these data. In fact, it is unlikely that in any one case a linear model or a quadratic model could be rejected statistically. These studies had only three experimental dose groups; hence, these shape calculations are not based on sufficient doses to guarantee a consistent estimate, and they should be viewed with caution.

The ED_{01} steady-state body burdens range from a low value of 14 ng/kg, based on the linear model associated with liver tumors in female rats, to as high as 1190 ng/kg, based on a cubic model associated with thyroid follicular cell adenomas in female rats. Lower bounds on the steady-state body burdens in the animals range from 10 ng TCDD/kg to 224 ng/kg. The corresponding estimates of daily intake level at the ED_{01} obtained from an empirical linear model range from 0.77 to 43 ng TCDD/kg body weight/day, depending on the tumor site, species, and sex of the animals investigated. Lower confidence bounds on the estimates of daily intake level at the ED_{01} in the animals range from 0.57 to 14 ng TCDD/kg body weight/day.

In addition, using a mechanistic approach to modeling, Portier and Kohn (1996) combined the biochemical response model by Kohn et al. (1993) with a single initiated-phenotype two-stage model of carcinogenesis to estimate liver tumor incidence in female

Sprague-Dawley rats from the 2-year cancer bioassay by Kociba et al. (1978). By way of comparison, the ED_{01} estimate obtained from this linear mechanistic model was 0.15 ng TCDD/kg body weight/day, based on intake, which is equivalent to 2.7 ng TCDD/kg steady-state body burden. No lower bound on this modeled estimate of steady-state body burden was provided.

As discussed in Part II, Chapter 8, Section 8.2, the use of different dose metrics can lead to widely diverse conclusions. For example, the ED_{01} intake for the animal tumor sites presented above ranges from less than 1 to tens of ng/kg/day, and the lowest dose with an increased tumorigenic response (thyroid tumors) in a rat is 1.4 ng TCDD/kg/day (NTP, 1982a). The daily intake of dioxins in humans is estimated at approximately 1 pg TEQ/kg/day. This implies that humans are exposed to doses 1400 times lower than the lowest tumorigenic daily dose in rat thyroid. However, 1.4 ng TCDD/kg/d in the rat leads to a steady-state body burden of approximately 25 ng TCDD/kg, assuming a half-life of TCDD of 25 days and absorption from feed of 50%[2]. If the body burden of dioxins in humans is approximately 20 ng TEQ/kg lipid, or 5 ng TEQ/kg body weight (assuming about 25% of body weight is lipid), "average" humans are exposed to about five times less TCDD than the minimal carcinogenic dose for the rat. The difference between these two estimates is entirely due to the approximately 100-fold difference in the half-life of TCDD in humans and rats. At least for this comparison, if cancer is a function of average levels in the body, the most appropriate metric for comparison is the average or steady-state body burden, because this accounts for the large differences in animal and human half-lives.

Comparisons of human and animal ED_{01}s from Part II, Chapter 8, Section 8.3, for cancer response on a body burden basis show similar potential for the carcinogenic effects of TCDD. In humans, cancer ED_{01}s ranged from approximately 6 ng/kg to 62 ng/kg (excluding the Steenland et al., 2001, power model). This is similar to the empirical modeling estimates from the animal studies, which ranged from 14 ng/kg to 1190 ng/kg (most estimates were in the range of 14 to 500 ng/kg). The lower bounds on the human body burdens at the ED_{01}s (based on a modeled 95% CI) ranged from 11.5 ng TCDD/kg to 31 ng TCDD/kg (again, the lower values that would have resulted from the Becher et al., 1998, analysis could not be included because error bounds on the models were unavailable). Lower bounds on the steady-state body burdens in the animals ranged from 10 ng TCDD/kg to 224 ng/kg. The estimate for the single mechanism-based model presented earlier (2.7 ng/kg) is below the lower end of the human ED_{01} estimates.

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[2]Steady-state body burden (ng/kg) = (daily dose (ng/kg/day) * (half-life)/Ln(2)) (f), where f is the fraction absorbed from the exposure route (unitless) and half-life is the half-life in days.

Using human and animal cancer ED_{01}s, their lower bound estimates, and the value of 2.7 ng TCDD/kg from the single mechanism-based model, slope factors and comparable risk estimates for a human background body burden of approximately 5 ng TEQ/kg (20 ng TEQ/kg lipid) can be calculated using the following equations:

Slope factor (per pg TEQ/kgBW/day) = risk at ED_{01} / intake (pg TEQ/kgBW/day) associated with human equivalent steady-state body burden at $ED_{01,}$ where:

Risk at ED_{01} = 0.01; and

$$\text{Intake (pg TEQ/kg BW/day)} = \frac{[\text{body burden at } ED_{01} \text{ (ng TEQ/kg)} * \text{Ln(2)}]}{\text{half-life (days)} \times f} * 1000 \text{ (pg/ng)} \quad (5\text{-}1)$$

half-life = 2593 days in humans and 25 days in rats (see Table 8.1 in Part II, Chapter 8)

f = fraction of dose absorbed; assumed to be 0.8 (80%)

and

Upper bound on excess risk at human background body burden = (human background body burden (ng/kg))(risk at ED_{01})/lower bound on human equivalent steady-state body burden (ng/kg) at ED_{01}, where: (5-2)

Risk at ED_{01} = 0.01

Use of these approaches reflects methodologies being developed within the context of the revised draft carcinogen risk assessment guidelines (U.S. EPA, 1999, 2003). Under these draft guidelines (EPA, 2003, section 5.4), risk estimates may be based on linear extrapolation or nonlinear hazard quotients, depending on the mode of action, accompanied by a statement on the extent of extrapolation generally expressed as the margin of exposure (MOE = POD/exposure). The formulae used in this quantitative linear analysis for dioxin are approximate for a number of the cancer slope factors derived from human data in Table 5.4 because of the calculation of risk for 1pg TCDD/kg body weight/day above background, the use of lifetable analysis to derive the expected cancer rates, and the changing gradient of the dose-response curves as body burden increases, especially for the power formulae. As discussed below, these methods can be compared to previous approaches using the linearized multistage (LMS) procedure to determine whether the chosen approach has significantly changed the estimation of slope. The estimates of ED_{01}/LED_{01} represent the human-equivalent body burden for 1% excess cancer risk based on exposure to TCDD and are assumed for purposes of this analysis to be equal for TCDD

equivalents (total TEQ). This assumption is based on the toxic equivalency concept discussed throughout this report and in detail in Part II, Chapter 9. All cancer slope factors can be compared to the Agency's previous slope factor of 1.6×10^{-4} per pg TCDD/kg body weight/day, which is equivalent to 1.6×10^{5} per mg TCDD/kg body weight/day (U.S. EPA, 1985).

5.2.1.1. *Estimates of Slope Factors and Risk at Current Background Body Burdens Based on Human Data*

Traditionally, EPA has relied on central estimates of risk from epidemiological studies rather than on upper bound estimates, which can exhibit substantial statistical spread in these results. This practice developed because epidemiological data were most often from high-end occupational exposures—as with the principal dioxin literature—where the data were likely to provide upper estimates of cancer slope and where all excess cancer increases were attributed to the single exposure of interest, amidst a variety of other potential carcinogenic exposures. For the analyses conducted herein, the Agency has presented both central (e.g., ED_{01}) and upper bound (e.g., LED_{01}) estimates where these are available.

The estimates of slope factors (risk per pg TCDD/kg body weight/day) calculated from the human ED_{01}s presented in Part II, Chapter 8, Table 8.3.1, range from 5.1×10^{-3} if the ED_{01} for all cancer deaths in the Hamburg cohort is used to 0.57×10^{-3} if the ED_{01} for all cancer deaths in the smaller BASF cohort is used. All of the other slope factors for all cancer deaths in the three cohorts fall within this range (Table 5-4). The meta-analysis by Crump et al. (2003) leads to similar results, with the reported ED_{01} of 46 ng/kg (95% lower bound = 31 ng/kg) BB, resulting in a cancer slope factor of 0.65 (95% upper confidence limit = 0.97) $\times 10^{-3}$ risk per pg TCDD/kgBW/day (adopting the EPA assumptions of baseline SMR = 100, halflife = 7.1 years, 80% absorption; alternatively, adopting a floating SMR results in a CSF = 0.37 (0.69) $\times 10^{-3}$).

There is no compelling reason to choose one slope factor over the next from among those calculated, given that each study had particular strengths and weaknesses (See Part II, Chapter 7a). The results cluster around a cancer slope factor of 10^{-3} risk/pgTCDD/kg body weight/day above background, which represents EPA's most current upper bound slope factor for estimating human cancer risk based on human data. By inference, this risk value could also apply to total TEQ intake. As described in Section 4.4.2, current intakes in the United States are approximately 1 pg TEQ_{DFP}-WHO_{98}/kg body weight/day, and body burdens are approximately 5 ng TEQ_{DFP}-WHO_{98}/kg body weight (which equates to a serum level of approximately 20 pg/g lipid). Uncertainties associated with these estimates from human studies are discussed in Part II, Chapter 8, Section 8.3, and in Becher et al. (1998).

These estimates compare well with the published estimates of cancer slope and risk for the Hamburg and NIOSH cohorts by Becher et al. (1998) and Steenland et al. (2001), respectively. The risk estimates by Becher et al. were derived from data on TCDD exposure to male workers with a 0 or 10-year latency. These estimates range from 1.3×10^{-3} to 5.6×10^{-3} per pg TCDD/kg body weight/day, and were calculated using German background cancer rates. The fraction of dioxin assumed absorbed is not stated by Becher et al. but, presumably, if the absorption fraction was set at 100%, this would contribute to the slight differences to the EPA values in Table 5.5. The Steenland et al. calculations were performed for either no lag or a 15-year lag. The authors calculated a lifetime all cancer excess risk above background of between 5 x 10^{-4} (piecewise linear) to 9.4 x 10^{-3} (power model) per pgTCDD/kg/day. The Steenland et al. results are lower than those presented in Table 5-4 because the authors assumed 50% absorption and a lower additional dose (i.e., incorporating a two-fold doubling of dose over background into the Steenland et al. results reproduces their calculations).

In both analyses, all excess cancers are attributed to TCDD exposure, despite significant levels of other dioxin-like compounds in blood measurements. Notable, though, is the Becher et al. determination of a very similar slope coefficient for total TEQ and TCDD, based on their measured data, which is consistent with the TEF methodology. The results from Steenland et al. are more consistent with a reduced cancer slope factor when based on TEQ. Although risk estimates using TCDD alone in these cohorts might suggest an overestimate of risk because dose is underestimated, no evidence for this has emerged from the analysis because TCDD dominates the total TEQ in these occupational cohorts.

5.2.1.2. *Estimates of Slope Factors and Risk at Current Background Body Burdens Based on Animal Data*

Upper bound slope factors (per pg TCDD/kg body weight/day) for human cancer risk calculated from lower bounds on ED_{01}s (LED_{01}s) for the animal cancers presented in Table 5-5 range from 3×10^{-3} to 0.1×10^{-3}, that is, from 19 times greater than the previous upper bound estimate on cancer slope (1.6×10^{-4} [U.S. EPA, 1985]) to less than 50% of this value. The highest slope factor is derived from the same study as the 1985 estimate; that is, the slope factor derived from the female liver cancer in the Kociba et al. (1978) study continues to give the highest slope factor.

5.2.1.2.1. ***Reconciling the Portier (1984) and EPA (1985) slope estimates.*** In attempting these comparisons, two issues became apparent. First, the body burden and the intake at the ED_{01} from Portier et al. (1984) does not result in the same slope factor as EPA's (U.S. EPA, 1985). Despite the use of the same study results, a slope factor of 1.8×10^{-5} per pg TCDD/kg body weight/day results when using the LMS approach in Portier et al. (1984), which is approximately a factor of 10 lower than EPA's estimate of the slope (U.S. EPA, 1985). The differences are attributable to the aims of the respective calculations at the time. Portier et al. calculated "virtually safe doses" assuming that rodent and human doses scaled on a mg/kg basis, and they used the original tumor counts from the study. EPA, on the other hand, used $(\text{body weight})^{2/3}$ to arrive at a human equivalent dose and the pathology results from a reread of the original Kociba study (U.S. EPA, 1980). In addition, EPA adjusted tumor counts for early mortality in the study. The factor to adjust for $(\text{body weight})^{2/3}$ scaling in the rat is 5.8. The correction for early mortality can be accounted for with a factor of 1.6 (this is the ratio of the intake values at the ED_{01} with and without the early mortality correction). If the Portier et al. slope factor (1.8×10^{-5} per pg TCDD/kg body weight/day) is multiplied by these two factors, a slope of 1.7×10^{-4} per pg TCDD/kg body weight/day is calculated. This is essentially equivalent to the EPA estimate of 1.6×10^{-4} per pg TCDD/kg body weight/day. Reconciling these issues is important to ensuring appropriate comparisons of slope factor estimates.

5.2.1.2.2. ***Calculating a revised estimate of cancer slope from Kociba et al. (1978)***. Of greater consideration is the calculation of slope factor estimates using current methods of analysis that recognize the importance of the dose metric and the differences in half-life of dioxins in the bodies of laboratory animals and humans (see Part II, Chapter 8, Section 8.2, for detailed discussion). The major difference between the approaches used to calculate risks in the mid-1980s (Portier et al., 1984; U.S. EPA, 1985) and the current approach is the use of body burden as the dose metric for animal-to-human dose equivalence. The decision to use body burden accounts for the approximately 100-fold difference between half-lives of TCDD in humans and rats (2593 days vs. 25 days [see Part II, Chapter 8, Table 8.1]).

The use of equation 5-1 results in an estimated body burden at the LED_{01} of 6.1 ng TEQ/kg, derived from the EPA (U.S. EPA, 1985) Kociba et al. tumor counts. This compares favorably with the Portier estimate of 10 ng TEQ/kg found in Table 5-5. The difference is entirely accounted for by the early deaths adjustment by EPA. Use of these body burdens at the LED_{01} results in slope factor estimates of 3.3×10^{-3} per pg TCDD/kg body weight/day and 4.9×10^{-3} per pg TCDD/kg body weight/day for the Portier at al. (1984) (10 ng/kg) and the newly

derived body burden (6.1 ng/kg), respectively. Again, the difference is due solely to the adjustment for early mortality, which EPA considers a better estimate of upper bound lifetime risk than the unadjusted estimate. EPA's revised slope factor (4.9×10^{-3} per pg TCDD/kg body weight/day) would be 31 times greater than the slope factor from 1985.

However, a second issue with the modeling of the Kociba et al. data relates to the use of the appropriate tumor counts. As mentioned in Section 2.2, Goodman and Sauer (1992) reported a second re-evaluation of the female rat liver tumors in the Kociba et al. study using the latest pathology criteria for such lesions. Results of this review are discussed in more detail in Part II, Chapter 6, Section 6.2. The review confirmed only approximately one-third of the tumors seen in the previous review (U.S. EPA, 1980). Although this finding did not change the determination of carcinogenic hazard, because TCDD induced tumors in multiple sites in this study, it does have an effect on evaluation of dose-response and on estimates of risk. Because neither the original EPA slope factor estimate (U.S. EPA, 1985) nor that of Portier et al. (1984) reflect this reread, it is important to factor these results into the estimate of the ED_{01} and slope factor.

Using the LMS procedure used by EPA in 1985 and the tumor counts as reported in Part II, Chapter 6, Table 6.2, the revised slope factor is reduced by approximately 3.6-fold to yield a slope factor of 4.4×10^{-5} per pg TCDD/kg body weight/day. However, because the original estimates used a $(\text{body weight})^{2/3}$ scaling, an adjustment must also be made to remove this interspecies scaling factor in order to obtain a correct result when comparing with body burden as the interspecies metric. When dose is adjusted and equation 5-1 is used, an LED_{01} of 22.2 ng TEQ/kg and a slope factor of 1.4×10^{-3} per pg TCDD/kg body weight/day are derived. This represents EPA's most current upper bound slope factor for estimating human cancer risk based on animal data. It is 8.7 times larger than the slope factor calculated in U.S. EPA (1985). This number reflects the increase in slope factor based on the use of the body burden dose metric (31 times greater) and the Goodman and Sauer (1992) pathology (3.6 times less). These results can also be obtained using EPA's Benchmark Dose software and entering adjusted tumor counts and dose data to obtain a $BMDL_{01}$ from which an LED_{01} body burden of 22 ng/kg can be derived (see Tables 5-2, 5-4).

5.2.1.3. *Estimates of Slope Factors and Risk at Current Background Body Burdens Based on a Mechanistic Model*

As discussed above, Portier and Kohn (1996) combined the biochemical response model of Kohn et al. (1993) with a single initiated-phenotype two-stage model of carcinogenesis to estimate liver tumor incidence in female Sprague-Dawley rats from the Kociba et al. (1978)

bioassay. The model is described in more detail in Part II, Chapter 8, Section 8.4. This model adequately fit the tumor data, although it overestimated the observed tumor response at the lowest dose in the Kociba et al. study. The shape of the dose-response curve was approximately linear, and the estimated ED_{01} value for this model was 1.3 ng/kg/day. The corresponding body burden giving a 1% increased effect was 2.7 ng/kg.

The model authors believe that the use of CYP1A2 as a dose metric for the first mutation rate is consistent with its role as the major TCDD-inducible estradiol hydrolase in liver and with its hypothesized role in the production of estrogen metabolites leading to increased oxidative DNA damage and increased mutation (Yager and Liehr, 1996; Hayes et al., 1996; Dannan et al., 1986; Roy et al., 1992). Although no lower bound estimate of the ED_{01} is calculated, a maximum likelihood estimate of the slope factor of 7.1×10^{-3} per pg TCDD/kgBW/day can be calculated. This estimate represents an example of the type of modeling based on key events in a mode of action for carcinogenesis that is consistent with the future directions in dose-response modeling described in EPA's revised proposed cancer risk assessment guidelines (U.S. EPA, 1999). Although a number of uncertainties remain regarding structure and parameters of the model, the slope estimate is consistent with those derived from humans and animals. More details on this model can be found in Part II, Chapter 8, Section 8.4.

An alternative mechanistic model has been proposed (Conolly and Andersen, 1997). This model was developed for focal lesion growth, based on two types of initiated cells and applying the negative selection mechanism for hepatic tumor promotion proposed by Jirtle et al. (Jirtle and Meyer, 1991; Jirtle et al., 1991). In this model, even though the two types of initiated cells express the same biochemical marker, they respond differently to promotional stimulation in the liver. The model presumes that a promotional stimulus to the liver is countered by mito-inhibitory signals generated by the liver to constrain proliferation. One set of mutated cells is sensitive to this mito-inhibition, whereas the other set of mutated cells is insensitive and responds only to the promotional stimulus. The result is that, under increasing doses of the promoter, one group of focal lesions is decreasing in size—and hence, number of cells—whereas the other group is increasing in size.

The Conolly and Andersen model is different from the Portier and Kohn (1996) model in that it can result in U-shaped dose-response curves for the total number and mean size of observable focal lesions without using U-shaped parametric forms for the mutation rates or the birth rates. Conolly and Andersen did not apply their model to cancer risk estimation. Presently, there are insufficient experimental data to support or refute the use of either the Portier and Kohn or the Conolly and Andersen model.

5.2.2. Noncancer Endpoints

The analysis of noncancer endpoints following dioxin exposure uses the same dose metrics as for the preceding cancer analysis, although with increased emphasis on LOAELs and NOAELs. Summarized here are noncancer results based on the 200+ ED_{01} calculations performed in Part II, Chapter 8, combined with a tabulation (Table 5-6; Appendix A) of the lower range of measured, empirical, LOAEL/NOAEL results. Noncancer endpoints following dioxin exposure present similar—lower for some effects—PODs as compared to cancer ED_{01}s, with many of the PODs falling in a range of ~10–50 ng/kg BB and lower still for subclinical endpoints.

Before presenting these results, consideration should be give to a number of difficulties and uncertainties associated with comparing the same or different endpoints across species, such as differences in sensitivity of endpoints, times of exposure, exposure routes, and species and strains; the use of multiple or single doses; and variability between studies even for the same response. The estimated ED_{01}s may be influenced by experimental design, suggesting that caution should be used when comparing values from different designs. Caution should also be used when comparing studies that extrapolate ED_{01}s outside the experimental range. Furthermore, it may be difficult to compare values across endpoints. For example, the human health risk for a 1% change of body weight may not be equivalent to a 1% change in enzyme activity. Similarly, a 1% change in response in a population for a dichotomous endpoint is different from a 1% change in a continuous endpoint, where the upper bound of possible values may be very large, leading to a proportional increase in what constitutes the 1% effect level. Finally, background exposures are often not considered in these calculations simply because they were not known.

Part II, Chapter 8, presents estimated ED_{01}s for more than 200 data sets. These data sets were categorized by exposure regimen (single exposure vs. multiple exposures), effect (biochemical, hepatic, tissue, immune, and endocrine) and developmental stage (adult vs. developmental). The Hill model was fit to a majority of the data sets. This model not only provides estimates of the ED_{01}, it also provides insight into the shape of the dose-response curve in the form of a shape parameter. The shape parameter, or the Hill coefficient, can be used to determine whether the dose-response curve is linear or threshold-like. An analysis of the shape parameters for the different response categories implies that many dose-response curves are consistent with linearity over the range of doses tested. This analysis does not imply that the curves would be linear outside this range of doses, but it does inform the choices for

extrapolation. This is particularly true when body burdens or exposures at the lower end of the observed range are close to body burdens or exposures of interest for humans, which is the case with dioxin-like chemicals and biochemical effects.

Several general trends were observed and discussed in Part II, Chapter 8, relating to the ED_{01} results. The lowest ED_{01}s tended to be for biochemical effects, followed by hepatic responses, immune responses, and responses in tissue weight. However, there was a wide range of ED_{01}s within each category. For example, in the immune category, there was a range of almost six orders of magnitude in the ED_{01} estimates. In addition, some of the lowest ED_{01} estimates were for changes in immune function in adult mice, with ED_{01}s ranging from 2 to 25 ng TCDD/kg. Overall shape parameter data suggest that biochemical responses to TCDD are more likely to be linear within the experimental dose range. The more complex responses are more likely to assume a nonlinear shape. Nonetheless, a large number (> 40%) of the more complex responses have shape parameters that are more consistent with linearity than with nonlinearity.

