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GUIDANCE FOR ASSESSING CHEMICAL CONTAMINANT DATA FOR USE IN FISH ADVISORIES

VOLUME II: RISK ASSESSMENT AND FISH CONSUMPTION LIMITS

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EXECUTIVE SUMMARY

State, local, and federal agencies currently use various methods to estimate risks to human health from the consumption of chemically-contaminated, non-commercial fish. A 1988 survey, funded by the U.S. Environmental Protection Agency (EPA) and conducted by the American Fisheries Society, identified the need for standardizing the approaches to evaluating risks and developing fish consumption advisories that are comparable across different jurisdictions (RTI, 1990). Four key components were identified as critical to the development of a consistent risk-based approach: standardized practices for sampling and analyzing fish, standardized risk assessment methods, standard procedures for making risk management decisions, and standardized approaches to risk communication (RTI, 1990).

To address concerns raised by the survey respondents, EPA is developing a series of four documents designed to provide guidance to state, local, regional, and tribal environmental health officials responsible for issuing fish advisories. The documents are meant to provide guidance only and do not constitute a regulatory requirement. The documents are:

Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories
- *Volume 1: Fish Sampling and Analysis*
- *Volume 2: Risk Assessment and Fish Consumption Limits*
- *Volume 3: Risk Management*
- *Volume 4: Risk Communication*

Volume 1 was released in September, 1993. Volumes 3 and 4 are scheduled for release in early-1995 and late-1994, respectively. It is essential that all four documents be used together, since no single volume addresses all of the topics involved in the development of risk-based fish consumption advisories.

The objective of *Volume 2: Risk Assessment and Fish Consumption Limits* is to provide guidance on the development of risk-based meal consumption limits for 23 high-priority chemical fish contaminants (target analytes). The target analytes addressed in this guidance series (See Table 1-1) were selected as particularly significant fish contaminants by EPA's Office of Water, based on their occurrence in fish, their potential for bioaccumulation, and their toxicity to humans. The criteria for their selection are discussed in Volume 1 of this series. In addition to a presentation of consumption limits, Volume 2 contains a discussion of risk assessment methods used to derive the consumption limits,

as well as a discussion of methods to modify these limits to reflect local conditions. Additional sources of information are listed for those seeking a more detailed discussion of risk assessment methods.

Earlier drafts of Volume 2 have been reviewed by experts at the federal, state, tribal, and local levels. Their input was used to revise the document to make it more useful and informative to public health professionals. For example, Volume 2 contains many refinements of the previous guidance *Assessing Human Health Risks from Chemically Contaminated Fish and Shellfish: A Guidance Manual* (U.S. EPA, 1989a), including the addition of consumption limit tables and detailed toxicity data on the target analytes.

Part I of this document contains the information needed to use and modify the consumption limit tables provided for the 23 target analytes. The tables list a number of alternative consumption limits for each target analyte, based upon different meal sizes, contaminant levels, risk levels, and toxicity endpoints. Specific consumption limits have been developed, and are presented separately, for young children and adults in the general population. In addition, consumption limits specifically targeted to women of reproductive age have been developed for methylmercury. Information is also provided on methods for calculating consumption limits for multiple species diets and for multiple contaminant exposures.

Part II contains an overview of the current EPA risk assessment methodology used to derive the recommended meal consumption limits. This includes a discussion of the four main steps of the risk assessment: hazard identification, dose-response evaluation, exposure assessment, and risk characterization. Detail has been added on the toxicity of the target analytes, including new information on developmental toxicity. EPA risk values (chronic Reference Doses and cancer potency factors) from sources such as EPA's Integrated Risk Information System (IRIS) and the Office of Pesticide Programs are provided, with a discussion of supporting dose-response data.

The information in this document may be used in conjunction with contamination data from local sampling programs and fish consumption surveys (or from consumption data provided in Volume 3), to select or calculate risk-based consumption limits for contaminated non-commercial fish. The consumption limits may be used with other types of information (e.g., cultural and dietary characteristics of the populations of concern, social and economic impacts, and health issues, including benefits of fish consumption and accessibility of other food sources) to establish health advisories. The decision-making process for the development of advisories will be discussed in the risk management document in this series (Volume 3).