Table 5-6 summarizes the range of experimental LOAEL, NOAEL, and ED_{01} values for critical endpoints from animal studies. The published data supporting these values are presented in Appendix A. These endpoints were chosen because they are considered adverse (e.g., developmental or reproductive toxicity) or are on the critical path for cancer and noncancer effects. In addition, these effects were chosen because the body burdens at which the effects occur are approximately 50 ng/kg or lower. The use of ED_{01}s and NOAELs and/or LOAELs in this analysis provides a "point of departure" for a discussion of margins of exposure for a variety of health endpoints. No one endpoint has been chosen as the "critical effect," as is often done in RfD calculations. For the effects listed in Table 5-6 and Appendix A, the MOE is approximately 10 or less. In some cases, particularly for ED_{01} values for the developmental toxicities of TCDD in rats (Mably et al., 1992a-c; Gray et al., 1997a, b; Faqi et al., 1998; Markowski et al., 2001), the MOE is less than 1. These estimates of the MOE assume a background human body burden of 5 ng TEQ/kg body weight.

Results from the analysis of ED_{01}s and an examination of LOAELs in additional studies suggest that noncancer effects can occur at body burden levels in animals equal to or less than body burdens calculated for tumor induction in animals. This is especially true when considering biochemical changes that may be on the critical path for both noncancer and cancer effects, such as enzyme induction or impacts on growth factors or their receptors. Although human noncancer effects were not modeled in Part II, Chapter 8, the observation of effects in the Dutch studies (discussed in Section 2.2.2 in this document) suggest that subtle but important noncancer human

effects may be occurring at body burden levels equivalent to those derived for many biochemical—and some clearly adverse—effects in animals.

5.3. MODE-OF-ACTION–BASED-DOSE-RESPONSE MODELING

As described in Part II, Chapter 8, Section 8.3, mechanism-based modeling can be a powerful tool for understanding and combining information on complex biological systems. Use of a truly mechanism-based approach can, in theory, enable reliable and scientifically sound extrapolations to lower doses and between species. However, any scientific uncertainty about the mechanisms that the models describe is inevitably reflected in uncertainty about the predictions of the models. The assumptions and uncertainties involved in the mechanistic modeling described in Chapter 8 are discussed at length in that chapter and in cited publications.

The development and continued refinement of PBPK models of the tissue dosimetry of dioxin has provided important information concerning the relationships between administered dose and dose-to-tissue compartments (Part II, Chapter 8, Section 8.2). Aspects of these models have been validated in the observable response range for multiple tissue compartments, species, and class of chemical. These models will continue to provide important new information for future revisions of this health assessment document. Such information will likely include improved estimates of tissue dose for liver and other organs where toxicity has been observed, improved estimates of tissue dose(s) in humans, and improved estimates of tissue dose for dioxin-related compounds.

In this reassessment, the development of biologically based dose-response models for dioxin and related compounds has led to considerable and valuable insights regarding both mechanisms of dioxin action and dose-response relationships for dioxin effects. These efforts, described in some detail in Part II, Chapter 8, Section 8.3, have provided additional perspectives on traditional methods such as the linearized multistage procedure for estimating cancer potency or the uncertainty factor approach for estimating levels below which noncancer effects are unlikely to occur. These methods have also provided a biologically based rationale for what had been primarily statistical approaches. The development of models like those in Chapter 8 allows for an iterative process of data development, hypothesis testing, and model development.

5.4. SUMMARY OF DOSE-RESPONSE CHARACTERIZATION

All humans tested contained detectable body burdens of TCDD and other dioxin-like compounds that are likely to act through the same mode of action. The receptor modeling theory outlined in Chapter 8 indicates that xenobiotics that operate through receptor binding

mechanisms, such as dioxin, will follow a linear dose-response binding in the 1–10% receptor occupancy region. This theoretical basis suggests—and this is supported by empirical findings—that the proximal biochemical and transcription reactions for dioxins, such as effects on DNA transcription and enzyme induction, may also follow linear dose-response kinetics. More distal toxic effects could be linear or sublinear/threshold depending on (1) the toxic mechanism, (2) location on the dose-response curve, and (3) interactions with other processes such as intracellular protein binding and co-factor induction/repression.

Empirical data provide dose-response shape information down to approximately the 1% effect level for many toxic endpoints. Many examples of adverse effects experienced at these low levels have too much data variability to clearly distinguish on a statistical basis (goodness of fit) between dose-response curve options and whether dose-response follows linear, supra/sublinear, power curve, or threshold kinetics. Toxic effects seen only at higher doses are presumably more likely to result from multiple cellular perturbations and are thus less likely to follow linear relationships.

Empirical dose-response data from cancer studies—both human epidemiological and bioassays—do not provide consistent or compelling information supportive of either threshold or supralinear models (see Tables 2-3 and 5-2) and are insufficient to move from EPA's default linear extrapolation policy in the proposed carcinogen risk assessment guidelines (U.S. EPA, 1996, 1999, 2003). This policy indicates that, for cancer dose-response, the data are to be modeled within the observed range and a POD calculated from which a linear extrapolation to the origin is generated. For noncancer endpoints, EPA proposes using an MOE approach, rather than an RfD approach, due to the inability to determine levels that are likely to be without appreciable effects of lifetime exposure to the population (including susceptible subpopulations) for all adverse effects, particularly given the current level of background exposure and human body burdens. Data on background levels of dioxins, furans and coplanar PCBs (see Part I, Volume 3, and Section 4.4 in this document) indicate that current levels in humans are already substantially along the dose-response curve. Thus, theoretical issues regarding increases from zero body burden levels are moot, and assessments must consider both background and additional increments of dose to this background level.

MOEs between population levels and the empirically observed (not modeled) 1% effect levels for a number of biochemical/toxic endpoints are on the order of less than 1 to 2 orders of magnitude. Thus, the extrapolation between observed effects and background levels is not large, with any increments to background further advancing along the dose-response curve through or toward the observed range. This further reduces the level of uncertainty when evaluating the

significance of MOEs. It is possible that any additional exposure above current background body burdens will be additive to ongoing responses. The magnitude of the additional response will be a function of the toxic equivalency of the incremental exposure. This observation, the relatively small MOE for "key events" potentially on the pathway to cancer and noncancer effects, and the high percentage of observed linear responses suggest that a proportional model should be used when extrapolating beyond the range of the experimental data. Short of extrapolating linearly over one to two orders of magnitude to estimate risk probabilistically for cancer and noncancer effects in the face of the uncertainties described above, a simple MOE approach may be useful to decision makers when discussing risk management goals. However, this decision would have to be based on a policy choice, because this analysis does not strongly support either approach.

Because human data for cancer dose-response analysis were available and because of a strong desire to stay within the range of responses estimated by these data, the risk chosen for determining a POD was the 1% excess risk. Doses and exposures associated with this risk (the ED_{01}s) were estimated from the available data using both mechanistic and empirical models. Comparisons were made on the basis of body burdens to account for differences in half-life across the numerous species studied.

In humans, restricting the analysis to log-linear models resulted in cancer ED_{01}s ranging from 6.0 ng/kg to 62 ng/kg. These were similar to the estimates from empirical modeling of the animal studies, which ranged from 14 ng/kg to 1190 ng/kg (most estimates were in the range of 14 to 500 ng/kg), and 2.7 ng/kg for the single mechanism-based model. Lower bounds on these ED_{01} estimates were used to calculate upper bound slope factors and risk estimates for average background body burdens.

Table 5-4 summarizes the ED_{01}/LED_{01} and slope factor calculations for the occupational cohort and bioassay studies. The slope factor calculations are performed by linearly extrapolating the ED/LED_{01} values to the background response rates, consistent with procedures outlined in the draft proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996, 1999, 2003). A slope factor estimate of approximately 1×10^{-3} per pg TCDD/kg body weight/day represents EPA's most current upper bound slope factor for estimating human cancer risk based on human data. A slope factor of 1.4×10^{-3} per pg TCDD/kg body weight/day represents EPA's most current upper bound slope factor for estimating human cancer risk based on animal data. Details on the specific procedures and calculations are provided in the footnotes. Additional details on the study characteristics and dose-response data and graphs are available in Section 5.2 and Table 5-2. The Agency, although fully recognizing the range and the public health-conservative nature of the slope factors that make up the range, suggests the use of 1×10^{-3} per

pg TEQ/kg body weight/day as an estimator of upper bound cancer risk for both background intakes and incremental intakes above background.

Upper bound slope factors allow the calculation of the high end (greater than 95%) of the probability of cancer risk in the population. This means that there is a greater than 95% chance that cancer risks will be less than the upper bound. Use of the ED_{01} rather than the LED_{01} to provide more likely estimates based on the available epidemiological and animal cancer data result in slope factors and risk estimates that are within a factor of 2 from the upper bound estimates. Even though there may be individuals in the population who might experience a higher cancer risk on the basis of genetic factors or other determinants of cancer risk not accounted for in epidemiologic data or animal studies, the vast majority of the population is expected to have less risk per unit of exposure, and some may have zero risk. On the basis of these slope factor estimates (per pg TEQ/kg body weight/day), upper bound cancer risk at average current background body burdens (5 ng TEQ/kg body weight) exceed 10^{-3} (1 in 1000). Current background body burdens reflect higher average intakes from the past (approximately 3 pg TEQ/kg body weight/day). For a very small percentage of the population (< 1%), estimated upper bound risks may be two to three times higher than this upper bound, based on average intake, if their individual cancer risk slope is represented by the upper bound estimate and they are among the most highly exposed (among the top 5%), based on dietary intake of dioxin and related compounds.

Estimates for noncancer endpoints show greater variability. In general, when compared on a body burden basis, the noncancer endpoints displayed lower ED_{01}s and NOAELs and/or LOAELs for short-term exposures versus longer-term exposures and for simple biochemical endpoints versus more complex endpoints such as tissue weight changes or toxicity. A number of significant, adverse, noncancer responses occurred at LOAEL/NOAEL/ED_{01}s of < 10–50 ng/kg, levels that are similar to the ED_{01}s estimated for cancer effects (see Tables 5-4, 5-6 and Appendix A). The mechanism-based models for noncancer endpoints gave a lower range of ED_{01}s (0.17 to 105 ng/kg) when compared to the broader noncancer data set. Although most of these estimates were based on a single model, the estimate from a different model—the hepatic zonal induction model—gave an ED_{01} for CYP1A2 induction of 51 ng/kg and, hence, was within the same range.

Although highly variable, these estimates suggest that any choice of body burden of more than 100 ng/kg as a POD would likely yield > 1% excess risk for some endpoint in humans, including those with clear clinical significance. Also, choosing a POD of less than 1 ng/kg would likely be an extrapolation below the range of these data. Any choice in the middle range

of 1 to 100 ng/kg would be supported by the analyses, although the data provide the greatest support in the range of 10 to 50 ng/kg. This range of body burdens should also provide a useful point of comparison when evaluating impacts of risk management on average body burdens in the general population or on estimates of impact of incremental exposures above background on individual body burdens at various ages.

Table 5-1. Peak serum dioxin levels in the background population and epidemiological cohorts

Cohort	No.	Total TEQ (ppt lipid)			2,3,7,8-TCDD (ppt lipid)	PCBs	Non-2,3,7,8-TCDD TEQ (ppt lipid)	Comment
		Lower	Central Tendency	Upper	Central Tendency	Mean TEQ	Central Tendency	
CDC comparison population, USA 1995–1997; CDC (2000)	316	2[a]	25.4 mean[b]	50[a]	2.1 mean 1.9 median (95% UCL = 4.2)	5.3 (est.)[b]	23.3 mean	TEQ_{DFP}-WHO_{98}; serum; missing PCBs 105, 118, 156 estimated
Background, Dioxin Assessment, USA ~1990s	pooled results	30	52.8 mean 55 median	70	5.2 mean SD ~1.32[c]	18.8 mean 20 median	47.6 mean	TEQ_{DFP}-WHO_{98}; serum, adipose, breast milk[d]
Back-calculated								
Ranch Hand, low; Ketchum et al. (1999)	276				52.3 median (range 27–94)			serum
Ranch Hand, high; Ketchum et al. (1999)	283				195.7 median (range 94–3,290)			serum
Hamburg cohort, women; Flesch-Janys et al. (1999)	$65_{2,3,7,8}$ 64_{TEQ}	19.3	811.2 mean[e] 172.8 median[e]	6789.1	506.8 mean 125.8 median (range 2.4–6397.4)		304.4 mean[e]	I-TEQs, dioxin and furan TEQ only; serum
NIOSH, Fingerhut et al. (1991b), NTIS	253				2,000 mean (range[f] 2–32,000)			serum
BASF, severe chloracne; Ott et al. (1993)	56				1008 geom. mean (range[g] 20–13360)			serum

Table 5-1. Peak serum dioxin levels in the background population and epidemiological cohorts (continued)

Cohort	No.	Total TEQ (ppt lipid)			2,3,7,8-TCDD (ppt lipid)	PCBs	Non-2,3,7,8-TCDD TEQ (ppt lipid)	Comment
		Lower	Central Tendency	Upper	Central Tendency	Mean TEQ	Central Tendency	
BASF, moderate chloracne; Ott et al. (1993)	59				420.8 geom. mean (range[g] 2.72–4915)			serum
BASF, no chloracne; Ott et al. (1993)	139				38.4 geom. mean (range[g] 2.72–2981)			serum
Seveso Zone A; Landi et al. (1998)	7				230 geom. mean 325.9 median (range 41.2–399.7)			serum
Seveso Zone A, medical; Needham et al. (1999)[h]	296				381–489 median (range 1.5–56,000)			Samples taken 1976, not back-calculated; serum; using ½ DL
Seveso Zone B; Landi et al. (1998)	51				47.5 geom. mean 52.5 median (range 5.3–273)			serum
Seveso Zone B, medical; Needham et al. (1999)[h]	80				87–147 median (range 1.8–725)			Samples taken 1976, not back-calculated; serum; using ½ DL
Seveso Zone R, medical; Needham et al. (1999)[h]	48				15–89 median (range 1–545)			Samples taken 1976; not back-calculated; serum; using ½ DL
Seveso NonABR; Landi et al. (1998)	52				4.9 geom. mean 5.5 median (range 1.0–18.1)			serum

Table 5-1. Peak serum dioxin levels in the background population and epidemiological cohorts (continued)

Cohort	No.	Total TEQ (ppt lipid)			2,3,7,8-TCDD (ppt lipid)	PCBs	Non-2,3,7,8-TCDD TEQ (ppt lipid)	Comment
		Lower	Central Tendency	Upper	Central Tendency	Mean TEQ	Central Tendency	
Dutch Accident; Hooiveld et al. (1996)	14				1841.8 arith. mean 1433.8 geom. mean (range 301–3683)			serum
Dutch Main Production; Hooiveld et al. (1996)	5				608.2 arith. mean 285.9 geom. mean (range 17–1160)			serum

[a] Estimated from ATSDR (1999b) Calcasieu comparison population graph.
[b] CDC data scaled upward to adjust for missing data on PCB congeners 105, 118 and 156 by matching to PCB congener ratios measured in the early 1990s.
[c] SD approximated from unweighted estimate.
[d] Weighted average levels for the subset of serum lipid TEQs were 4.54 ng/kg for 2,3,7,8-TCDD and 55.4 ng/kg for total TEQ (PCB contribution not adjusted for missing congeners).
[e] PCDD- and PCDF-derived TEQ only, using I-TEFs.
[f] Lower interval on current level.
[g] Range estimated from exponential log distribution graph.
[h] Ranges for median values for Seveso result from age groupings in original publication (Needham et al., 1999; Tables 1, 2, 5)

Table 5-2. Published cancer epidemiology and bioassay data and dose-response formulae

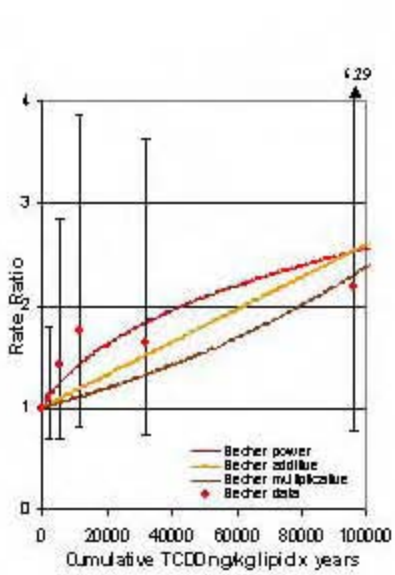
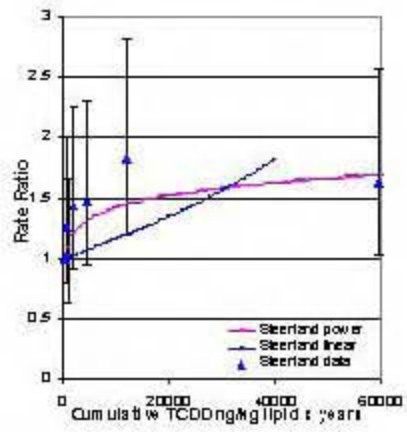
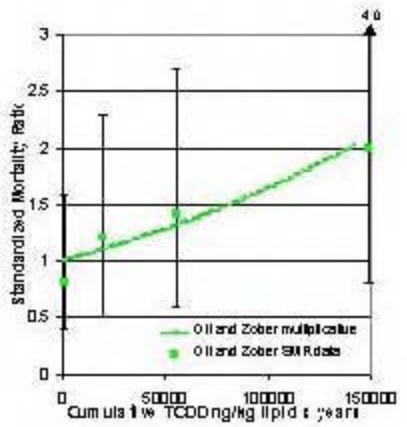
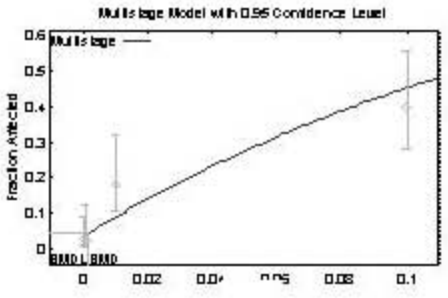
Study	Exposure groups	Central estimate of range (ng/kg fat x years)[a]	All cancer deaths observed (latency)	
Hamburg cohort, Becher et al. (1998)	0–1	0	1.00 RR	
	1–4	2000	1.12 (0-yr lag)[b]	
	4–8	5657	1.42 P trend = 0.03	
	8–16	11314	1.77	
	16–64	32000	1.63	
	64+	96000	2.19	
	µg/kg fat*Years	Harmonic mean, 1.5 x upper limit	Power: p=0.026 RR = (0.00017x+1)^0.326	
	n = 1189 male; measured = 275; cancer deaths = 124		Additive: p=0.031 RR = 1+0.000016 x	
			Multiplicative: p=0.043 RR = exp(0.00000869 x)	
NIOSH cohort, Steenland et al. (2001)	<335	260	1.00 RR	
	335–<520	402	1.26 (15-yr lag)	
	520–<1212	853	1.02	
	1212–<2896	1895	1.43	
	2896–<7568	4420	1.46	
	7568–<20455	12125	1.82	
	>20455	59838	1.62	
	ppt lipid *Years	Median	Power: p=0.003 RR = (x/background)^0.097	
	n = 3538 male; measured = 199; cancer deaths = 256		Piecewise linear, <40000:[c] RR = exp(0.000015 x)	
BASF cohort, Ott and Zober (1996)	<0.1	598	0.80 SMR	
	0.1–0.99	19407	1.2 (0-yr lag)	
	1.0–1.99	55057	1.4	
	2.0+	148800	2.0	
	µg/kg bw. peak; n = 243 male; measured = 138; cancer deaths = 31	Arithmetic mean	Conditional risk ratio = 1.22 (95% CI 1.00–1.50)[d] RR = exp(0.00000503 x)	

Table 5-2. Published cancer epidemiology and bioassay data and dose-response formulae (continued)

Study	Exposure groups	Central estimate of range (ng/kg fat x years)[a]	All cancer deaths observed (latency)
S-D Rats, Kociba et al. (1978); Goodman and Sauer (1992) pathology	0	0	2/86 Tumors
	0.001	540	1/50
	0.01	1700	9/50
	0.1	8100	18/45
	µg/kg/day	ng/kg lipid, not AUC	



[a] Central estimates provided courtesy of Drs. Steenland, Zober, and Becher.
[b] RR data provided only for the zero-lag analysis in Becher et al. (1998)
[c] Coefficient for the piecewise linear model (0.000015) provided by Dr. Steenland. The initial slope in the piecewise regression is applicable only to 40,000 ng/kg lipid years.
[d] Slope factor calculated from the conditional risk ratio, CR=1.22; see Chapter 8

Table 5-3. All cancer risk in humans through age 75[a]

Study	Model and Sex	ED_{01}	95% CI (lower, upper)	Unit excess risk for 1 ppt body burden above background
Steenland et al. (2001)	power male	1.38	0.71, 8.95	0.0079 (0.0027, 0.0132)
	power female	1.84	0.92, 14.9	0.0064 (0.0022, 0.0107)
	piecewise linear male	18.6	11.5, 48.3	0.00052 (0.00020, 0.00084)
	piecewise linear female	23.1	14.3, 59.8	0.00042 (0.00016, 0.00067)
Becher et al. (1998)	power-male	5.971		0.0018
	power-female	7.58		0.0014
	additive-male	18.22		0.00055
	additive-female	22.75		0.00044
	multiplicative-male	32.16		0.0003
	multiplicative-female	39.82		0.00024
Ott and Zober (1996)	multiplicative-male	50.9	25.0, ∞	0.00019 (0, 0.00039)
	multiplicative-female	62.1	30.5, ∞	0.00015 (0, 0.00032)

[a] Units are constant body burden in ng/kg not adjusted for lipid: see Part III, Chapter 8, Table 8-2, for details.

Table 5-4. Summary of all site cancer ED_{01} and slope factor calculations

Study	ED_{01} (LED_{01}) (ng/kg)	Cancer slope factor for 1 pg/kg/day above background[a] (UCL)
Hamburg cohort, Becher et al. (1998), power	6	5.1 E-3
Hamburg cohort, Becher et al. (1998), additive	18.2	1.6 E-3
Hamburg cohort, Becher et al. (1998), multiplicative	32.2	0.89 E-3
NIOSH cohort, Steenland et al. (2001), piecewise linear[b]	18.6 (11.5)	1.5 E-3 (2.5 E-3)
BASF cohort, from Ott and Zober (1996), multiplicative	50.9 (25.0)	0.57 E-3 (1.2 E-3)
Sprague-Dawley rats, Kociba et al.(1978); Goodman and Sauer (1992), pathology	31.9 (22)[c] BMD dose 38 (27.5) BMD adipose	0.97 E-3 (1.4 E-3) 0.8 E-3 (1.1 E-3)

[a] Assumes 25% of body weight is lipid; 80% of dioxin dose is absorbed from the normal diet in humans; the TCDD half-life is 7.1 years in humans. Background all cancer mortality rate calculated through lifetable analysis to 75 years. Summary results are for male all cancer risk, because the male lifetime (to 75 years) all cancer risk is greater than for females, leading to correspondingly higher cancer slope factors. As detailed in Part III, Chapter 8, $RelRisk_{(ED01)} = 0.99 + 0.01/Risk_{(0\ dose)}$. Based on the manner in which the dose-response data were calculated using Cox Regression rate ratio analyses, risks are given as cancer slope factors for 1 pg/kg/day above background, assumed 5 ppt TCDD in lipid.

[b] Steenland et al. (2001) power model results are not included, as this formula predicts unreasonably high attributable risks at background dioxin levels in the community due to the steep slope of the power curve formula at very low levels.

[c] Modeled using U.S. EPA Benchmark Dose Software, version 1.2, with either dose or adipose concentration as the metric. Absorption from food pellets in animals is assumed to be 50%. BMD = 0.00176849 ug/kg/day. BMDL = 0.00122517 ug/kg/day. Therefore, rat LED_{01} = 1.2251 x 25 x 0.5/ln2 = 22 ng/kg; human equivalent LED_{01} = 22 x ln2 x 1000/2593/0.8 = 7.38 pg/kg/day; slope factor = 0.01/7.38 = 1.4 E-3 risk/pg/kg/day.

Table 5-5. Doses yielding 1% excess risk (95% lower confidence bound) based upon 2-year animal carcinogenicity studies using simple multistage (Portier et al., 1984) models[a]

Tumor	Shape	ED_{01}	
		Animal intake for 1% excess risk in ng/kg/day (95% lower confidence bound)	Steady-state body burden in ng/kg at ED_{01} (95% lower confidence bound)
Liver cancer in female rats (Kociba)	Linear	0.77 (0.57)	14 (10)
Squamous cell carcinoma of the tongue in male rats (Kociba)	Linear	14.1 (5.9)	254 (106)
Squamous cell carcinoma of the nasal turbinates or hard palate in male rats (Kociba)	Cubic	41.4 (1.2)	746 (22)
Squamous cell carcinoma of the lung in female rats (Kociba)	Cubic	40.4 (2.7)	730 (48)
Squamous cell carcinoma of the nasal turbinates or hard palate in female rats (Kociba)	Linear	5.0 (2.0)	90 (36)
Thyroid follicular cell adenoma in male rats (NTP)	Linear	4.0 (2.1)	144 (76)
Thyroid follicular cell adenoma in female rats (NTP)	Cubic	33.0 (3.1)	1190 (112)
Liver adenomas and carcinomas in female rats (NTP)	Quadratic	13.0 (1.7)	469 (61)
Liver adenomas and carcinomas in male mice (NTP)	Linear	1.3 (0.86)	20.6 (13.6)
Liver adenomas and carcinomas in female mice (NTP)	Linear	15.1 (7.8)	239 (124)
Thyroid follicular cell adenomas and carcinomas in female mice (NTP)	Linear	30.1 (14.0)	478 (222)
Subcutaneous tissue sarcomas in female mice (NTP)	Lin-Cubic	43.2 (14.1)	686 (224)
Leukemias and lymphomas in female mice (NTP)	Linear	10.0 (5.4)	159 (86)

[a] Reprinted with slight modifications from Part II, Chapter 8, Table 8.3.2.

Table 5-6. Body burdens for critical endpoints in animals with human equivalent daily intake

Animal	Endpoint	Study	Estimated body burden (ng/kg)			Human equiv.[a] intakes (pg/kg/day)
			LOAEL	NOAEL	ED_{01}	
Rats	Cancer	Kociba et al. (1978)	180	18	32	60; 6; 11
Rhesus monkeys	Fetal mortality	Bowman et al. (1989)	90	21	NC	30; 7
	Developmental neurotoxicity	Schantz et al. (1992)	21	–	NC	7
	Endometriosis	Rier et al. (1993)	21	–	NC	7
Rats	Reproductive tox. (multigenerational)	Murray et al. (1979)	180	18	NC	60; 6
Rats	Developmental/ reproductive toxicity	Mably et al. (1992)	38	–	0.34	13; 0.1
		Gray et al. (1997)	30	–	0.08	10; 0.03
		Faqi et al. (1998)	25	–	0.6	8; 0.2
		Ohsako et al. (2001)	30	8	NC	10; 3
Rats	Developmental immunotoxicity	Gehrs and Smialowicz (1999)	60	–	NC	20
Rats	Developmental Neurotoxicity	Markowski et al. (2001)	108	36[b]	0.7	36; 12; 0.2
Mice	Immunological effects (adult)	Burleson et al. (1996)	6	3	NC	2; 1
		Smialowicz et al. (1994)	300	–	2.9	100; 1
		Narasimhan et al. (1994)	100	50[b]	1.5	33; 17; 0.5
		Vecchi et al. (1983)	1200	–	7	401; 2
Rats	Thyroid effects	Sewall et al. (1995)	76	22	26	25; 7; 8
Mice	CYP1A1/1A2 enzyme induction	DeVito et al. (1994)	24	–	22	8; 7
		Diliberto et al. (2001)	2.8	–	67	0.9; 22
		Vogel et al. (1997)	5.1	0.51	0.003	1.6; 0.16; 0.001
		Narasimhan et al (1994)	25	10	3	8; 3; 2; 1
Rats	CYP1A1/1A2 enzyme induction	van Birgelen et al. (1995)	243	–	19	81; 6
		Schrenk et al. (1994)	72	–	26	24; 9
		Sewall et al. (1995)	8	2	3.5	3; 0.7; 1
		Walker et al. (1999)	76	–	59	25; 20

Table 5-6. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

[a] Human equivalent intakes were estimated according to the following equation: daily intake (pg/kg/day) = (body burden (ng/kg)*Ln2*1000)/(t½*absorption) where t½ = 2593 days and absorption fraction = 0.8 (Poiger and Schlatter 1986; see Section II). Corresponding human equivalent intake values are arranged in sequence from the previous three columns.

[b] NOAEL values are based on the highest individual dose group in which there are no statistically significant changes. Statistically significant dose response trends plus apparent declines are also evident at all dose levels—20 and 60 ng/kg orally—in all fixed-ratio test groups in Markowski et al. (2001) and in the 50 ng/kg dose group in Narasimhan et al. (1994).

- - = no NOAEL value, as effects seen in the lowest dose group in the study.
NC = Not calculated due to insufficient dose response information (less than three doses and a control) or due to presentation of the data in graphical form without tabulation of mean and variance estimates.
Note: This table is reproduced in Appendix A with explanatory details of study design, results, and calculation procedures, formulae, and assumptions.

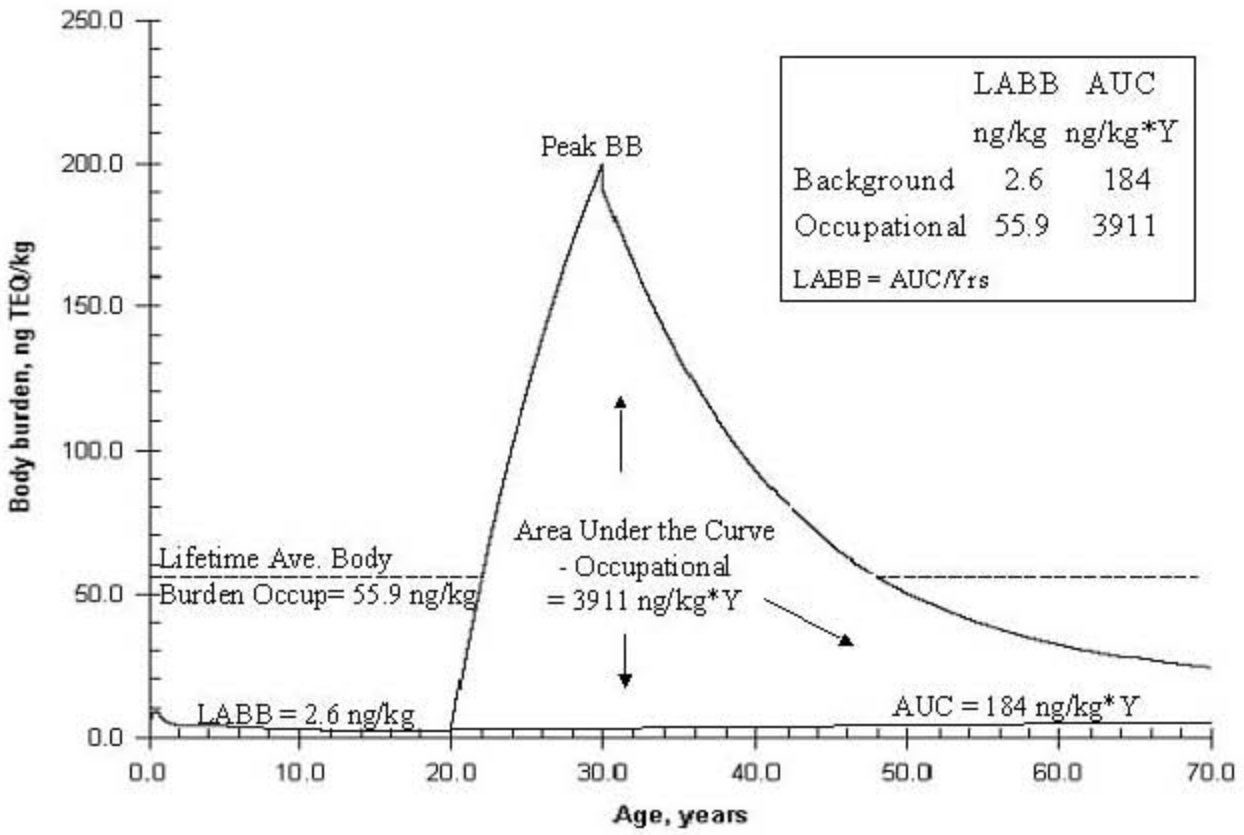


Figure 5-1. Comparison of lifetime average body burden and area under the curve in hypothetical background and occupational scenarios.

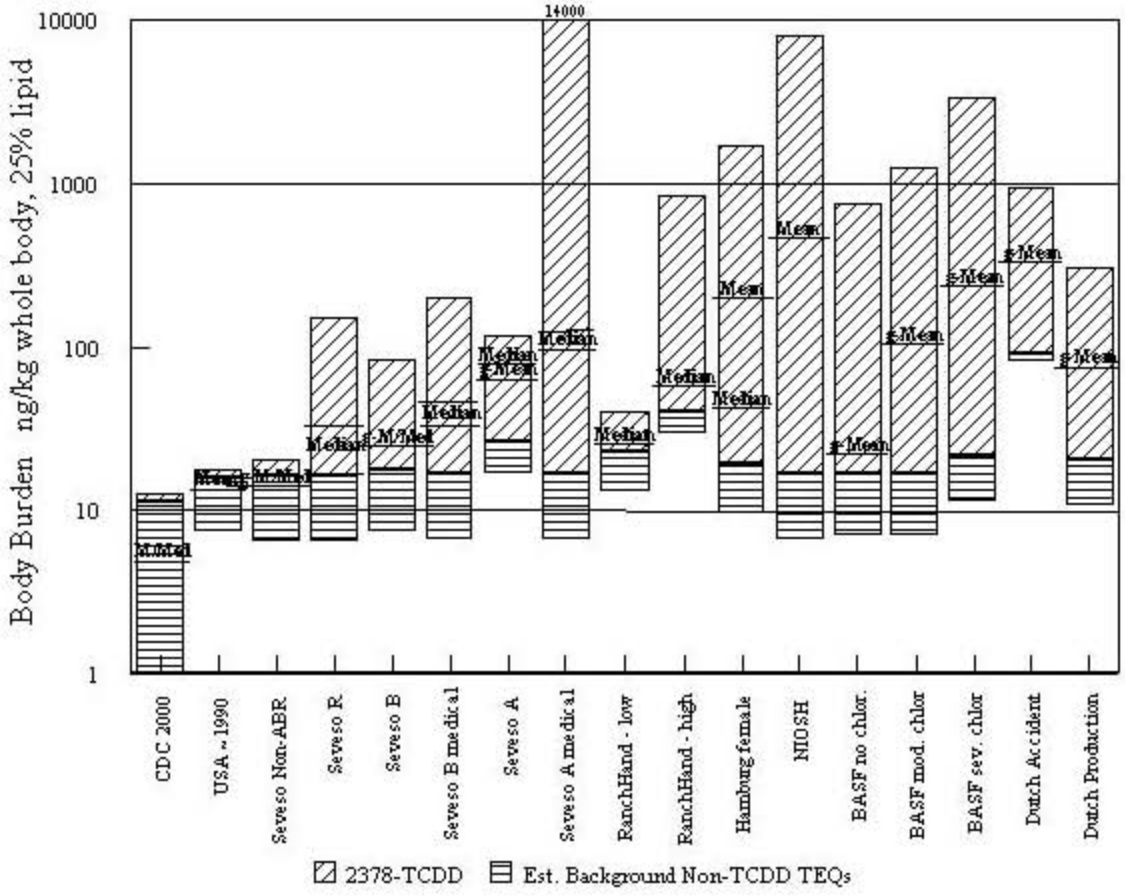


Figure 5-2. Peak dioxin body burden levels in background populations and epidemiological cohorts (back-calculated) (See Table 5-1). For the background U.S. populations (CDC; USA ~1990s), the bars represent the range of total TEQ measured in the population. The lower shaded portion represents the variability from non-2,3,7,8-TCDD-derived TEQs, the upper shaded portion the variability in the 2,3,7,8-TCDD. Note that the respective bar sizes do not represent the total non-2,3,7,8-TCDD TEQ or 2,3,7,8-TCDD contributions, because a portion of each of these contributions is contained within the region between the x-axis and bottom of the bar, namely the minimum estimated body burden. For each of the back-calculated epidemiological cohort exposures, the bar was estimated on the basis of the combination of two distributions: the 2,3,7,8-TCDD levels measured in the respective cohort plus the estimated range of background non-2,3,7,8-TCDD-derived TEQs from the U.S. population. The lower estimate is the combination of the lower 2,3,7,8-TCDD and lower non-2,3,7,8-TCDD TEQ contributions; the shading junction represents the variability in background U.S. population non-2,3,7,8-TCDD levels that have been added to this bar; the mean/median/geometric mean indicators represent the addition of the measured 2,3,7,8-TCDD central estimate with the mean background U.S. population non-2,3,7,8-TCDD TEQ level (~47.6 ppt lipid, 11.9 ng/kg body burden at 25% body fat); and the upper limit is the combination of the upper 2,3,7,8-TCDD and upper non-2,3,7,8-TCDD TEQs.

6. RISK CHARACTERIZATION

Characterizing risks from dioxin and related compounds requires the integration of complex data sets and the use of science-based inferences regarding hazard, mode of action, dose response, and exposure. It also requires consideration of incremental exposures in the context of an existing background exposure that, for the majority of the population, is independent of local sources and dominated by exposure through the food supply. Finally, this characterization must consider risks to special populations and developmental stages (subsistence fishers, children, etc.) as well as to the general population. It is important that this characterization convey the current understanding of the scientific community regarding these issues, highlight uncertainties in this understanding, and specify where assumptions have been used or inferences made in the absence of data. Although characterization of risk is inherently a scientific exercise, it must by nature go beyond empirical observations and draw conclusions in untested areas. In some cases, these conclusions are, in fact, untestable, given the current capabilities in analytical chemistry, toxicology, and epidemiology. This situation should not detract from one's confidence in the conclusions of a well-structured and well-documented characterization of risk, but it should serve to confirm the importance of considering risk assessment as an iterative process that benefits from evolving methods and data collection and is subject to change as the knowledge base improves.

Dioxin and related compounds can produce a wide variety of effects in animals and may produce many of the same effects in humans.

There is adequate evidence, based on all the available information, as discussed in Parts I and II of this Reassessment and in this Integrated Summary, to support the inference that the potential exists for humans to respond with a broad spectrum of effects from exposure to dioxin and related compounds, depending on the magnitude and duration of exposure. This inference is based on the similarities in receptor and receptor binding and their sequellae observed in animals and in humans. Effects will likely range from detection of biochemical changes at or near background levels of exposure to detection of adverse effects with increasing severity as body burdens increase above background levels. Data presented in Part II, Chapter 8, and illustrated in Table 5-6 and Appendix A support this general conclusion.

Enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals represent effects of unknown clinical significance but that may be early indicators of toxic response. Induction of activating/metabolizing enzymes at or

near background levels, for instance, may be adaptive and, in some cases, beneficial, or it may be considered adverse. Induction may lead to more rapid metabolism and elimination of potentially toxic compounds, or it may lead to increases in reactive intermediates and may potentiate toxic effects. Examples of both of these situations are available in the published literature, and events of this type formed the basis for a biologically based model discussed in Part III, Section 5.

Subtle effects, such as the impacts on neurobehavioral and developmental outcomes in laboratory animals and humans, the thyroid function and immune system alterations seen in the Dutch children exposed to background levels of dioxin and related compounds, or the changes in circulating reproductive hormones in men exposed to TCDD, illustrate the types of responses that support the finding of subtle yet arguably adverse effects at or near background body burdens. Clearly adverse effects, including, perhaps, cancer, may not be detectable until exposures contribute to body burdens that exceed current background by one or two orders of magnitude (10 or 100 times). MOEs in this range are considerably less than those typically seen for environmental contaminants of toxicologic concern, particularly when the health endpoint is cancer, as observed in epidemiologic studies.

Clear mechanistic relationships between biochemical and cellular changes seen at or near background body burden levels and production of adverse effects detectable at higher levels remain uncertain, but modes of action consistent with available data have been discussed in several chapters in Part II. Information on these mechanistic relationships and modes of action is useful in hazard characterization, and data are accumulating to suggest refined mode of action hypotheses for further testing.

It is well known that individual species vary in their sensitivity to any particular dioxin effect. Laboratory rodents (typically strains of rats and mice) are not necessarily the most sensitive responders for several well-studied effects. However, the evidence available to date indicates that humans most likely fall in the middle rather than at either extreme of the range of sensitivity for individual effects among animals. In other words, evaluation of the available data suggests that humans, in general, are neither extremely sensitive nor insensitive to the individual effects of dioxin-like compounds.

Human data provide direct or indirect support for evaluation of likely effect levels for several of the endpoints observed in laboratory studies (e.g., cancer and neurobehavioral and endocrine endpoints), although the influence of variability among humans remains difficult to assess. Discussions have highlighted certain prominent, biologically significant effects of TCDD and related compounds. In TCDD-exposed men, subtle changes in biochemistry and physiology, such as enzyme induction, altered levels of circulating reproductive hormones, or reduced

glucose tolerance and, perhaps, diabetes, have been detected in a limited number of epidemiologic studies.

These findings, coupled with the knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism and developmental and/or reproductive biology and, perhaps, other effects in the range of current human exposures. These biochemical, cellular, and organ-level endpoints have been shown to be affected by TCDD, but specific data on these endpoints do not generally exist for other congeners. Despite this lack of congener-specific data, there is reason to infer that these effects may occur for all dioxin-like compounds, based on the concept of toxic equivalency.

In this document, dioxin and related compounds are characterized as developmental, reproductive, immunological, endocrinological, and carcinogenic hazards. The deduction that humans are likely to respond with noncancer effects from exposure to dioxin-like compounds is based on the finding that these compounds impact cellular regulation at a fundamental level and on the demonstration of adverse effects among a broad range of species. For example, because developmental toxicity following exposure to TCDD-like congeners occurs in fish, amphibians, reptiles, birds, and mammals, it is likely to occur at some level in humans.

It is not currently possible to state exactly how or at what levels individuals will respond with specific adverse impacts on development or reproductive function, but the analyses of the Dutch cohort data and laboratory animal studies suggest that some effects may occur at or near background levels. Fortunately, there have been few human cohorts identified with TCDD exposures high enough to raise body burdens significantly over background levels (see Table 5-1 and Figure 5-2 in this document), and when these cohorts were examined, relatively few clinically significant effects were detected. However, the power of these studies to detect these effects remains an issue. The lack of sufficient exposure gradients and adequate human information and the focus of most currently available epidemiologic studies on occupationally TCDD-exposed adult males make it difficult to evaluate the inference that noncancer effects associated with exposure to dioxin-like compounds may be occurring in the broader human population. It is important to note, however, that when exposures to very high levels of dioxin-like compounds have been studied—such as in the Yusho and Yu-Cheng cohorts—a spectrum of adverse effects have been detected in men, women, and children. Many of these effects are similar to what has been observed not only in small laboratory animals, but in wildlife and in nonhuman primates.

Some have argued that in the absence of better human data, deducing that a spectrum of noncancer effects will occur in humans overstates the science; however, most of the scientists

involved as authors and reviewers in the reassessment have indicated that such inference is reasonable, given the weight of evidence from available data. As presented, this logical conclusion represents a testable hypothesis that may be evaluated by further data collection. EPA, its federal colleagues, and others in the general scientific community are continuing to fill critical data gaps, which will reduce our uncertainty regarding both hazard and risk characterization for dioxin and related compounds. However, as discussed by EPA's SAB (U.S. EPA, 2001b) "neither knowledge breakthroughs nor fully developed techniques for producing more unbiased risk assessments can be expected to be available in the near future."

Dioxin and related compounds are structurally related and elicit their effects through a common mode of action.

The scientific community has identified and described a series of common biological steps that are necessary for most, if not all, of the observed effects of dioxin and related compounds in vertebrates, including humans. Binding of dioxin-like compounds to a cellular protein called the aryl hydrocarbon receptor (AhR) represents the first step in a series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue-level changes in normal biological processes. Binding to the AhR appears to be necessary for all well-studied effects of dioxin, but it is not sufficient in and of itself to elicit these responses.

There remains some uncertainty as to whether every dioxin response is AhR-mediated. Some data from the use of sensitive biological tools, such as AhR-deficient ($AhR^{-/-}$) mice, suggest a small residual of effects from exposure to TCDD, and, thus, we cannot rule out receptor-independent alternative pathways. However, these reported non-AhR-mediated responses occur in animals at doses that are orders of magnitude higher than current human exposures and require much higher doses than other AhR-mediated effects in animals. Thus, these putative non-AhR-mediated mechanisms are unlikely to impact any of the assumptions made in this reassessment.

Exposure of animals—and in some cases humans—to chemicals whose structure and AhR binding characteristics are similar to those of 2,3,7,8-TCDD can elicit similar effects. In the past 5 years, significant data have accumulated that support the concept of toxic equivalence, a concept that is at the heart of risk assessment for the complex mixtures of dioxin and related compounds encountered in the environment. These data have been analyzed and summarized in Part II, Chapter 9. This chapter was added to EPA's dioxin reassessment to address questions raised by the SAB in 1995. The SAB suggested that, because the TEQ approach was a critical component of risk assessment for dioxin and related compounds, the Agency should be explicit

in its description of the history and application of the process and go beyond reliance on the Agency's published reference documents on the subject (U.S. EPA, 1987, 1989a).

The analyses in Parts II and III of this document demonstrate that, although variability in the data underpinning the scientific judgments regarding toxic equivalency exists, when data are restricted to longer exposure and in vivo data, the empirical analysis strongly supports the judgment of experts in setting TEF values. This is particularly true for the use of TEFs for assessing the animal cancer endpoint but will likely apply even more strongly to noncancer effects as additional congener-specific data are collected. A focus on the five congeners that make up greater than 80% of human body burden on a TEQ basis reveals rather robust data sets, which form the basis for assigned TEFs. This focus reduces the impact of the uncertainties in TEFs assigned to less-studied congeners. In its recent review (U.S. EPA, 2001b), EPA's SAB agreed that the general framework for calculating TEFs and applying them to obtain a TEQ is well described in Part II, Chapter 9. The Board recognized that uncertainties remained regarding toxicities of joint exposures that are not dominated by well-studied congeners, and recommended further development of the TEF methodology (e.g., development of probability density functions around experimental results to assist future expert judgment in reviewing and revising TEFs) (see Finley et al., 2003).

EPA and the international scientific community have adopted toxic equivalency of dioxin and related compounds as prudent science policy.

Dioxin and related compounds always exist in nature as complex mixtures. As discussed in the exposure document, these complex mixtures can be characterized through analytic methods to determine concentrations of individual congeners. Dioxin and related compounds can be quantified and biological activity of the mixture can be estimated using relative potency values and an assumption of dose additivity. Such an approach has evolved over time to form the basis for the use of TEQ in risk assessment for this group of compounds. Although such an approach is dependent on critical assumptions and scientific judgment, it has been characterized by the SAB as a "useful, interim" way to deal with the complex mixture problem, and it has been accepted by numerous countries and several international organizations. Alternative approaches, including the assumption that all congeners carry the toxic equivalency of 2,3,7,8-TCDD or that all congeners other than 2,3,7,8-TCDD can be ignored, have been rejected as inadequate for risk assessment purposes.

Significant additional literature is now available on the subject of toxic equivalency of dioxin and related compounds, as summarized (through 2000) in Part II, Chapter 9. An

international evaluation of all of the available data (van den Berg et al., 1998) reaffirmed the TEQ approach and provided the scientific community with the latest values for TEFs for PCDDs, PCDFs, and dioxin-like PCBs. Consequently, we can infer with greater confidence that humans will respond to the cumulative exposure of AhR-mediated chemicals. This reassessment recommends that the WHO_{98} TEF scheme be used to assign toxic equivalency to complex environmental mixtures for assessment and regulatory purposes. Further research is needed to address remaining uncertainties inherent in the current approach, in particular those regarding the impact of actual exposures compared to measured body burdens of highly persistent congeners and the continuing debate regarding the role of other Ah-agonists in the diet on the toxicity of dioxin-like compounds. WHO has suggested that the TEQ scheme be reevaluated on a periodic basis and that TEFs and their application to risk assessment be reanalyzed to account for emerging scientific information. EPA supports this suggestion and intends to participate in future re-evaluations.

Complex mixtures of dioxin and related compounds are highly potent, "likely" carcinogens.

A weight-of-evidence evaluation suggests that mixtures of dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs) are strong cancer promoters and weak direct or indirect initiators and that they are likely to present a cancer hazard to humans. Because dioxin and related compounds always occur in the environment and in humans as complex mixtures of individual congeners, it is appropriate that the characterization apply to the mixture. According to the Agency's revised proposed guidelines for carcinogen risk assessment, the descriptor "likely to be carcinogenic to human" is appropriate when the available tumor effects and other key data are adequate to demonstrate carcinogenic potential to humans (U.S. EPA, 1999, 2003) yet are not sufficient to infer a cause-and-effect relationship.

"Adequate data" are recognized to span a wide range. Even though the database from cancer epidemiologic studies remains a point of scientific discussion, it is the view of this reassessment that this body of evidence is supported by the laboratory data that indicate that TCDD increases cancer mortality of several types. Although not all confounders were ruled out in any one study, positive associations between surrogates of dioxin exposure, either length of occupational exposure or proximity to a known source combined with some information based on measured blood levels, and cancer have been reported.

These epidemiologic data strongly suggest a role for dioxin exposure to contribute to a carcinogenic response but are not sufficient to confirm a causal relationship between exposure to

dioxin and increased cancer incidence. Available human studies alone cannot demonstrate whether a cause-and-effect relationship between dioxin exposure and increased incidence of cancer exists. Therefore, evaluation of cancer hazard in humans must include an evaluation of all of the available animal and in vitro data as well as the data from exposed human populations.

The data for complex mixtures of dioxin and related compounds represent a case that, according to discussions in the draft guidelines, would approach the strong-evidence end of the adequate data spectrum. Epidemiologic observations of an association between exposure and cancer responses (TCDD); unequivocal positive responses in both sexes, multiple species, multiple sites, and different routes in lifetime bioassays or initiation-promotion protocols or other shorter-term in vivo systems such as transgenic models (TCDD plus numerous PCDDs, PCDFs, dioxin-like PCBs); and mechanistic or mode-of action data that are assumed to be relevant to human carcinogenicity, including, for instance, initiation-promotion studies (PCDDs, PCDFs, dioxin-like PCBs) all support the description of complex mixtures of dioxin and related compounds as likely to be human carcinogens. On the basis of these observations, complex environmental mixtures of TCDD and dioxin-like compounds should be characterized as "likely" carcinogens, with the degree of certainty of the characterization being dependent on the constituents of the mixture, when known. For instance, the hazard potential, although "likely," would be characterized differently for a mixture whose TEQ was dominated by octaCDD as compared with one dominated by pentaCDF.

As discussed in Section 2.2.1.5, under EPA's current approach for carcinogen risk assessment, individual congeners can also be characterized as to carcinogenic hazard. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is best characterized as "carcinogenic to humans." This means that, on the basis of the weight of all of the evidence (human, animal, mode of action), TCDD meets the criteria that allow EPA and the scientific community to accept a causal relationship between TCDD exposure and cancer hazard. The guidance suggests that "carcinogenic to humans" is an appropriate descriptor of human carcinogenic potential when there is an absence of conclusive epidemiologic evidence to clearly establish a cause-and-effect relationship between human exposure and cancer but there is compelling evidence of carcinogenicity in animals and mechanistic information in animals and humans demonstrating similar modes of carcinogenic action. The "carcinogenic to humans" descriptor is suggested for TCDD because all of the following conditions are met:

- There is strong and consistent evidence from occupational epidemiologic studies for an association between TCDD exposure and increases in cancer at all sites, in lung cancer

and, perhaps, at other sites, but the data are insufficient on their own to support a causal association. This point was discussed in detail by the International Agency for Research on Cancer (IARC, 1997).

- There is extensive carcinogenicity in both sexes of multiple species at multiple sites.

- There is general agreement that the mode of TCDD's carcinogenicity is as an AhR-dependent promoter and proceeds through gene expression and/or a modification of the action of a number of receptor and hormone systems involved in cell growth and differentiation, such as the epidermal growth factor receptor and the estrogen receptor.

- The human AhR and the rodent AhR are similar in structure and function and, once activated, both bind to the same DNA response elements, designated DREs.

- Human and rodent tissue and organ cultures respond to TCDD and related chemicals in a similar manner and at similar concentrations. TCDD has the ability to transform immortalized human and rodent cells that then have demonstrable tumorigenicity.

Other individual dioxin-like compounds are characterized as "likely to be carcinogenic to humans" primarily because of the lack of epidemiological evidence associated with their carcinogenicity, although the inference based on toxic equivalency is strong that they would behave in humans as TCDD does. Other factors, such as the available congener-specific chronic bioassays, also support this characterization. For each congener, the degree of certainty is dependent on the available congener-specific data and their consistency with the generalized mode of action that underpins toxic equivalency for TCDD and related compounds.

Although uncertainties remain regarding quantitative estimates of upper-bound cancer risk from dioxin and related compounds, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in evaluation of the slope of the dose-response curve at the low end of the observed range (using the LED_{01}) using a simple proportional (linear) model and a calculation of both upper-bound risk and MOE based on human equivalent background exposures and associated body burdens. Evaluation of shape parameters (used to estimate degree of linearity or nonlinearity of dose-response within the range of observation) for biochemical effects that can be hypothesized as key events in a generalized dioxin mode-of-action model do

not argue for significant departures from linearity below a calculated ED_{01}, extending down to at least one to two orders of magnitude lower exposure.

Risk estimates for intakes associated with background body burdens or incremental exposures based on this slope factor represent a plausible upper bound on risk, based on the evaluation of animal and human data. The slope factors, based on the most sensitive cancer responses calculated by authors of peer-reviewed publications and presented in Part II, Chapter 8, and Section 5 for both animals and humans, fall in a range of approximately 0.6×10^{-3} to 5×10^{-3} per pg TEQ/kg body weight/day.

The ranges of estimates of upper-bound cancer potency calculated from the human and animal data overlap. The range above is bounded on the upper end by the estimate of slope from the Hamburg cohort epidemiology study and on the lower end by the estimates from the Ott and Zober epidemiology study, with the NIOSH piece-wise linear epidemiology model and the reanalyzed Kociba rat study falling intermediate in this range. Consequently, the Agency, although fully recognizing this range and the public health-conservative nature of the slope factors that make up the range, suggests the use of 1×10^{-3} per pg TEQ/kg body weight/day as an estimator of upper-bound cancer risk for both background intakes and incremental intakes above background.

This decision reflects the weight given to the individual estimates from the human studies and the comparability of the revised estimate from the animal data. A recently published meta-analysis (Crump, 2003) is consistent with this estimate. In addition, this decision reflects the judgment that, because ED_{01} estimates require little extrapolation from the range of observation and current body burdens are within a factor of 10 of the ED_{01} estimates, use of a linear model is both consistent with the data and unlikely to require more than an order of magnitude extrapolation. This bounding on extrapolation would apply to both estimates of risk at current background exposures and to additional increments above current background. Application of upper-bound slope factors allows the calculation of a high-end bounding estimate of the probability of cancer risk in the population. This means that there is greater than a 95% chance that "true" population cancer risks will be less than the upper-bound estimate.

Use of the human ED_{01}s rather than the LED_{01}s to provide more likely upper-bound estimates based on the available epidemiological data is a matter of EPA science policy and compares well with upper-bound animal cancer data. Use of either ED_{01} or LED_{01} results in slope factors and risk estimates that are within a factor of 2; well within the inherent uncertainty of these estimates. Although there may be individuals within a population who may experience a higher cancer risk on the basis of genetic factors or other determinants of cancer risk not

accounted for in epidemiologic data or animal studies, the vast majority of the population is expected to have less risk per unit of exposure than the bounding estimate would suggest, and some may have zero risk.

On the basis of these slope factor estimates (per pg TEQ/kg body weight/day), upper-bound risks at average current background body burdens (5 ng TEQ/kg body weight) that result from historical average intakes of approximately 3 pg TEQ/kg body weight/day may exceed 10^{-3} (1 in a 1000). A very small percentage of the population (< 1%) has estimated risks that are a few times higher than an upper bound based on average intake if their individual cancer risk slope is represented by the upper bound estimate and they are among the most highly exposed (among the top 5%), based on dietary intake of dioxin and related compounds. This estimate of the range of upper-bound risk for the general population has increased by approximately an order of magnitude from the estimate described at background exposure levels in EPA's earlier draft of this reassessment (10^{-4}–10^{-3}) (U.S. EPA, 1994). This has occurred because, despite the fact that average intakes and body burdens are going down, estimates of upper-bound risk per unit dose have gone up by a factor of approximately 6 over the Agency's 1985 estimate and the range of exposure through the diet has been characterized.

EPA's approach to the development of an upper-bound estimate on cancer risk is consistent with its own past practices described above and with FDA's approach. In its recent report (U.S. EPA, 2001b), the SAB agreed that the treatment of the range of upper-bound risks obtained for the general population in this assessment is consistent with past EPA practice. FDA's past estimates of a risk-specific dose associated with a one-in-a-million risk (0.057 pg/kg body weight/day) (FDA 1990) have been based on animal data and have differed from EPA's only in minor ways regarding tumor counts and in the approach to cross-species scaling. In 1992, while EPA's reassessment was underway, FDA's risk-specific dose was adopted by the U.S. Public Health Service's Committee to Coordinate Environmental Health and Related Programs (CCEHRP) as the risk-specific dose for TEQ. In 1998, ATSDR used this risk-specific dose as a line of support for its policy guideline on dioxin and dioxin-like compounds in soil.

WHO and a number of individual countries have taken a different science-policy approach and have treated dioxins as nongenotoxic carcinogens and assumed that a safety factor approach, based on noncancer effects observed at lower doses than cancer in animals, would be adequate to account for concerns for both cancer and noncancer effects. This approach assumes that there is a virtual threshold for cancer effects above those for many noncancer effects. This position has been reiterated as recently as June 2001 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The differences between EPA (plus a number of other U.S. federal

agencies) and these international organizations in their approach to assessing potential cancer risk reflect differences in science policy.

Despite EPA's use of the epidemiology data to describe an upper bound on cancer risk, the peer panels who met to review earlier drafts of the cancer epidemiology chapter suggested that the epidemiology data alone were not adequate to support the characterization of dioxin and related compounds as "known" human carcinogens but that the results from the human studies were largely consistent with observations from laboratory studies of dioxin-induced cancer and, therefore, should be weighed in the assessment. Other scientists, including those who attended the peer panel meetings, felt either more or less strongly about the weight of evidence from cancer epidemiology studies, representing the range of opinions that still exists on the interpretation of these studies. Similar opinions were expressed in the comments documented in the SAB's reports in 1995 and in 2001 (U.S. EPA, 1995, 2001b).

In its reevaluation of the cancer hazard of dioxin and related compounds, IARC (1997) found that whereas the epidemiologic database for 2,3,7,8-TCDD was still "limited," the overall weight of the evidence provided by human, animal and mechanistic data was sufficient to characterize 2,3,7,8-TCDD as a Category 1 "known" human carcinogen. Other related members of the class of dioxin-like compounds were considered to have "inadequate" epidemiologic data to factor into hazard categorization. A similar classification of 2,3,7,8-TCDD as a "known" carcinogen has been published within the context of the Department of Health and Human Services' report on carcinogens (NTP, 2001). Here, too, the characterization is based on the weight of the human, animal, and mode of action information in humans and animals.

Therefore, given that 2,3,7,8-TCDD is contained in complex mixtures of dioxin and related compounds and that the TEQ approach has been adopted as a reasonable approach to assessing risks of these complex mixtures, it is also reasonable to apply estimates of upper-bound cancer potency derived from epidemiology studies where 2,3,7,8-TCDD was associated with excess cancer risk to complex mixtures of dioxin and related compounds.

The current evidence suggests that both receptor binding and most early biochemical events such as enzyme induction demonstrate linearity of dose-response within the range of observation. The mechanistic relationship of these early events to the complex process of carcinogenesis remains uncertain, although modes of dioxin action have been proposed. If these findings imply low-dose linearity in biologically based cancer models under development, then the probability of cancer risk may also be linearly related to exposure to TCDD. Until the mechanistic relationship between early cellular responses and the parameters in biologically

based cancer models is better understood, the shape of the dose-response curve for cancer below the range of observation can be inferred only with uncertainty.

Initial attempts to construct a biologically based model for certain dioxin effects as described in this reassessment will need to be continued and expanded to accommodate more of the available biology and to apply to a broader range of potential health effects associated with exposure to dioxin-like compounds. Associations between exposure to dioxin and certain types of cancer have been noted in occupational cohorts with average body burdens of TCDD approximately one to three orders of magnitude (10 to 1000 times) higher than average TCDD body burdens in the general population. In terms of TEQ, the average body burden in these occupational cohorts level is within one to two orders of magnitude (10 to 100 times) of average background body burdens in the general population (see Table 5-1 and Figure 5-2). Thus, there is no need for large-scale, low-dose extrapolations when applying models based on curve-fitting empirical data in order to evaluate background intakes and body burdens, and there are few if any data to suggest large departures from linearity in this somewhat narrow window between the lower end of the range of observation and the range of general population background exposures. Nonetheless, the relationship of apparent increases in cancer mortality in these worker populations to calculations of general population risk remains a source of uncertainty.

Use of a "margin of exposure" approach to evaluate risk for noncancer and cancer endpoints.

The likelihood that noncancer effects may be occurring in the human population at environmental exposure levels has received increased attention in recent years and is a major focus of this reassessment. This likelihood is often evaluated using an MOE approach. An MOE is calculated by dividing a "point of departure" at the low end of the range of observation in human or animal studies (the human-equivalent LOAEL, NOAEL, BMD, or effective dose [EDxx]) by the comparable surrogate of human exposure at the level of interest. It differs from a reference dose (RfD), which establishes a level of exposure below which the Agency considers it unlikely that any adverse effects will occur. The Agency has used the MOE approach for a number of years in its noncancer assessment of the safety of pesticides. The MOE concept has also been incorporated into the *Draft Final Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2003) as an alternative approach to dose-response analysis if the shape of the dose-response curve is uncertain. These draft cancer guidelines recommend differing approaches and default assumptions for linear versus nonlinear cancer data, where linear data can be approximated through the cancer slope factor and nonlinear data through an RfD and Hazard

Index approach. For both linear and nonlinear approaches to cancer characterization, the Agency recommends a statement of the extent of extrapolation of risk estimates from observed data to exposure levels of interest and its implications for certainty or uncertainty in quantifying risk. The extent of this extrapolation can be expressed as a *margin of exposure* (MOE).

As the exposure of interest approaches the range of observation of effects and MOEs get smaller, reaching any conclusion regarding the certainty of no harm is much more difficult and relies heavily on scientific judgment regarding the adequacy of the available data. In order for a decision relying on the MOE to be adequately protective of health, information is provided to allow the decisionmaker, to the extent information allows, to take into account the nature of the effect at the POD; the shape and slope of the dose-response curve; the adequacy of the overall database to assess human hazard; interindividual variability in the human population with regard to exposure, metabolism, and toxic response; and other factors. Background exposures should be factored into the calculation. Considering MOEs based on estimates of incremental exposure alone divided by the human exposure of interest is not considered to give an accurate portrayal of the implications of that exposure unless background exposures are insignificant.

One of the difficulties in assessing the potential health risk of exposure to dioxins is that background exposures are often a significant component of total exposure when based on TEQ. The average levels of background intake and current average body burdens of dioxin-like compounds in terms of TEQs in the general population (1 pg TEQ/kg body weight/day and 5 ng TEQ/kg body weight, respectively) are within a factor of 10 of human-equivalent levels associated with NOELS, LOAELs, or ED_{01} values derived from studies in laboratory animals exposed to TCDD or TCDD equivalents for both cancer and noncancer toxic effects (see Table 5-6 and Appendix A). Therefore, in many cases, the MOE compared to background using these toxic endpoints is a factor of 10 or less. These estimates and others are presented and discussed in Part II, Chapter 8.

As discussed in Chapter 8, these data, although variable, suggest that choosing a human-equivalent body burden associated with an ED_{01} value above 100 ng/kg as a point of departure would likely yield a greater than 1% excess risk for some toxicity endpoint in humans. Also, choosing a POD below 1 ng/kg would likely be an extrapolation below the range of these data. Given the nature of the data and the range of uncertainty around individual data sets, any choice for a 1% effect point of departure in the middle range of 1 ng/kg to 100 ng/kg would be supported by the analyses, although the data provide the greatest support for defining a point of departure consistent with principles of safety assessment in the range of 10 ng/kg to 50 ng/kg. This range also includes body burdens consistent with the empirically derived NOAELs and

LOAELs for many of the effects that have traditionally been used as a POD for safety assessment by WHO, JECFA, and ATSDR.

Although somewhat dependent on experimental design or the model chosen to derive the ED_{01}, NOAEL, and LOAEL values, this range provides a perspective on the nature and variety of effects that have been evaluated within approximately an order of magnitude, from biochemical markers of exposure to more clearly adverse effects in animals. This range of body burdens should also provide a useful point of comparison when evaluating impacts of risk management on average body burdens in the general population or on estimates of impact of incremental exposures above background on the range of individual body burdens at various ages.

Because of the relatively high background levels as compared to effect levels, the Agency is not recommending the derivation of a reference dose (RfD) for dioxin and related compounds. Although RfDs are often useful because they represent a health risk goal below which there is likely to be no appreciable risk of noncancer effects over a lifetime of exposure, their primary use by the Agency is to evaluate increments of exposure from specific sources when background exposures are low. Any RfD that the Agency would recommend using a traditional approach for setting an RfD using uncertainty factors to account for limitations of knowledge is likely to be below—perhaps significantly below (by a factor of 10 or more)—current background intakes and body burdens. Because exceeding the RfD is not a statement of risk, comparing an incremental exposure to an RfD when the RfD has already been exceeded by average background exposures has little value for evaluating possible risk management options. In addition, the calculation of an RfD (with its traditional focus on a single "critical" effect) distracts from the large array of effects associated with similar body burdens of dioxin.

The Agency's SAB, in its comments on an earlier draft of this document, remarked that there might be value in calculating an RfD, despite a recognition of these concerns. The RfD could be used for purposes of comparison with other chemical-specific RfDs, to ensure that proper emphasis was given to noncancer effects and to set a goal for future exposure reductions. These comments notwithstanding, the Agency feels that all of these ends can be accomplished without the establishment of an RfD.

As discussed earlier, a range of values has been presented that indicates that dioxin and related compounds can produce effects, some of which are indicative of a biological response to dioxin exposure and some of which are arguably adverse, at or near current background body burdens or intake levels. Several of the studies within this range could logically be chosen as the "critical" effect upon which an RfD could be set. No one effect provides the obvious choice, as evidenced by approaches taken by WHO, JECFA and ATSDR, all of which chose different

effects upon which to base their tolerable or minimal risk levels. A range of ED_{01}s has been described in Chapter 8 and a summary of NOAELs, LOAELs, and ED_{01}s for low-dose effects is presented in Table 5-6 and Appendix A.

Depending on the choice of the endpoint, a composite uncertainty factor would need to be determined in order to set an RfD. This composite uncertainty factor should account for, at a minimum, pharmacodynamic aspects of cross-species scaling (traditionally, a factor of 3)—because pharmacokinetic factors are assumed to be accounted for by cross-species scaling on the basis of body burden—and interindividual human variability (traditionally, a factor of 10). In addition, selection of a LOAEL within the range would suggest an additional factor of uncertainty as large as 10. Recently published results also indicate neurobehavioral impacts on adult rats exposed perinatally at levels that yield body burden ED_{01}s below current average human body burdens and as low as the lowest noncancer effects previously evaluated (Markowski et al., 2001). In addition, many of the developmental reproductive effects observed in rats (Mably et al., 1992a-c) have ED_{01} values less than current background exposures. These results suggest that there may be additional database needs regarding risks to children. The above considerations would traditionally yield a composite uncertainty factor in the range of 30 to 100 or more.

Coupled with the relatively narrow range of possible "critical" effects discussed above, the range of plausible composite uncertainty factors make the selection of any particular value as the Agency's RfD more difficult than usual and probably unnecessary, particularly in light of the fact that any value that the Agency might choose using traditional approaches would be below current background body burden or intake levels.

When evaluating incremental exposures associated with specific sources, knowing the increment relative to background may help in understanding the impact of the incremental exposure. For instance, it would be misleading to focus on only the incremental exposure in evaluating the potential impact on human health when a relatively large background body burden of dioxin already exists in the exposed population. In these circumstances, the incremental exposure needs to be evaluated in the context of these background levels to aid in determining whether these incremental exposures have regulatory significance. This approach would parallel the Agency's approach to evaluating lead exposures. Other parallel science and management issues between dioxin-like compounds and lead are under discussion within the Agency. Providing guidance on the how to judge the significance of incremental increases to background using the MOE approach is beyond the science scope of the reassessment and will have to be addressed elsewhere by EPA. However, it is clear, in light of relatively high background

exposures, that the MOE approach is more useful than an RfD for characterizing dioxin noncancer risks.

Other national and international bodies have chosen to define "safe" or "tolerable" levels for dioxin and related compounds (e.g., WHO, 1998; ATSDR, 1999a; SCF, 2000). These estimates cluster within a factor of 4 of current average intake levels, although estimates in the past have spanned many orders of magnitude. Some commenters on earlier drafts of this reassessment have suggested that EPA's approach is inconsistent with these efforts and overly "conservative." Two distinctions can help in understanding these apparent differences. First, in its reassessment, EPA has not tried to establish a tolerable or acceptable level of risk. Rather, it has tried to provide a science-based description of hazard and potential risk without making a policy judgment of acceptability. Second, whether one is providing a risk descriptor or an acceptable risk determination, a number of judgments need to be made as one moves from experimental observation to conclusion. Apparently subtle differences in these judgments can result in significantly different conclusions. These differences in judgment fall into three major areas: (1) the original focus on cancer rather than noncancer effects as the primary endpoint of regulatory concern and the assumption by some that all nongenotoxic compounds have thresholds below which cancer risk is minimal or nonexistent; (2) the use of intake as the cross-species dose metric despite the large difference in half-life in animals versus humans (for TCDD, for instance, the difference between rats and humans is over a factor of 100); and (3) the size of the "safety" factor or "uncertainty" factors used to derive a "safe or "tolerable" level.

The latter factor is currently the most widely divergent. More recent assessments have taken noncancer endpoints into account and have applied a range of uncertainty factors. For instance, ATSDR (1999a) set a minimal risk level (MRL), which is defined similarly to EPA's RfD, for dioxin and related compounds of 1.0 pg TEQ/kg body weight/day. The ATSDR assessment is based on the results of Schantz et al. (1992), a study that is included in Table 5-6 and Appendix A. ATSDR used intake as the interspecies dose metric and a composite uncertainty factor of 90, accounting for intraindividual human variability (10), a minimal LOAEL/NOAEL (3), and residual pharmacodynamic differences (3).

Hypothetically, had ATSDR relied on the TCDD body burdens measured during this series of rhesus monkey experiments (see Bowman et al., 1989) and had all other factors been equal, the MRL would likely have been determined to be in the range of 0.07 pg TEQ/kg body weight/day (see Table 5-6 and Appendix A), or more than 10 times lower than the existing ATSDR MRL and current average intake levels. The ATSDR assessment, however, selects a

single "critical" effect from among a number of choices and uses "traditional" uncertainty factors, but it uses intake rather than body burden as the dose metric.

Several recent assessments have recognized the value of body burden rather than daily intake as the preferred dose metric. WHO (1998) has set a tolerable daily intake (TDI) of 1–4 pg TEQ/kg body weight/day using a range of effects and body burden and has indicated that, although current exposures in that range are "tolerable" (a decision taking into account risk management in addition to traditional hazard assessment), efforts should be made to ultimately reduce intake levels to the lower end of the range and perhaps further. Findings in this reassessment and comments made by the SAB (U.S. EPA, 2001b) are consistent with this recommendation. The WHO assessment relied on an evaluation of the most sensitive effects that are considered adverse (hormonal, reproductive, and developmental effects) and were seen at low doses in animal studies (rats and monkeys). Body burden was used as a dose metric, and a composite uncertainty of 10 was recommended to account for a number of factors, including the use of a LOAEL rather than a NOAEL, differences in animal-to-human susceptibility, and differences in half-lives of elimination for the different components of the TEQ mixture.

In May 2001, the European Commission Scientific Committee on Food (SCF, 2000) established a tolerable weekly intake of 14 pg TEQ/kg body weight/week (equivalent to a TDI of 2 pg TEQ/kg body weight/day), based on several new studies, which are also now included in EPA's range of low-dose effects, and on a composite uncertainty factor of 9.6. This factor accounts for interindividual variability in toxicokinetics (a factor of 3.2) and marginal effects close to a NOAEL (a factor of 3). The committee concluded that no uncertainty factor needed to be applied for differences in toxicodynamics between experimental animals and humans and for interindividual variation among humans. In June 2001, WHO JECFA determined a provisional tolerable monthly intake (PTMI) of 70 pg TEQ/kg body weight/month (equivalent to 2.33 pg TEQ/kg body weight/day), based on an approach similar to that used by the SCF. The same two studies and safety factors of 3.2 or 9.6 were used, but two models were used to extrapolate the maternal body burden at the NOEL/LOEL of the studies. The committee chose the PTMI as the mid-point of the range of values from its analysis.

It should be clear from the discussion above that there is a consensus that sensitive animal responses falling within a relatively narrow range of body burdens can be used as a POD for regulatory guidance, but the choice of individual studies varies. The EPA assessment is the only one to bound the full range of effects (from arguably adaptive and questionably adverse to arguably adverse to clearly adverse) observed through the application of a uniform modeling approach, as well as through evaluating experimental LOAELs and NOAELs. There is also an

emerging consensus that body burden should often be used as a cross-species dose metric. This has implications for ATSDR's current MRL derivation. Finally, there is no consensus on the size or nature of uncertainty factors to be applied. Traditional approaches that might be applied by EPA or that have been applied by ATSDR would likely require additional information to support the choice or removal of uncertainty factors as performed by WHO, SCF, and JECFA. In particular, the focus on accounting for residual toxicodynamic differences in cross-species scaling and interindividual variability in the general population to account for sensitive individuals, including children, would suggest larger uncertainty factors than have been proposed by these groups if EPA were to set an RfD.

The choice of any composite uncertainty factor greater than 10 applied to effect levels based on body burden in any of the analyses described above would result in TDIs or MRLs below current background intakes. The use of uncertainty factors in the range of 30 to 100 or more, as traditionally used by EPA, would result in values even further below some current background body burdens or intake levels than the values presented by other organizations. Given the range of choices for a POD, the range of potential composite uncertainty factors and the uninformative nature of an RfD below current background levels, the Agency has chosen to continue to focus on MOE analyses and to not establish an RfD for dioxin and related compounds.

Children's risk from exposure to dioxin and related compounds may be increased, but more data are needed to fully address this issue.

The issue of children's risk from exposure to dioxin-like compounds has been addressed in a number of sections throughout this reassessment. Data suggest a sensitivity of response in both humans and animals during the developmental period, both prenatal and postnatal. However, these data are limited. Because evaluation of the impacts of early exposures on both children's health and health later in life is important for a complete characterization of risk, collection of additional data should be a high priority in order to reduce uncertainties in future risk assessments.

Data from the Dutch cohort of children exposed to PCBs and dioxin-like compounds suggest subtle impacts on neurobehavioral outcomes, thyroid function, and immune system alterations from prenatal—and perhaps postnatal—exposure to 1980s background levels of dioxin and related compounds. Although these effects cannot be attributed solely to dioxin and related compounds, several associations suggest that these effects are, in fact, likely to be Ah-mediated. An investigation of background dioxin exposure and tooth development was done in

Finnish children as a result of studies of dental effects in dioxin-exposed rats, mice, and nonhuman primates and in PCB-exposed children. The Finnish investigators examined enamel hypomineralization of permanent first molars in 6- and 7-year-old children. The length of time that infants breast fed was not significantly associated with either mineralization changes or with TEQ levels in the breast milk. However, when the levels and length of breast feeding were combined in an overall score, a statistically significant association was observed.

In addition, effects have been seen in cases where significantly elevated exposure occurred. The incidents at Yusho and Yu-Cheng resulted in increased perinatal mortality and low birth weight in infants born to women who had been exposed. Rocker bottom heal was observed in Yusho infants, and functional abnormalities have been reported in Yu-Cheng children. The similarity of effects observed in human infants prenatally exposed to the complex mixture in Yusho and Yu-Cheng and those reported in adult monkeys exposed perinatally to only TCDD suggests that at least some of the effects on children are due to the TCDD-like congeners in the contaminated rice oil ingested by the mothers of these children. The similar responses include a clustering of effects in organs derived from the ectodermal germ layer, referred to as ectodermal dysplasia, including effects on the skin, nails, and Meibomian glands, and developmental and psychomotor delay during developmental and cognitive tests.

Some investigators believe that because all of the effects in the Yusho and Yu-Cheng cohorts do not correlate with TEQ, some of the effects are due exclusively to nondioxin-like PCBs or to a combination of all the congeners. In addition, on the basis of these data, the extent of the association between overt maternal toxicity and embryo/fetal toxicity in humans is still not clear. Further studies in the offspring as well as follow-up of the Seveso incident may shed further light on this issue. In addition to the chloracne and acute responses to TCDD exposure seen in Seveso children, elevated levels of serum GGT have been observed within a year after exposure in some of the more highly exposed Seveso children. Long-term pathologic consequences of elevated GGT have not been illustrated by excess mortality from liver disorders or cancer or in excess morbidity, but further follow-up is needed. It must be recognized that the absence of an effect thus far does not obviate the possibility that the enzyme levels increased concurrently with the exposure but declined after cessation. The apparently transient elevations in ALT levels among the Seveso children suggest that hepatic enzyme levels other than GGT may react in this manner to TCDD exposure. Recent studies in Seveso have also demonstrated an altered sex ratio in the second generation (Mocarelli et al., 2000).

Impacts on thyroid hormones provide an example of an effect of elevated postnatal exposure to dioxin and related compounds. Several studies of nursing infants suggest that

ingestion of breast milk that has a higher dioxin TEQ may alter thyroid function. Thyroid hormones play important roles in the developing nervous system of all vertebrate species, including humans. In the United States, all infants are tested for hypothyroidism shortly after birth. Results from the studies mentioned above suggest a possible shift in the population distribution of thyroid hormone levels, particularly T4, and point out the need for collection of longitudinal data to assess the potential for long-term effects associated with developmental exposures.

A large number of studies in animals, including studies of single congeners and exposures to complex mixtures, have addressed the question of effects of dioxin-like chemicals after in utero or lactational exposure. However, the vast majority of the data are derived from studies of 2,3,7,8-TCDD, single congeners (e.g., PCB 77), or commercial mixtures of PCBs. Exposure patterns have included single doses to the dams as well as dosing on multiple days during gestation beginning as early as the first day of gestation. These studies are discussed in detail in Part II, Chapter 5. The observed toxic effects include developmental toxicity, neurobehavioral and neurochemical alterations, endocrine effects, and developmental immunotoxicity. For instance, results of this body of work suggest that 2,3,7,8-TCDD clearly has the potential to produce alterations in male reproductive function (rats, mice, hamsters), male sexual behavior (rats), and female genitalia (rats, hamsters) after prenatal exposure. In addition, impacts on neuromotor and cognitive behavior as well as on development of the immune system have been indicated in a number of studies.

No epidemiological data and limited animal data are available to address the question of the potential impact of exposure to dioxin-like compounds on childhood cancers or on cancers of later life. The direct impacts of increased early postnatal exposure on the carcinogenic process may be small, noting the limited impact of nursing on total body burden (see the discussion of breast milk exposures and body burdens below), the assumption that cancer risk is a function of average lifetime body burden, and the possibility that, because dioxin is a potent cancer promoter rather than a direct initiator of the cancer process, exposures later in life might be more important than those received earlier. However, recent studies of Brown et al. (1998) suggest that prenatal exposure of rats to dioxin and related compounds may indirectly enhance their sensitivity as adults to chemical carcinogenesis from other chemical carcinogens. Further work is needed to evaluate this issue.

Fetuses, infants, and children are exposed to dioxins through several routes. The fetus is exposed in utero to levels of dioxin and related compounds that reflect the body burden of the mother. It is important to recognize that the greatest impact on the mother's body burden is from

of her lifetime exposure history rather than from the individual meals she eats during pregnancy. Good nutrition, including a diet with appropriate levels of fat, has consequences on dietary intake and consequent body burdens of dioxin and related compounds. Nursing infants represent special cases because for a limited portion of their lives they may have elevated exposures on a body-weight basis when compared with non-nursing infants and with adults (see discussion below).

In addition to breast milk exposures, intakes of CDD/CDFs and dioxin-like PCBs are more than three times higher for a young child than for an adult, on a body-weight basis. Table 4-7 in Section 4 of this document describes the variability in average intake values as a function of age using age-specific food consumption rates and average food concentrations, as was done for adult intake estimates. However, as with the nursing infants, the differences in body burden between children and adults are expected to be much less than the differences in daily intake. Assuming that body burden is the relevant dose metric for most if not all effects, there is some assurance that these short-term increased intake levels will have limited additional impact on risk as compared with overall lifetime exposure.

Background exposures to dioxin and related compounds need to be considered when evaluating both hazard and risk.

The term "background exposure" has been used throughout this reassessment to describe exposure of the general population to environmental media (food, air, soil, etc.) that have dioxin concentrations within the normal background range. Adult daily intakes of CDD/CDFs and dioxin-like PCBs are estimated to average 43 and 23 pg TEQ_{DFP}-WHO_{98}/day, respectively, for a total intake of 66 pg/day TEQ_{DFP}-WHO_{98}. On a body-weight basis, this corresponds to approximately 1 pg TEQ_{DFP}-WHO_{98}/kg-day. Daily intake is estimated by combining exposure media concentrations (food, soil, air) with contact rates (ingestion, inhalation). Table 4-6 summarizes the intake rates derived by this method. The intake estimate is supported by an extensive database on food consumption rates and food data. Pharmacokinetic modeling provides further support for the intake estimates. Current adult tissue levels reflect intakes from past exposure levels, which are thought to be higher than current levels.

CDD/CDF and dioxin-like PCB intakes for the general population may extend to levels at least three times higher than the mean. Variability in general population exposure is primarily a result of differences in the dietary choices that individuals make in terms of both quantity and types of food consumed. A diet that is disproportionately high in animal fats will result in an increased background exposure over the mean. Data on the variability of fat consumption

indicate that the 95th percentile is about twice the mean and the 99th percentile is approximately three times the mean. Additionally, a diet that substitutes meat sources that are low in dioxin (e.g., beef, pork, or poultry) with sources that are high in dioxin (e.g., freshwater fish) could result in elevated exposures.

Evidence of widespread background exposure can also be seen by examining data on human tissue. These data indicate that the average CDD/CDF tissue level for the general adult U.S. population appears to be declining. A pharmacokinetic modeling evaluation of this declining trend suggests that the CDD/CDF tissue level will drop below 10 ppt TEQ_{DF}-WHO_{98}, lipid basis, by 2030 (Lorber, 2002). The best estimate of current (mid to late 1990s) levels is 25 ppt (TEQ_{DFP}-WHO_{98}, lipid basis). The tissue samples collected in North America in the late 1980s and early 1990s showed an average TEQ_{DFP}-WHO_{98} level of about 55 pg/g lipid. This finding is supported by a number of studies, all conducted in North America, that measured dioxin levels in adipose tissue, blood, and human milk. However, the number of people in most of these studies is relatively small, and the participants were not statistically selected in ways that ensured their representativeness of the general U.S. adult population. One study, the 1987 National Human Adipose Tissue Survey (NHATS), involved more than 800 individuals and provided broad geographic coverage, but it did not address coplanar PCBs. Similar tissue levels of these compounds were measured in Europe and Japan during similar time periods.

Because dioxin levels in the environment have been declining since the 1970s, it is reasonable to expect that levels in food, human intake, and, ultimately, human tissue have also declined over this period. The changes in tissue levels are likely to lag the decline seen in environmental levels, and the changes in tissue levels cannot be assumed to occur proportionally with declines in environmental levels. CDC (2000) summarized levels of CDDs, CDFs, and PCBs in human blood collected between 1995 and 1997. The individuals sampled were all U.S. residents who had no known exposures to dioxin other than normal background. The blood was collected in six different locations from 316 individuals ranging in age from 20 to 70 years. All TEQ calculations were made assuming that nondetects were equal to half the detection limit. Although these samples were not collected in a manner that can be considered statistically representative of the national population and they lack wide geographic coverage, they are judged to provide a better indication of current tissue levels in the United States than the earlier data (see Table 4-5).

PCBs 105, 118, and 156 are missing from the blood data for the comparison populations reported by CDC (2000). These congeners account for 62% of the total PCB TEQ estimated in the early 1990s. Assuming that the missing congeners from the CDC study data contribute the

same proportion to the total PCB TEQ as in earlier data, they would increase the estimate of current body burdens by another 3.3 pg TEQ/g lipid, for a total PCB TEQ of 5.3 pg/g lipid and a total TEQ_{DFP}-WHO_{98} of 25.4 pg/g lipid.

As noted, characterizing national background levels of dioxins in tissues is uncertain because the current data cannot be considered statistically representative of the general population. The task is also complicated by the fact that tissue levels are a function of both age and birth year. Because intake levels have varied over time, the accumulation of dioxins in a person who turned 50 in 1990 is different from that in a person who turned 50 in 2000. Future surveys should help to characterize national levels of CDD/CDF/PCBs during the last years of the 20th century and into the 21st century. The National Health and Nutrition Examination Survey (NHANES) conducted in 1999-2000 included measurements of dioxin blood levels in 1921 individuals, aged 12 and higher, from numerous locations around the country (CDC, 2003). Unfortunately, not enough blood serum was available per individual to be able to quantify the dioxin concentrations at low background levels, so the majority of measurements were nondetects. An effort is currently underway to pool remaining NHANES 1999-2000 samples and reanalyze them. This will allow for an estimate of average background body burdens of dioxin-like compounds representative of the turn of the century, and in future years should provide a picture of dioxin levels in the general U.S. population.

As described above, current intake levels from food sources are estimated in this reassessment to be approximately 1 pg TEQ/kg body weight/day. Certain segments of the population may be exposed to additional increments of exposure by being in proximity to point sources or because of dietary practices. These types of exposure are described below.

Evaluating the exposure of "special" populations and developmental stages is critical to risk characterization.

As discussed above, background exposures to dioxin-like compounds may extend to levels at least three times higher than the mean. This upper range is assumed to result from the normal variability of diet and human behaviors. Exposures from local elevated sources or unique diets would be added to this background variability. Elevated exposures may occur in small segments of the population, such as individuals living near discrete local sources or subsistence or recreational fishers. Nursing infants represent a special case. For a limited portion of their lives, they may have elevated exposures on a body-weight basis when compared to non-nursing infants and to adults. This exposure will be discussed in a separate section.

Dioxin contamination incidents involving the commercial food supply have occurred in the United States and other countries. For example, in the United States, contaminated ball clay was used as an anticaking agent in soybean meal, resulting in elevated dioxin levels in some poultry and catfish. This incident involved only a small fraction of national poultry production and the practice has since been eliminated. Elevated dioxin levels have also been observed in a few beef and dairy animals, where the contamination was associated with contact with pentachlorophenol-treated wood. This type of elevated exposure was not detected in the national beef survey; consequently, its occurrence is likely to be low, although it has not been determined.

These incidents may have led to small increases in dioxin exposure to the general population; however, it is unlikely that they have led to disproportionate exposures to populations living near where they occurred because, in the United States, meat and dairy products are highly distributed on a national scale. If contamination events were to occur in foods that are predominantly distributed on a local or regional scale, then such events could lead to higher exposure among local populations.

Elevated exposures associated with the workplace or with industrial accidents have also been documented. U.S. workers in certain segments of the chemical industry had elevated levels of TCDD exposure, with some tissue measurements in the thousands of parts per trillion TCDD. There is no clear evidence that elevated exposures are currently occurring among U.S. workers. Documented examples of past exposures for other groups include certain Air Force personnel exposed to Agent Orange during the Vietnam War and individuals exposed as a result of industrial accidents in Europe and Asia.

The discussion in Section 4.5 identified the general population distribution of exposure as extending up to roughly three times the mean. Most people will have exposures within this range even if they have unusual diets in terms of meat and dairy products because most people eat food from multiple sources, which tends to average out the contamination levels, and meat and dairy products have similar dioxin levels, so substitution of one type of meat for another should not have a great impact on total exposure. Clearly elevated exposures are possible in unusual situations where an individual consumes high quantities of meat or dairy products that have significantly increased dioxin levels. Elevated exposures resulting from fish consumption can occur in different situations because concentrations in freshwater fish are significantly greater than in meat and dairy products. Therefore, people who consume large quantities of freshwater fish at background contamination levels may have intakes elevated above the general population distribution.

Consumption of fish, meat, or dairy products containing elevated levels of dioxins and dioxin-like PCBs can lead to elevated exposures in comparison to the general population. Most people eat some fish from multiple sources, both fresh and salt water. If individuals obtain their fish from areas where the concentration of dioxin-like chemicals is elevated, they may constitute a highly exposed subpopulation. Although this scenario seems reasonable, very little supporting data could be found for such a highly exposed subpopulation in the United States. One study that measured dioxin-like compounds in blood of sports fishers in the Great Lakes area showed elevations over mean background but within the range of normal variability.

Another study that measured 90 PCB congeners—of which 7 were dioxin-like mono-ortho PCBs (although PCB 126 was not measured)—in Lake Michigan "sport-fish eaters" showed a significant elevation in these PCBs versus a control group (little or no sport fish consumption). Significantly elevated concentrations of dioxins, furans, and coplanar PCBs were measured in Great Lakes fish by the Ontario Ministry of the Environment, although this study was conducted in known or suspected hot spots for the purpose of setting consumption advisories. It is not known to what extent individuals would be consuming fish at the high concentrations measured. Elevated CDD/CDF levels in human blood have been measured in Baltic fishermen. Similarly, elevated levels of coplanar PCBs have been measured in the blood of fishers on the north shore of the Gulf of the St. Lawrence River who consume large amounts of seafood.

High exposures to dioxin-like chemicals as a result of consuming meat and dairy products would most likely occur in situations where individuals consume large quantities of these foods and the level of these compounds is elevated. Most people eat meat and dairy products from multiple sources, and even if large quantities are consumed, unusually high exposures are not likely. Individuals who raise their own livestock for basic subsistence have the potential for higher exposures if local levels of dioxin-like compounds are high. One study in the United States showed elevated levels in chicken eggs near a contaminated soil site. European studies at several sites have shown elevated CDD/CDF levels in milk and other animal products near combustion sources.

In summary, in addition to general population exposure, some individuals or groups of individuals may also be exposed to dioxin-like compounds from local discrete sources or pathways within their environment. Examples of these "special" exposures include contamination incidents, occupational exposures, direct or indirect exposure to local populations from discrete sources, or exposures to subsistence or recreational fishers.

Breast-feeding infants have higher intakes of dioxin and related compounds for a short but developmentally important part of their lives; however, the benefits of breast feeding are widely recognized to outweigh the risks.

Three studies have compared dioxins in infants who were breast fed with those who were formula fed, and all have shown elevations in the concentrations of dioxins in infants being breast fed. Formula-fed infants had lipid-based concentrations < 5 ppt TEQ_{DF}-WHO_{98}, whereas breast-fed infants had average lipid-based concentrations > 20 ppt TEQ_{DF}-WHO_{98}. A similar disparity is seen in more limited data on dioxin-like PCBs.

The dose to the infant varies as a function of infant body weight, the concentration of dioxins in the mother's milk, and the trend of dioxins in the mother's milk to decline over time. Using typical values for these parameters, dioxin intakes at birth were estimated to equal 242 pg TEQ_{DFP}-WHO_{98}/kg/day, which would drop to 18 pg TEQ_{DFP}-WHO_{98}/kg/day after 12 months. The average infant dose over a year was calculated to be 87 pg TEQ_{DFP}-WHO_{98}/kg/day. Although this dose exceeds the currently estimated adult dose of 1 pg TEQ_{DFP}-WHO_{98}/kg/day, the effect on infant body burdens is expected to be less dramatic, that is, infant body burdens will not exceed adult body burdens by 87 times. This is due to the rapidly expanding infant body weight and lipid volume, the decrease in concentration of dioxins in the mother's milk over time, and more rapid elimination in infants.

A pharmacokinetic exercise comparing 6-month, 1-year, and 2-year nursing scenarios with formula feeding showed peak infant lipid concentrations of 44 ppt TEQ_{DFP}-WHO_{98} at 9 weeks of age, compared with peak lipid concentrations of less than 10 ppt for the formula-fed infants and average adult lipid concentrations of 25 ppt TEQ_{DFP}-WHO_{98}. The dioxin concentrations in breast-fed and formula-fed children were predicted to merge at about 10 years of age, at a lipid concentration of about 13 ppt TEQ_{DFP}-WHO_{98}. Breast feeding for 1 year was predicted to result in a lifetime accumulated exposure about 13% higher as compared to formula feeding only.

The American Academy of Pediatrics (1997) has made a compelling argument for the diverse advantages of breast feeding for infants, mother, families, and society. These include health, nutritional, immunologic, developmental, psychological, social, economic, and environmental benefits. Breast milk is the point of comparison for all infant food, and the breast-fed infant is the reference for evaluation of all alternative feeding methods. In addition, increasing the rates of breast-feeding initiation is a national health objective and one of the goals of the United States Government's Healthy People 2010. WHO (1988) maintained that the

evidence did not support an alteration of its recommendations that promote and support breast feeding. A more recent consultation in 1998 (WHO, 2000) reiterated these conclusions.

Although it is important that the recommendations of these groups continue to be reevaluated in light of emerging scientific information, the Agency does not believe that the findings contained in this reassessment provide a scientific basis for initiating such a reevaluation. This conclusion is based on the fact that stronger data have been presented that body burden, not intake, is the best dose metric; that many of the noncancer effects, particularly those seen in children, are more strongly associated with prenatal exposure and the mother's body burden than with postnatal exposures and breast milk levels; and that dioxin-like compounds are strong promoters of carcinogenicity, a mode of action that depends on late-stage impacts rather than on early-stage impacts on the carcinogenic process.

Many dioxin sources have been identified and emissions to the environment are being reduced.

Current emissions of CDDs/CDFs/PCBs to the United States environment result principally from anthropogenic activities. Evidence for this finding includes matches in time of the rise of environmental levels with the rise in general industrial activity (see discussion in Section 4.1), lack of any identified large natural sources, and observations of higher CDD/CDF/PCB body burdens in industrialized versus less industrialized countries (see discussion on human tissue levels in Section 4.4).

The principal identified sources of environmental releases are (1) combustion and incineration sources; (2) chemical manufacturing/processing sources; (3) industrial/municipal processes; (4) biological and photochemical processes; and (5) reservoir sources. Development of national estimates of annual environmental releases to air, water, and land is complicated by the fact that only a few facilities in most industrial sectors have been evaluated for CDD/CDF emissions. Thus, an extrapolation is needed to estimate national emissions. The extrapolation method involves deriving an estimate of emissions per unit of activity (i.e., an emission factor) at the tested facilities and multiplying this by the total activity level in the untested facilities.

In order to convey the level of uncertainty in both the measure of activity and the emission factor, EPA developed a qualitative confidence rating scheme. The confidence rating scheme, presented in Section 4, Table 4-1, uses qualitative criteria to assign a high, medium, or low confidence rating to the emission factor and activity level for those source categories for which emission estimates can be reliably quantified. The dioxin reassessment has produced an inventory of source releases for the United States (Table 4-2). The inventory is limited to

sources whose releases can be reliably quantified (i.e., those with confidence ratings of A, B, or C, as defined in Table 4-1). The inventory presents the environmental releases in terms of two reference years: 1987 and 1995. For both of these periods, emissions from combustion and incineration sources dominated total releases. EPA's best estimates of releases of CDD/CDFs to air, water, and land from reasonably quantifiable sources were approximately 3300 g (7 pounds) TEQ_{DF}-WHO_{98} in 1995 and 14,000 g (31 pounds) TEQ_{DF}-WHO_{98} in 1987. The decrease in estimated releases of CDD/CDFs between 1987 and 1995 (approximately 76%) was due primarily to reductions in air emissions from municipal and medical waste incinerators.

Although this inventory is one of the most comprehensive and well-documented in the world, it is likely to underestimate total releases because a number of known sources lacked sufficient data to be included in the inventory and the possibility remains that truly unknown sources exist.

Further reductions in environmental releases since the inventory for 1995 can be anticipated as a result of EPA regulations for waste combustion sources and pulp and paper facilities. EPA's regulatory programs estimate that, under full compliance with these regulations, an additional 1800 g I-TEQ reduction in CDD/CDF emissions should occur. With these anticipated emission reductions, uncontrolled burning of household waste would become the largest quantifiable source. Although the full magnitude of reservoir releases remains uncertain, their relative contribution to total annual releases be can reasonably anticipated to increase as contemporary formation sources continue to decrease.

No significant release of newly formed dioxin-like PCBs is occurring in the United States. Unlike CDD/CDFs, PCBs were intentionally manufactured in the United States in large quantities from 1929 until production was banned in 1977. Although it has been demonstrated that small quantities of coplanar PCBs can be produced during waste combustion, no strong evidence exists that the dioxin-like PCBs make a significant contribution to TEQ releases during combustion. The occurrences of dioxin-like PCBs in the U.S. environment most likely reflect past releases associated with PCB production, use, and disposal. Further support for this finding is based on observations of reductions since the 1980s in PCBs in Great Lakes sediment and in other areas.

As described in Section 4.1, combustion appears to be the most significant process of CDD/CDF formation today. Important factors that can affect the rate of dioxin formation include overall combustion efficiency, post-combustion flue gas temperatures and residence times, and the availability of surface catalytic sites to support dioxin synthesis. Although chlorine is an essential component for the formation of CDDs/CDFs in combustion systems, the empirical

evidence indicates that, for commercial-scale incinerators, chlorine levels in feed are not the dominant controlling factor for rates of CDD/CDF stack emissions. The conclusion that chlorine in feed is not a strong determinant of dioxin emissions applies to the overall population of commercial scale combustors. For any individual commercial-scale combustor, circumstances may exist in which changes in chlorine content of feed could affect dioxin emissions. For uncontrolled combustion, such as open burning of household waste, chlorine content of wastes may play a more significant role than commercial-scale combustors in levels of dioxin emissions.

Dioxins are widely distributed in the environment at low concentrations, primarily as a result of air transport and deposition.

The dioxin-like compounds are essentially insoluble in water, they are generally classified as semivolatile, and they tend to bioaccumulate in animals. Once introduced into the environment, they are widely distributed in the environment as a result of a number of physical and biological processes. There is some evidence that these compounds can degrade in the environment, but in general they are considered very persistent and relatively immobile in soils and sediments.

The dioxin-like compounds are transported through the atmosphere as vapors or attached to airborne particulates and they can be deposited on soils, plants, or other surfaces (by wet or dry deposition).

They enter water bodies primarily via direct deposition from the atmosphere or by surface runoff and erosion. From soils, these compounds can reenter the atmosphere as resuspended soil particles or as vapors. In water, they can be resuspended into the water column from sediments, volatilized out of the surface waters into the atmosphere, or buried in deeper sediments. Immobile sediments appear to serve as permanent sinks for the dioxin-like compounds. Anthropogenic materials (such as pentachlorophenol), although not always considered an environmental compartment, may also contain these compounds, and they have the potential to be released from these materials into the broader environment.

The two primary pathways by which dioxin-like compounds enter the ecological food chains and human diet are air to plant to animal and water/sediment to fish. Vegetation receives these compounds via atmospheric deposition in the vapor and particle phases. The compounds are retained on plant surfaces and bioaccumulated in the fatty tissues of animals that feed on these plants. In the aquatic food chain, dioxins enter water systems via direct discharge or deposition and runoff from watersheds. Fish accumulate these compounds through direct contact

with water, suspended particles, and bottom sediments and through the consumption of aquatic organisms.

Although these two pathways are thought to normally dominate contribution to the commercial food supply, others can also be important. Animal feed contamination episodes have led to elevations of dioxins in poultry in the United States, in milk in Germany, and in meat/dairy products in Belgium. Gaining a quantitative understanding of how dioxin moves in the environment will be particularly important in understanding the relative contributions of individual point sources to the food chain and assessing the effectiveness of control strategies to reduce human exposure. Although the emissions inventory shows the relative contribution of various sources to total emissions, it is unlikely that these sources make the same relative contributions to human exposure.

It is quite possible that the major contributors of dioxin to food may not be those sources that represent the largest fractions of total emissions in the United States (see discussion in Section 4.4 indicating that the diet is the dominant exposure pathway for humans). The geographic locations of sources relative to the areas from which much of the beef, pork, milk, and fish are produced should be considered. Most of the agricultural areas that produce dietary animal fats are not located near or directly downwind of the major sources of dioxin and related compounds.

The contribution of reservoir sources to human exposure is likely to be significant. Several factors support this finding. First, human exposure to the dioxin-like PCBs is thought to be derived almost completely from reservoir sources. Because approximately one-third of general population TEQ intake is due to PCBs, then at least one-third of the calculated overall risk from dioxin-like compounds comes from reservoir sources. Second, CDD/CDF releases from soil via soil erosion and runoff to waterways appear to be greater than releases to water from the primary sources included in the inventory. CDD/CDFs in waterways can bioaccumulate in fish, leading to human exposure via consumption of fish. This suggests that a significant portion of the CDD/CDF TEQ exposure could be due to releases from the soil reservoir. Finally, soil reservoirs could have vapor and particulate releases that deposit on plants and enter the terrestrial food chain. However, the magnitude of this contribution is unknown. Collectively, these three factors suggest that reservoirs are a significant source of current background TEQ exposure, perhaps contributing half or more of the total.

Environmental levels, emissions, and human exposures have declined during recent decades.

The most compelling supportive evidence of a general decline in environmental levels for CDD/CDF/PCBs comes from dated sediment core studies. CDD/CDF/PCB concentrations in sediments began to increase around the 1930s and continued to increase until about 1970. Decreases began in 1970 and have continued to the time of the most recent sediment samples (about 1990). Sediment studies in lakes located in several European countries have shown similar trends.

It is reasonable to assume that sediment core trends are driven by a similar trend in emissions to the environment. The period of increase generally matches the time when a variety of industrial activities began rising, and the period of decline appears to correspond with growth in pollution abatement. Decreases in dioxin emissions will presumably have resulted from many of these abatement efforts, which included elimination of most open burning, particulate controls on combustors, phase-out of leaded gas, and bans on PCBs, 2,4,5-T, hexachlorophene and restrictions on the use of pentachlorophenol. Also, the national source inventory of this assessment documented a significant decline in emissions from the late 1980s to the mid-1990s.

Evidence of declines in human exposure can be inferred from the overall declines in environmental levels and emissions, and it is directly supported by limited data on concentrations in food and human tissues (see Sections 4.3 and 4.4). Because of the lag between environmental levels and body burdens, it is anticipated that further declines in tissue concentrations should occur as individuals with higher body burdens from past exposure age out of the population. A pharmacokinetic modeling exercise suggested that levels of TEQ_{DF}-WHO_{98} in the U.S. population should decline from levels of about 20 ppt lipid-basis measured in the mid-1990s CDC study to below 10 ppt lipid-basis by 2030. This analysis includes CDD/CDFs only, not PCBs. Dioxin-like PCBs currently make up approximately 20% of the current total TEQ body burden but may increase in percentage as CDD/CDFs decline. This modeling result is based on the assumption that current CDD/CDF intakes remain the same into the 21st century.

Risk Characterization Summary Statement

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD; "dioxin") is highly toxic to many animal species, producing a variety of noncancer and cancer effects. Other 2,3,7,8-substituted polychlorinated dibenzo-*p*-dioxins and dibenzofurans and coplanar polychlorinated biphenyls (PCBs) exhibit similar effects, albeit at different doses and with different degrees of confidence in the database.

The similarities in toxicity between species and across different dioxin congeners stem from a common mode of action via initial binding to the aryl hydrocarbon (AhR) receptor. This common mode of action is supported by the consistency in effects evident from multiple congener databases, although uncertainty remains due to data gaps for some congeners. The databases supportive of dioxin-like toxicity, both cancer and noncancer, are strongest for those congeners that are the major contributors to the risk to human populations. This has led to an international scientific consensus that it is prudent science policy to use the concept of toxic equivalency factors (TEFs) to sum the contributions of individual PCDD, PCDF, and coplanar PCB congeners with dioxin-like activity.

In addressing receptor-mediated responses resulting from complex mixtures of dioxin-like congeners, this assessment has provided a basis for the use of integrated measures of dose such as lifetime average body burden as more appropriate default metrics than average lifetime daily intake. Although average body burden over a lifetime appears to be the most useful dose metric for chronic effects, average body burden during the window of sensitivity may be the most appropriate metric for developmental effects. The Agency recognizes, therefore, that the final choice of the appropriate metric may depend on the endpoint under evaluation.

Dioxin and related compounds have been shown to be developmental, reproductive, immunological, endocrinological, and cancer hazards, among others in multiple animal species. There is no reason to expect, in general, that humans would not be similarly affected at some dose, and indeed, a growing body of data supports this assumption. On the basis of the animal data, current margins of exposure are lower than generally considered acceptable, especially for more highly exposed human populations. The human database supporting this concern for potential effects near background body burdens is less certain. Occupational and industrial accident cohorts exposed at higher levels show correlations with exposure for cancer and a number of noncancer effects consistent with those seen in the animal studies.

For cancer outcomes, the epidemiological evidence provides consistent findings of statistically significant elevations, with dose-response trends for all cancers combined and lung cancer risk in occupational cohorts along with evidence of possible additional tissue-specific cancer rate elevations. Given this substantial yet still not definitive epidemiological data, the positive cancer bioassays at multiple sites and in all animal species tested, in vitro studies, and the mechanistic considerations common to animals and humans for dioxin carcinogenicity, EPA characterizes 2,3,7,8-tetrachlorodibenzo-*p*-dioxin as "carcinogenic to humans." On the basis of similarities of response in multiple positive animal bioassays for non-TCDD congeners and mixtures, mode of action studies, and consistent with the concept of toxic equivalency, complex mixtures of dioxin and related compounds are considered highly potent "likely" carcinogens.

The calculated body burdens of dioxin and dioxin-like substances leading to an estimated 1% increase (ED_{01}) in the lifetime risk of cancer in the three occupational studies with the best exposure information fall within a 10-fold range, and those calculated from the animal bioassay data fall in the middle of this range. The ED_{01} for all cancers combined from the three occupational cohorts range from 6 to 62 ngTCDD/kg body weight (excluding the NIOSH power model calculation), depending on the study and the model used. By comparison, current background body burdens in the United States are approximately 5 ngTEQ/kg body weight, suggesting little margin of exposure (MOE) at today's body burden levels.

From these same occupational and animal cancer studies, EPA estimates an upper bound on the lifetime risk of all cancers combined of 1×10^{-3} per pgTEQ/kg/day. This cancer slope factor is based on a statistical estimate of risks from occupational exposures—principally to healthy, adult, male workers—and it must be coupled with a recognition that a small number of people may be both more susceptible and consume up to three times the average level of fat per day (the principal exposure pathway for dioxins in the general population). Conversely, this risk estimate is based on assumptions that the extra cancer risk seen in the occupational cohorts is attributable to dioxin and not other chemical agents present; that the appropriate metric for cancer risk is lifetime average body burden and not a measure of peak exposure, which would tend to mitigate risks at low exposures; and that the dose-response model curve continues below the range of statistically significant data and does not then exhibit some nonlinearity. Using the best available estimates of cancer risks, the upper bound on general population lifetime risk for all cancers might be on the order of 1 in 1000 or more. Upper-bound risk estimates allow the calculation of the high end of the probability of cancer risk in the population. This means that there is greater than a 95% chance that cancer risks will be less than the upper bound, and it could be as low as zero in some individuals.

For noncancer effects, EPA generally calculates an RfD/RfC value that represents an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfD/RfCs are generally calculated by estimating a point of departure dose just below the lower end of the range of observed adverse effects, and dividing this by uncertainty factors to account for extrapolation issues and database deficits. Applying these standard procedures to the data reviewed in this assessment would result in an RfD/RfC below the current estimated average dose to the U.S. population (~1 pgTEQ/kg/day), and would, therefore, be uninformative for a safety assessment.

EPA has chosen instead to characterize the MOEs for noncancer endpoints in order to better inform risk management decisions. The MOE is the ratio of the effect level in the

comparison species (ED_{01} or low effect level; animal or human) to the human body burden. For the most sensitive endpoints identified, MOEs range from, for example, less than 1 for enzyme induction in mice and rats, < 4 for developmental effects, and 4 for endometriosis in non-human primates. In evaluating MOEs, consideration should be given to uncertainties in distinguishing between adaptive biochemical changes and adverse effects, both on an individual level and as these changes impact whole populations. The risks from dioxin and related compounds may be greater for children than for adults, but more data are needed to fully address this issue.

Releases of dioxins to the environment from characterized sources have decreased significantly over the last decade and are expected to continue to decrease. Other sources are still poorly characterized, and an environmental reservoir of dioxins from both man-made and natural sources has been recognized. Human body burdens have also declined and are anticipated to be further reduced as additional, recently implemented, dioxin emission controls impact environmental and food levels and, ultimately, human exposure, although the relationship with reservoir sources remains uncertain.

APPENDIX A

Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake

Animal	Endpoint	Study	Estimated body burden (ng/kg)			Human equiv.[a] intakes (pg/kg/day)
			LOAEL	NOAEL	ED01	
Rats	Cancer	Kociba et al. (1978)[1]	180	18	32	60; 6; 11
Rhesus monkeys	Fetal Mortality	Bowman et al. (1989)[2]	90	21	NC	30; 7
	Developmental Neurotoxicity	Schantz et al. (1992)[3]	21	–	NC	7
	Endometriosis	Rier et al. (1993)[4]	21	–	NC	7
Rats	Reproductive Tox. (multigenerational)	Murray et al. (1979)[5]	180	18	NC	60; 6
Rats	Developmental/ Reproductive Toxicity	Mably et al. (1992a, b, c)[6]	38	–	0.34	13; 0.1
		Gray et al. (1997)[7]	30	–	0.08	10; 0.03
		Faqi et al. (1998)[8]	25	–	0.6	8; 0.2
		Ohsako et al. (2001)[9]	30	8	NC	10; 3
Rats	Developmental Immunotoxicity	Gehrs and Smialowicz (1999)[10]	60	–	NC	20
Rats	Developmental Neurotoxicity	Markowski et al. (2001)[11]	108	36[b]	0.7	36; 12; 0.2
Mice	Immunological Effects (adult)	Burleson et al. (1996)[12]	6	3	NC	2; 1
		Smialowicz et al. (1994)[13]	300	–	2.9	100; 1
		Narasimhan et al. (1994)[14]	100	50[b]	1.5	33; 17; 0.5
		Vecchi et al. (1983)[15]	1200	–	7	401; 2
Rats	Thyroid Effects	Sewall et al. (1995)[16]	76	22	26	25; 7; 8
Mice	CYP1A1/1A2 Enzyme Induction	DeVito et al. (1994)[17]	24	–	22	8; 7
		Diliberto et al. (2001)[18]	2.8	–	67	0.9; 22
		Vogel et al. (1997)[19]	5.1	0.51	0.003	1.6; 0.16; 0.001
		Narasimhan et al (1994)[14]	25	10	3	8; 3; 2; 1
Rats	CYP1A1/1A2 Enzyme Induction	van Birgelen et al. (1995)[20]	243	–	19	81; 6
		Schrenk et al. (1994)[21]	72	–	26	24; 9
		Sewall et al. (1995)[16]	8	2	3.5	3; 0.7; 1
		Walker et al. (1999)[22]	76	–	59	25; 20

Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

[a] Human equivalent intakes were estimated according to the following equation: daily intake (pg/kg/day) = (body burden (ng/kg)*Ln2*1000)/(t½*absorption) where t½ = 2593 days and absorption fraction = 0.8 (Poiger and Schlatter 1986; see Section II). Corresponding human equivalent intake values are arranged in sequence from the previous three columns.

[b] NOAEL values are based on the highest individual dose group in which there are no statistically significant changes. Statistically significant dose response trends plus apparent declines are also evident at all dose levels—20 and 60 ng/kg orally—in all fixed-ratio test groups in Markowski et al. (2001) and in the 50 ng/kg dose group in Narasimhan et al. (1994).

- - = No NOAEL value, as effects seen in the lowest dose group in the study.

NC = Not calculated due to
insufficient dose response information (less than three doses and a control) or due to presentation of the data in graphical form without tabulation of mean and variance estimates.

1. **Kociba et al. (1978)**. Increased cancer in female Sprague-Dawley rats exposed for 2 years to TCDD in the food matrix. Statistical LOAEL and NOAEL body burden estimates modeled assuming 50% absorption from the food matrix and a 25-day half-life. Compare to measured lipid levels in the Kociba et al. (1978) rats of 540 and 1700 ppt at 1 and 10 ng/kg/day dose rates and to measured body burdens in the Hurst et al. (2000) subchronic 5/7 day gavage study in female Long-Evans rats of 19 and 120 ng/kg at 1 and 10 ng/kg/day dose rates. ED_{01} calculated for female rat tumors using a multistage formula and EPA Benchmark Dose Software result in an ED_{01} (LED_{01}) of 31.9 (22) ng/kg body burden using Kociba et al. (1978) data and Goodman and Sauer (1992) pathology.

Kociba et al. 1978: Tumors

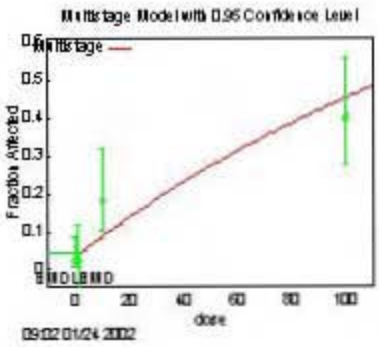
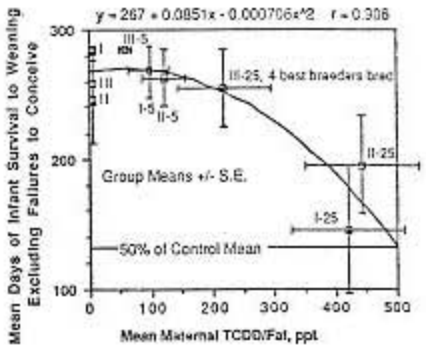


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

2. **Bowman et al. (1989)**. Offspring per cohort significantly reduced at the 25 ppt dose group in cohorts I and II (LOAEL) but not in the 5 ppt dose group (NOAEL; publication Fig. 5 attached). Estimated maternal body burdens are calculated at parturition of the 25 ppt cohort II group for the LOAEL (lowest value of 25 ppt cohorts I and II) and the 5 ppt cohort I for the NOAEL (highest value of 5 ppt cohorts I and II). Maternal TCDD fat levels are estimated according to the empirical formula and data supplied in Bowman et al. (1989; see publication figures 3 and 5): y = 14.9 + 4.29 x (r=0.924), where y=PCDD/fat ppt infant at weaning and x=TCDD/fat ppt mother at parturition. The measured TCDD fat levels in offspring ("y" value) of the 5 ppt cohorts I and II at parturition were 377±141 ppt and 323±70 ppt, respectively, resulting in estimated maternal fat levels at parturition of cohorts I and II of 84 and 72 ppt, respectively. Following the authors' recommendation, the fat level in the 25 ppt dose group is calculated following a 5:1 ratio to the 5 ppt groups, i.e., 420 and 360 ppt for cohorts I and II respectively. Measured maternal data in the 25 ppt dose group at the time of birth of cohort III (488 days post cessation of TCDD dose) were 335±119 ppt (3 non-bred females) and 219±75 ppt (all 7 monkeys) in fat. A 25% body lipid was assumed in converting to human equivalent body burden.

Bowman et al. 1989: Infant Survival



3. **Schantz et al. (1992)**. Increased rough-tumble play (publication Fig. 2 attached), fewer retreats during play bouts, and fewer displacements from preferred positions in the 5 ppt cohort I offspring. Maternal TCDD fat levels are estimated according to the empirical formula and data supplied in Bowman et al. (1989; see Figs. 3 and 5): y = 14.9 + 4.29 x (r=0.924), where y=PCDD/fat ppt infant at weaning and x=TCDD/fat ppt mother at parturition. The measured TCDD fat level in offspring ("y" value) of the 5 ppt cohort I group at parturition was 377±141 ppt, resulting in an estimated maternal fat level at parturition of 5 ppt cohort I of 84 ppt. Fat level converted to body burden by dividing by 4, approximating 25% body fat in a human equivalent comparison.

Schantz et al. 1992: Rough-tumble Play

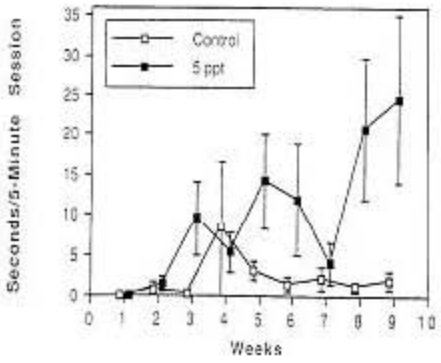
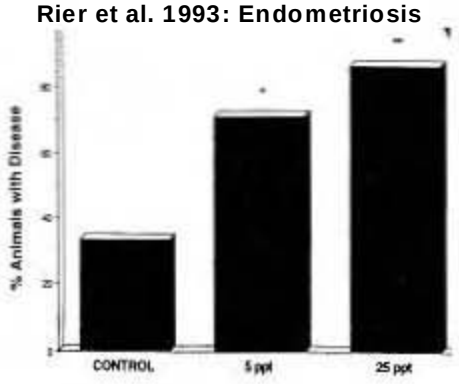


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

4. **Rier et al. (1993)**. Increased incidence, severity and dose-response for rhesus monkeys with endometriosis in the 5 and 25 ppt dose groups (rAFS classification; publication figure 2 attached, * $p<0.17$, ** $p<0.05$). LOAEL (no NOAEL) body burden adopted from the highest maternal fat level calculated according to the formula supplied by Bowman et al. (1989; see footnote 2) of 84 ppt for the 5 ppt dose group occurring at the parturition of cohort I. For comparison, the average of eight measured maternal fat levels at the birth of the 5 ppt cohort III (488 days post cessation of TCDD) was 54±11 ppt fat. A 25% body lipid was assumed in converting to human equivalent body burden.

Rier et al. 1993: Endometriosis



5. **Murray et al. (1979)**. Significant reductions in fertility (graph of publication table 1 data attached), litter size, gestation survival, and neonatal survival and growth in the 10 ng/kg/day food matrix maternal dose group in a three-generation reproduction study in Sprague-Dawley rats. Mathematically estimated body burden of 180 ng/kg at 10 ng/kg/day (half-life = 25 days, 50% absorption from food matrix). Comparison empirical measurements from a similar dose regimen in the related cancer study by Kociba et al. (1978) were 1700 ppt TCDD in lipid in the 10 ng/kg/day dose group, and the measured body burden in Hurst et al. (2000) subchronic 5/7 day gavage study in female Long-Evans rats was 120 ng/kg at the 10 ng/kg/day dose rate. The fertility index in the f_0 generation was so low that further studies with this dose group were discontinued. Thus, the study is essentially two dose levels and a control and was not modeled because of the limited dose response relationship data.

Murray et al. 1979: Rat Fertility Index

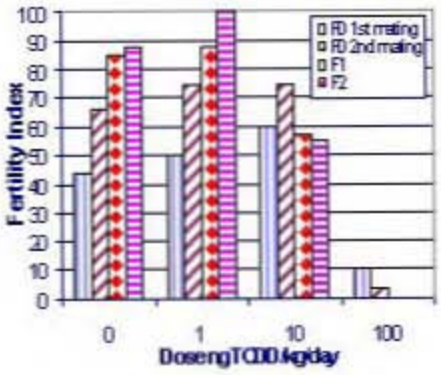
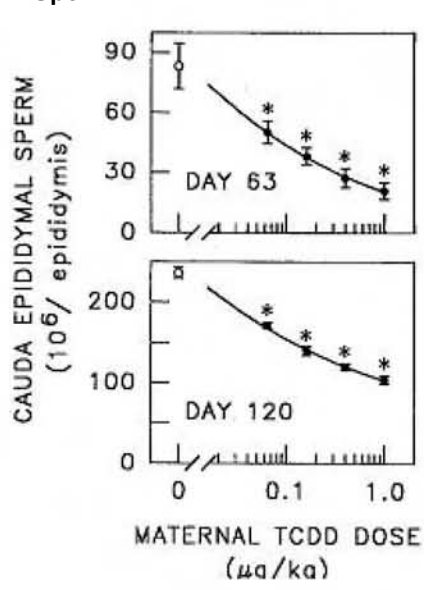


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

6. **Mably et al. (1992a,b,c)**. Decreased daily sperm production (publication Fig. 5 attached), cauda epididymal sperm, epididymis weights and altered sexual behavior in offspring at 64 ng/kg orally to Holtzman rat dams on gestation day 15. LOAEL (no NOAEL) body burden based on Hurst et al. (2000) GD16 body burden fraction of 60% following single GD15 50 ng/kg gavage dose to female Long-Evans rats. ED_{01} value modeled for caudal sperm count of 0.34 ng/kg body burden at day 63 using EPA Benchmark Dose Software Version 1.3, 60% absorption. ED_{01} modeling of Mably et al. (1992) using EPA Benchmark Dose Software Version 1.3 results in a broad range of ED_{01}s, from 0.34 ng/kg for daily sperm production on PND 63 to 461 ng/kg for pinna detachment, with a median value of 3.1 ng/kg for 15 different endpoints.

Mably et al. 1992: Epididymal Sperm



7. **Gray et al. (1997)**. Decrease in ejaculated sperm numbers in male offspring, pooled results from two studies (see publication Fig. 1; results pooled with Gray et al. 1995; attached graph of data from publication text p.15) at 50 ng/kg single dose, day 15 of gestation to female Long-Evans rats. LOAEL (no NOAEL) body burden based on Hurst et al. (2000) GD16 body burden fraction of 60% following single GD15 50 ng/kg gavage dose to female Long-Evans rats. ED_{01} modeling of Gray et al. (1997) using EPA Benchmark Dose Software Version 1.3, 60% absorption, results in a broad range of ED_{01}s from 0.08 ng/kg for epididymal sperm count on D49 to 327 ng/kg for daily sperm production on D49, with a median value of 80 ng/kg for 32 different endpoints.

Gray et al. 1997: Ejaculated Sperm

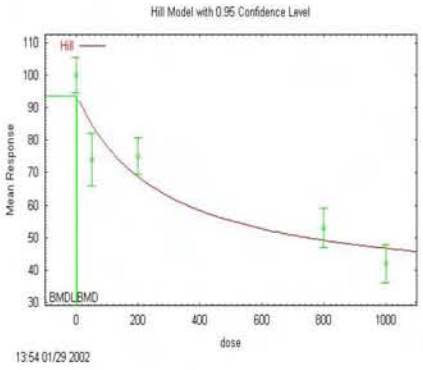
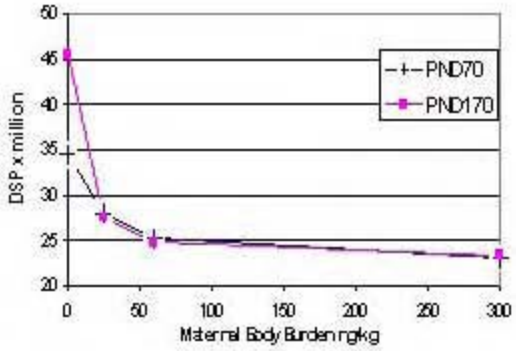


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

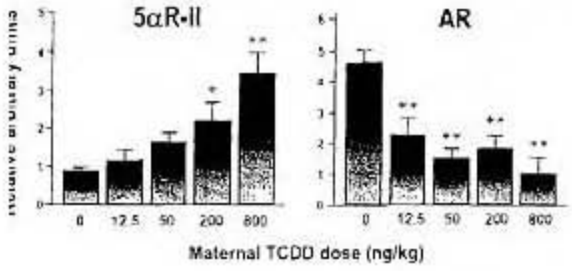
8. **Faqi et al. (1998)**. Decreased daily sperm production (graph attached of data from publication Table 3), cauda epididymus sperm, sperm transit rate, and percent abnormal sperm in offspring of 25/5 ng/kg (loading/weekly maintenance) maternal Wistar rat group. Maintenance dose of 5 ng/kg/week subcutaneous administered to maintain body burden of 25 ng/kg. Additional data on TCDD levels measured in maternal fat at gestation day 21 estimated from publication Figure 1 at 150 ng/kg in 25/5 group. Decreases in cauda epididymal sperm numbers (PND170) and daily sperm production (PND 70 and 170) were observed at all doses. In addition, increases in sperm transit rate and percent abnormal sperm were observed at all dose levels at PND 170. ED_{01} value of 0.6 ng/kg for decreases in daily sperm production, on PND70 and modeled using EPA Benchmark Dose Software Version 1.3.

Faqi et al. 1998; Daily Sperm Production



9. **Ohsako et al. (2001)**. Decreased ano-genital distance in male offspring of Holtzman rat dams receiving 50 ng/kg single dose or greater on gestation day 15 (publication Fig. 7 attached). NOAEL at 12.5 ng/kg single dose. Dose-dependent decreases in androgen receptor mRNA levels in ventral prostate in all dose groups (publication Fig. 8 attached). No changes in daily sperm production or sperm reserve. LOAEL/NOAEL body burdens based on Hurst et al. (2000) gestation day (GD) 16 body burden fraction of 60% following single GD15 50 ng/kg gavage dose to female Long-Evans rats. ED_{01} values for this study were not calculated because the significant data were not presented in tabular format.

Ohsako et al. 2001: Androgen Receptor



Ohsako et al. 2001: Ano-genital Distance

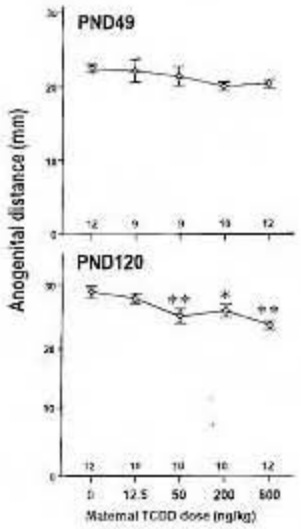
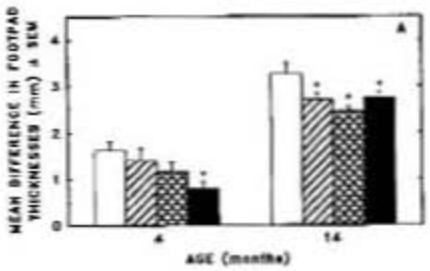


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

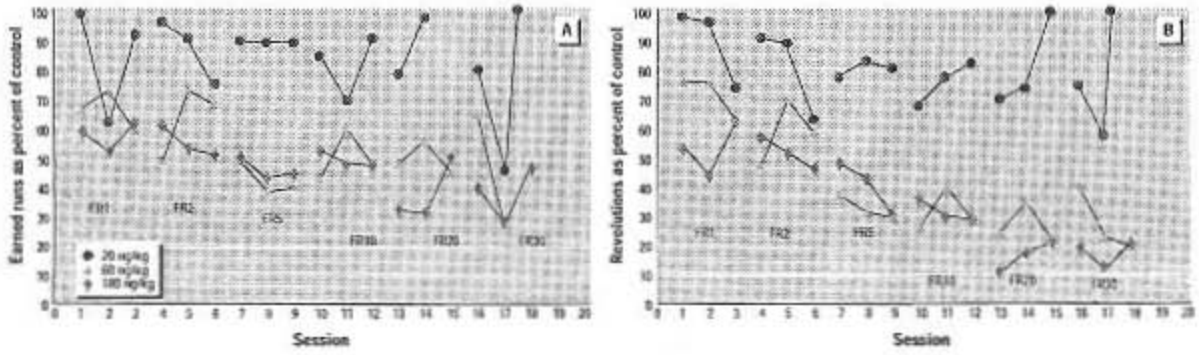
10. **Gehrs and Smialowicz (1999)**. Decreased delayed-type hypersensitivity (DTH; publication Fig. 2a attached; dose units for columns are 0, 100, 300, and 1000 ng/kg) in male offspring following single maternal oral dose of 100 ng/kg on gestation day 14 to F344 rats. LOAEL (no NOAEL) body burden based on Hurst et al. (2000) GD16 body burden fraction of 60% following single GD15 50 ng/kg gavage dose to female Long-Evans rats. Benchmark dose analysis was not performed on this study because the data were presented in graphical format.

Gehrs and Smialowicz 1999: Delayed-Type Hypersensitivity



11 **Markowski et al. (2001)**. Perinatal TCDD exposure produced a significant dose-related reduction in the number of earned opportunities to run, lever response rate, and total number of revolutions in the wheel in offspring of Holtzman rats exposed to single oral TCDD doses on GD18. Statistically significant dose group effects at 180 ng/kg dose (LOAEL). NOAEL at 60 ng/kg dose group, where apparent declines are not statistically significant (see publication Fig. 2 attached; publication Table 3). ED_{01} results modeled by the authors. Table includes result for total wheel revolutions. Body burdens based on 180 and 60 ng/kg single oral doses and Hurst et al. (2000) GD16 body burden fraction of 60% following single GD15 50 ng/kg gavage dose to female Long-Evans rats.

Markowski et al. 2001: Operant Conditioning



12. **Burleson et al. (1996)**. Increased susceptibility to influenza infection challenge in B6C3F1 mice following 10 ngTCDD/kg (LOAEL) and higher single oral gavage dose to 8-week-old mice (publication Fig. 1 attached). No significant effects seen at 1 and 5 ng/kg doses (NOAEL). Assume 60% absorption. Benchmark dose analysis was not performed on study because the data were not presented in tabular format.

Burleson et al. 1996: Influenza Susceptibility

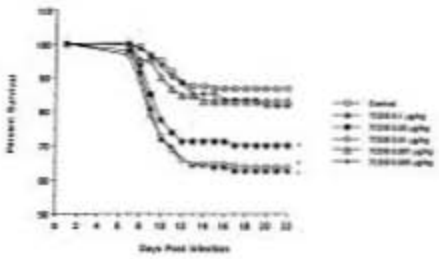
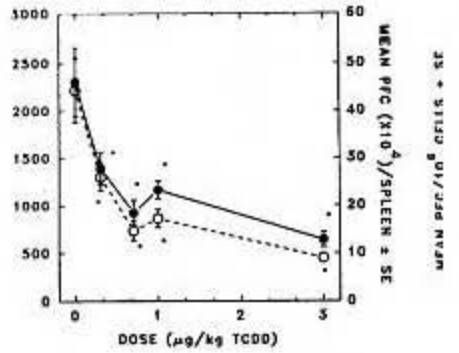


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

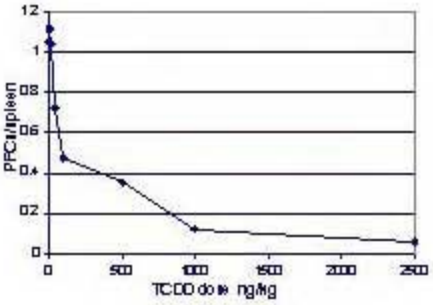
13. **Smialowicz et al. (1994)**. Dose-related suppression of antibody plaque forming cell (PFC; publication Fig. 1 attached) response in adult female B6C3F1 mice at 300 ng/kg single intraperitoneal injection and higher. PFC increases reported in high-dose-group male F344 and female Long-Evans rat species tested, accompanied by alterations to splenic $CD4^{-}CD8^{+}$ lymphocytes. ED_{01} values for mice calculated for plaque forming cells per million cells of 2.9 ng/kg body burden using EPA Benchmark Dose Software Version 1.3.

Smialowicz et al. 1994: PFC Immune Response



14. **Narasimhan et al. (1994)**. Decreased splenic antibody plaque-forming cell (PFC; graph of publication Table 5 data attached) response following single intraperitoneal dose administered to female B6C3F1 mice (7–9 weeks old). LOAEL for decreased SRBC and splenic PFC responses at 100 ng/kg, nonstatistically significant decrease evident at 50 ng/kg, NOAEL at 25 ng/kg. CYP1A1 LOAEL (NOAEL) at 25 (10) ng/kg dose (graph of publication table 1 data attached). ED_{01} values calculated for spleen PFC/million cells of 1.5 ng/kg body burden and for CYP1A1 mRNA induction of 3 ng/kg using EPA Benchmark Dose Software Version 1.3.

Narasimhan et al. 1994: PFC Immune Response



CYP1A1 mRNA Induction

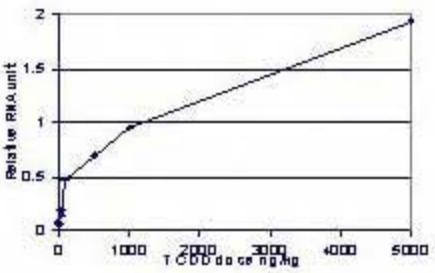
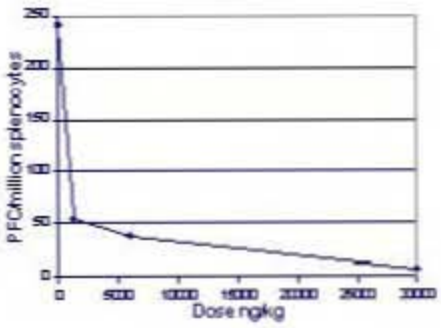


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

15. **Vecchi et al. (1983)**. Decreased plaque-forming cells (PFC) per million and PFC/spleen (graph of publication table 2 data attached) at all doses tested in aryl hydrocarbon hydroxylase sensitive mouse strains (B6, C3) following single intraperitoneal doses. Less sensitivity in other strains (e.g. DBA/2 and AKR). LOAEL (no NOAEL) of 1200 ng/kg. ED_{01} calculated for PFC/million splenocytes of 7 ng/kg for B6 mice using EPA Benchmark Dose Software Version 1.3.

Vecchi et al. 1983: PFC Immune Response



16. **Sewall et al. (1995)**. Statistically significant decreased ratio of thyroid parenchymal area to thyroid follicle area (publication Fig. 6 attached) was reported in female Sprague-Dawley rats following oral gavage biweekly dosing for 30 weeks at daily equivalent doses of 0.1–125 ng/kg/day. LOAEL (NOAEL) of 3.5 (1) ng/kg/day for thyroid parenchyma/follicle ratio, calculating to approximate body burdens of 76 and 22 ng/kg for the LOAEL and NOAEL, respectively. These calculations assume a half-life of 25 days and 60% body burden fraction following gavage dose, based on Hurst et al. (2000). Significant increases were also reported for thyroid stimulating hormone, with a LOAEL of 3.5 ng/kg/d and a NOAEL of 1 ng/kg/d. Serum thyroxine was significantly decreased at 10.5 ng/kg/day and at higher doses. ED_{01} values were not calculated for thyroid parenchymal/follicle ratio. ED_{01} for decreases in serum thyroxin of 43 ng/kg body burden using EPA Benchmark Dose Software Version 1.3. The ED_{01} for increased serum thyroid stimulating hormone is 26 ng/kg. LOAEL(NOAEL) for CYP1A1 mRNA induction of 0.35 (0.1) ng/kg/day, approximating to 8 (2) ng/kg body burden (assuming 60% absorption, 25 day halflife). ED_{01} for increases in CYP1A1 mRNA was 3.5 ng/kg using EPA Benchmark Dose Software Version 1.3.

Sewall et al. 1995: Thyroid Histology

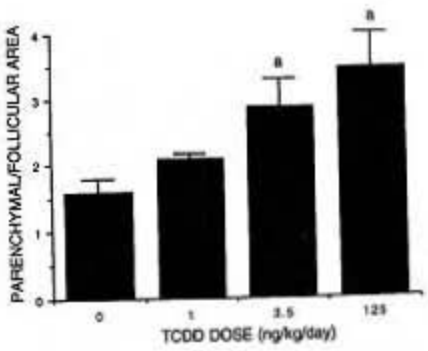
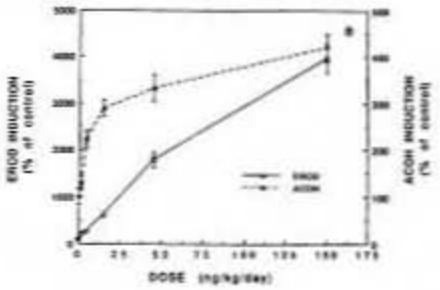


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

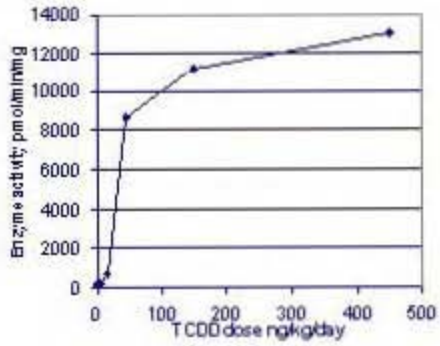
17. **DeVito et al. (1994)**. LOAEL (no NOAEL) of 1.5 ng/kg/day for induction of CYP1A1 and CYP1A2 (publication Fig. 2 attached) and increased phosphorylation of phosphotyrosyl proteins in female B6C3F1 mice gavage fed 1.5–150 ng/kg/day, 5 days per week, for 13 weeks. Approximate body burden after 13 weeks at 1.5 ng/kg/day of 24 ng/kg, based on Diliberto et al. (2001). ED_{01} value calculated at 22 ng/kg for CYP1A1 induction in the liver using EPA Benchmark Dose Software Version 1.3.

DeVito et al. 1994: Enzyme Induction



18. **Diliberto et al. (2001)**. Dose response relationship for CYP1A1 induction in female B6C3F1 mice (60 days old) at all oral gavage doses from 0.15 ng/kg/day (5/7 days, 13 weeks) and higher, corresponding to a radiolabel measured body burden of 2.75 ng/kg. Hepatic CYP1A1 activity (publication Table 5, graph of liver EROD data attached) modeled using EPA BMDS Software Version 1.3 results in an ED_{01} of 9.7 ng/kg/day. Body burden interpolated using linear regression of data from Diliberto et al. (2001; Table 4) with formula: body burden = 6.8782 * daily dose (M-F) (R^2 = 0.9994; Microsoft Excel), resulting in estimated ED_{01} body burden of 67 ng/kg.

Diliberto et al. 2001: EROD Induction



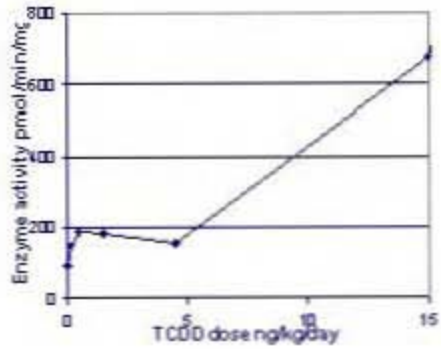
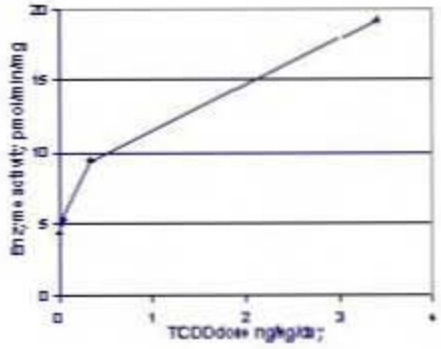


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

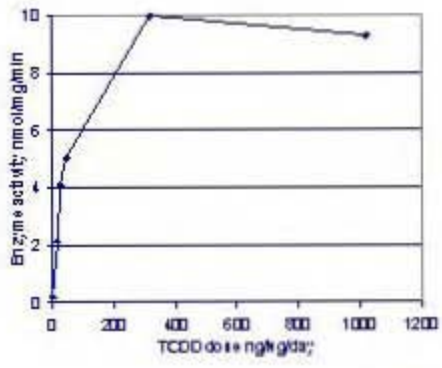
19. **Vogel et al. (1997)**. LOAEL(NOAEL) for CYP1A1 EROD induction (graph of publication Table 3 data attached) at 0.34 (0.034) ng/kg/day to C57 female mice administered 1, 10, 100 ng/kg loading doses followed by weekly injections of 0.2, 2, and 20 ng/kg for 135 days, calculating to 4.9 (0.49) ng/kg body burden (assuming 100% absorption, 10 day halflife). ED_{01} value calculated for CYP1A1 EROD induction of 0.003 ng/kg body burden using EPA Benchmark Dose Software Version 1.3.

Vogel et al. 1997: EROD Induction



20. **van Birgelen et al. (1995)**. Significant increases in CYP1A1 (graph of liver EROD data from publication table 3 attached) and CYP1A2, plus decreased relative thymus weights and loss of hepatic retinoids, at all doses tested in 8 week old female Sprague-Dawley rats exposed to dietary matrix intakes of 0, 0.2, 0.4, 0.7, 5, 20 µgTCDD/kg diet, corresponding to 0, 13.5, 26.4, 46.9, 320 and 1024 ng/kg/day oral intake. LOAEL (no NOAEL) calculated from 13.5 ng/kg/day dose to be 243 ng/kg body burden (50% absorption from dietary matrix, 25 day halflife). Calculated no effect levels (CNEL) by the authors of 0.7 to 4 ng TCDD/kg/day (Hill and Weibull models, based on the measured control value plus twice the standard deviation: mathematical calculated corresponding body burdens are 13 and 72 ng/kg at 50% absorption, halflife 25 days). Measured levels by authors in liver and fat of 1400 and 620 ppt, respectively. ED_{01} value calculated for CYP1A1 of 19 ng/kg body burden using EPA Benchmark Dose Software Version 1.3.

van Birgelen et al. 1995: EROD Induction



21. **Schrenk et al. (1994)**. CYP1A1 induction in female Wistar rats exposed via biweekly subcutaneous injection to average daily doses of 2, 20, and 200 ng/kg/day for 13 weeks. LOAEL (no NOAEL) for CYP1A1 EROD induction of 2 ng/kg/day (graph of publication table 1 data attached), approximating to 72 ng/kg body burden (25 day halflife, 100% absorption). ED_{01} for CYP1A1 induction of 26 ng/kg body burden using EPA Benchmark Dose Software Version 1.3.

Schrenk et al. 1994: EROD Induction

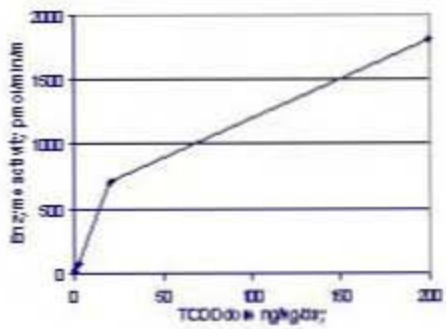
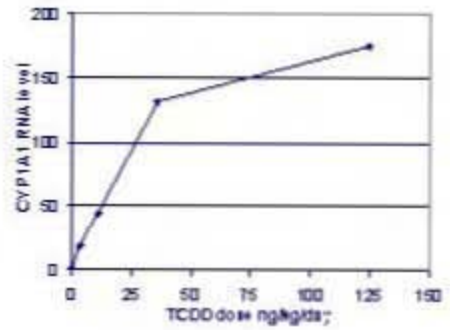


Table A-1. Body burdens for critical endpoints in animals with human equivalent daily intake (continued)

22. **Walker et al. (1999)**. Dose-dependent expression of CYP1A1 (graph of publication table 3 data attached) and CYP1A2 RNA (CYP1B1 less sensitive) in female Sprague-Dawley rats gavage fed biweekly for 30 weeks to average daily doses of 3.5 - 125 ng/kg/day. LOAEL value of 3.5 ng/kg/day (no NOAEL), calculates to 76 ng/kg body burden (assuming halflife of 25 days, 60% absorption following gavage). Measured liver level of 447 ng/kg. ED_{01} values calculated for CYP1A1 mRNA and CYP1A2 mRNA at 59 and 270 ng/kg body burdens, respectively, using EPA Benchmark Dose Software Version 1.3. High maximal induction potential of enzymes contributes to high 1% effective dose (ED_{01}).

Walker et al. 1999: CYP1A1 mRNA



GLOSSARY

Adverse effect: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism or reduces an organism's ability to respond to an additional environmental challenge.

Area Under the Curve (AUC): Area under the concentration versus time curve. The AUC is a summary measure that integrates serial assessments of a dose over the duration of the study.

Aryl hydrocarbon receptor (AhR): An intracellular protein that is a ligand-dependent transcription factor that functions in partnership with a second protein, the aryl hydrocarbon receptor nuclear translocator (Arnt).

Aryl hydrocarbon receptor nuclear translocator (Arnt): An intracellular protein that functions as a transcription factor in the cell in partnership with a second protein, the aryl hydrocarbon receptor (the AhR).

Background exposure: The exposure that regularly occurs to members of the general population from exposure media (food, air, soil, etc.) that have dioxin concentrations within the normal background range. Most (> 95%) of background exposure results from the presence of minute amounts of dioxin-like compounds in dietary fat, primarily from the commercial food supply. The origin of this background exposure is from three categories of sources: naturally formed dioxins, anthropogenic dioxins from contemporary sources, and dioxins from reservoir sources. The term "background exposure" as used in this document should not be interpreted as indicating the significance or acceptability of risk associated with such exposures.

Benchmark dose (BMD): A statistical lower confidence limit on the dose that produces a predetermined change in response rate of an adverse effect, typically 1–10%, compared to background.

Body burden: Body burden is defined as the concentration of TCDD and related chemicals in the body and is typically expressed as ng/kg body weight. In animals, these values are calculated from studies at or approaching steady-state and are associated with either biochemical or toxicological responses. In addition, these values are calculated on the basis of knowledge of the species-specific half-life and the exposure, or they are estimated on the basis of the TCDD tissue concentration, the size of the tissues, and the weight of the animal. In humans the values are typically presented as steady-state body burdens and are estimated on the basis of an intake rate and the half-life of TCDD in humans. Alternatively, body burdens in humans are estimated on the basis of lipid adjusted serum or adipose tissue TCDD or TEQ concentrations.

Cancer: A family of diseases affecting cell growth and differentiation, characterized by an abnormal, uncontrolled growth of cells.

Carcinogen: An agent capable of inducing cancer.

Carcinogenesis: The origin or production of a benign or malignant tumor. The carcinogenic event modifies the genome and/or other molecular control mechanisms of the target cells, giving rise to a population of altered cells.

Chronic effect: An effect that occurs as a result of repeated exposures over a long period of time in relation to the lifetime of the organism.

Chronic exposure: Multiple exposures occurring over an extended period of time or a significant fraction of the animal's or the individual's lifetime.

Chronic study: A toxicity study designed to measure the (toxic) effects of chronic exposure to a chemical.

Chronic toxicity: The capacity of a substance to cause adverse human health effects as a result of chronic exposure.

Cohort: A group of animals of the same species, including humans, that is identified by a common characteristic and that is studied over a period of time as part of a scientific or medical investigation.

Confidence interval (CI): A range of values for a variable of interest, for example, a rate, constructed so that this range has a specified probability of including the true value of the variable.

Confounder: A condition or variable that is both a risk factor for disease and is associated with an exposure of interest. This association between the exposure of interest and the confounder (a true risk factor for disease) may make it falsely appear that the exposure of interest is associated with disease.

Congeners: Compounds that have similar chemical structures or belong to closely related chemical families

Coplanar: Descriptive term referring to the fact that multi-ringed chemical structures can assume a flat configuration, with rings in the same spatial plane.

Dioxin-like: An adjective that describes compounds that have similar chemical structure and physical-chemical properties and invoke a common battery of toxic responses as does 2,3,7,8-TCDD. Because of their hydrophobic nature and resistance towards metabolism, these chemicals persist and bioaccumulate in fatty tissues of animals and humans. Certain members of the dioxin, furan, and PCB family are termed “dioxin-like” in this reassessment.

Effective dose (ED): The dose that corresponds to an increase, expressed as a percent response, in relation to expected levels of an adverse effect that can be defined as a percent increase over background rates or a percent increase between background and maximal rates.

Effective dose$_{01}$ (ED$_{01}$): The dose corresponding to a 1% increase in an adverse effect. Effective dose evaluation at the 10% response level (ED$_{10}$ or lower bound on ED$_{10}$ [LED$_{10}$]) is somewhat the norm, given the power of most chronic toxicology studies to detect an effect. In cases where the data allow evaluation at a lower effective dose level, the Agency suggests using the lower value. Such is the case for 2,3,7,8-TCDD.

Epidermal growth factor (EGF): A mitogenic polypeptide active on a variety of cell types, especially, but not exclusively, epithelial.

Follicle stimulating hormone (FSH): FSH is an acidic glycoprotein secreted by the anterior pituitary gland. In women, follicle stimulating hormone stimulates the development of ovarian follicles (eggs) and stimulates the release of estrogens. In men, follicle stimulating hormone stimulates the production of sperm.

Half-life: A measure of the time required to reduce to one-half the original concentration of a specified chemical in the body.

Hormone: Control chemicals produced by tissues or organs specialized for that function and that exert their highly specific effects on other tissues of the body.

Latency Period: The time between first exposure to an agent and manifestation or detection of a health effect of interest.

Ligand: Any molecule that binds to another. In normal usage, a soluble molecule such as a hormone or neurotransmitter that binds to a receptor, usually with high affinity.

Lower limit on effective dose$_{01}$ (LED$_{01}$): The 95% lower confidence limit of the dose of a chemical needed to produce a 1% increase of an adverse effect in those exposed to the chemical or to 1% of the maximal response relative to control.

Lowest-observed adverse effect level (LOAEL): The lowest exposure level at which there are statistically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group.

Luteinizing hormone (LH): A hormone that acts with the follicle stimulating hormone (FSH) to stimulate sex hormone release.

Margin of exposure (MOE): The LED$_{10}$, LED$_{01}$, or other point of departure divided by the actual or projected environmental exposure/dose of interest, expressed as a ratio.

Minimal risk level (MRL): An estimate of daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

No-observed-adverse effect level (NOAEL): The highest exposure level at which there are no statistically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or to be precursors to adverse effects.

No-observed-effect level (NOEL): An exposure level at which there are no statistically significant increases in the frequency or severity of any effect between the exposed population and its appropriate control.

Pharmacokinetics: The quantitative description of the process of chemical disposition: absorption, distribution, metabolism, and excretion (metabolism and excretion equal elimination).

Physiologically based pharmacokinetic (PBPK) model: Physiologically based model used to characterize pharmacokinetic behavior of a chemical. Available data on blood flow rates and metabolic and other processes that the chemical undergoes within each compartment are used to construct a mass-balance framework for the PBPK model.

Point of departure (POD): The dose-response point that marks the lower end of the range of observation and the beginning of a low-dose extrapolation. This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model or the lower bound on the dose associated with such an incidence.

Promoter: An agent that is not carcinogenic itself but that when administered after an initiator of carcinogenesis stimulates the clonal expansion of the initiated cell to produce a neoplasm.

Receptor: A molecular structure within a cell or on the cell's surface that is characterized by selective binding of a specific substance and a specific physiologic effect that accompanies the binding (for example, see aryl hydrocarbon receptor).

Receptor site: The portion of the receptor molecule or structure with which the compound (ligand) interacts.

Reference dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, a LOAEL, or a benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments.

Relative potency (REP): The ratio of the potency of the congener to the standard toxicant in that specific study; a concept similar to toxic equivalency but based on a single study, species, or matrix, etc., and not averaged to obtain a general toxic equivalency value.

Relative risk (RR): The relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. The relative risk is defined as the rate of disease among the exposed divided by the rate of the disease among the unexposed. A relative risk of 2 means that the exposed group has twice the disease risk as the unexposed group.

Reservoir sources: Reservoirs are materials or places that contain previously formed CDD/CDFs or dioxin-like PCBs and have the potential for redistribution and circulation of these compounds into the environment. Potential reservoirs include soils, sediments, biota, water, and some anthropogenic materials. Reservoirs become sources when they have releases to the circulating environment.

Risk (in the context of human health): The probability of injury, disease, or death from exposure to a chemical agent or a mixture of chemicals. In quantitative terms, risk is expressed in values ranging from zero (representing the certainty that harm will not occur) to one (representing the certainty that harm will occur).

Slope factor: An upper bound, generally approximating or exceeding a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. This estimate, usually expressed in units of proportion (of a population) affected per mg/kg/day, is generally reserved for use in the low-dose region of the dose-response relationship, that is, for exposures corresponding to risks less than 1 in 100.

Standardized mortality ratio (SMR): This is the relative measure of the difference in risk between the exposed and unexposed populations in a cohort study. The SMR is similar to the relative risk in both definition and interpretation. This measure is usually standardized to control for any differences in age, sex, and/or race between the exposed and the reference populations. It is frequently converted to a percent by multiplying the ratio by 100.

Statistical significance: The probability that a result may be due to chance alone. By convention, a difference between two groups is usually considered statistically significant if chance could explain it only 5% of the time or less. Study design considerations may influence the a priori choice of a different statistical significance level.

Thyroid stimulating hormone (TSH): A hormone secreted by the anterior pituitary gland that activates certain actions in thyroid cells leading to production and release of the thyroid hormones (T3 and T4). T3 and T4 blood levels feed back on the hypothalmus/pituitary gland and decrease TSH production when T3 and T4 levels are high.

Tolerable daily intake (TDI): A TDI is an estimate of the amount of a contaminant in food or drinking water that can be ingested daily over a lifetime without a significant health risk. The term is used frequently in World Health Organization (WHO) health assessments. The

term "tolerable" is used, as contaminants do not serve an intended function and as intake is unavoidably associated with the basic consumption of food and water. Tolerable does not generally connote "acceptable" or "risk free."

Toxic equivalence (TEQ): The toxic equivalency factor (TEF) of each dioxin-like compound present in a mixture multiplied by the respective mass concentration. The products are summed to represent the 2,3,7,8-TCDD toxic equivalence of the mixture.

Toxic equivalency factor (TEF): TEFs compare the potential toxicity of each dioxin-like compound present in a mixture to the well-studied and well-understood toxicity of 2,3,7,8-TCDD, the most toxic member of the group, with the TEF of 2,3,7,8-TCDD being 1. TEFs are the result of expert scientific judgment using all of the available data and taking into account uncertainties in the available data.

Transcription: The process of constructing a messenger RNA molecule using a DNA molecule as a template, with resulting transfer of genetic information to the messenger RNA.

Transcription factor: A substance, usually a protein, that is developed within the organism and that is effective in the initiation, stimulation, or termination of the genetic transcription process.

Upper bound: A plausible upper limit to the true value of a quantity or response. This is usually not a true statistical confidence limit.

Weight-of-evidence: An approach used for characterizing the extent to which the available data, including human, animal, and mechanism of action, support the hypothesis that an agent causes an adverse effect, such as cancer, in humans. The approach considers all scientific information, both positive and negative, in determining whether and under what conditions an agent may cause disease in humans.

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