In keeping with current EPA recommendations, discussions of uncertainty and assumptions are included in each section of the document. Although information was sought from a variety of sources to provide the best available data regarding the development of fish advisories, limited data exist for some critical parameters (e.g., toxicological properties of certain chemicals, and susceptibilities of specific population subgroups such as the elderly, children, and pregnant or nursing women). Although substantial toxicological information is available for all target analytes discussed in this document, readers are cautioned to always consider the methods and values presented in the context of the uncertainty inherent in the application of science to policies for safeguarding the general public from environmental hazards.

EPA welcomes your suggestions and comments. A major goal of this series is to provide a clear and usable summary of critical information necessary to make informed decisions regarding the development of fish consumption advisories. These documents are being prepared in binder form so that individual sections may be revised and replaced as significant new information becomes available. We encourage comments, and hope this document will be a useful adjunct to the resources used by states, local governments, and tribal bodies to make decisions regarding the development of fish advisories.

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GLOSSARY & ABBREVIATIONS

acute exposure	exposure at a relatively high level over a short period of time (minutes to a few days) (This is defined in IRIS as 24 hours or less; however, sources consulted utilized exposure periods of up to a few days. Consequently, the more encompassing definition is appropriate in reading this document.)
ARL	acceptable risk level. The maximum level of individual lifetime carcinogenic risk, usually calculated using a cancer potency value, which is considered "acceptable" by risk managers. See Section 4 for more detail.
ATSDR	Agency for Toxic Substances and Disease Registry, U.S. Dept. of Health and Human Services, Public Health Service
BW	body weight of an individual consumer (kg)
C_m	concentration of contaminant *m* in the edible portion of fish (mg/kg)
$C_{m,j}$	concentration of contaminant *m* in the edible portion of fish species *j* (mg/kg)
C_{tm}	Total concentration of chemical *m* in an individual's fish diet,
carcinogen	an agent capable of inducing a carcinogenic response

cancer potency	(often used interchangeably with slope factor) the slope of the dose-response curve in the low-dose region used with exposure to calculate the estimated lifetime cancer risk. Often expressed as risk per one milligram of exposure to the toxic chemical per kilogram body weight per day (mg/kg-d).
chronic exposure	multiple exposures occurring over an extended period of time, or a significant fraction of the lifetime
CNS	central nervous system
confounder	condition or variable that may be a factor in producing the same response as the agent under study.
CR	mean daily consumption rate of fish (kg/day)
CR_j	consumption rate of fish species *j* (kg/day)
CR_{lim}	limit on the amount of fish that can be consumed per day (kg/day)
CR_{mm}	limit on the number of fish meals that can be consumed per month (meals/mo)
CR_{md}	limit on the number of fish meals that can be consumed per day (meals/day)
critical effect	the first adverse effect, or its known precursor, that occurs as the dose rate increases
d	day, as in mg/kg/d
developmental toxicity	study of adverse effects on the developing organism resulting from exposure prior to conception, during prenatal development, or postnatally up to the time of sexual maturation.

dose-response relationship	relationship between the amount of an agent and changes in aspects of the biological system apparently in response to that agent
E_m	exposure to contaminant *m* from ingesting fish (mg/kg-day)
E_{mc}	exposure to a given contaminant in a given species of fish associated with a given risk of cancer (mg/kg-day)
$E_{m,j}$	exposure to contaminant *m* from ingesting fish species *j* (mg/kg-day)
E_{mn}	maximum acceptable exposure (dose) of a noncarcinogen from a specific contaminant in a specific fish species (mg/kg-day)
endpoint	response measure in a toxicity study
EPA	United States Environmental Protection Agency
exposure limits	a daily limit on exposure based upon health and toxicity data, which the reader may calculate, using the study data provided in this or other sources (mg/kg-day)
FDA	United States Food and Drug Administration
FRAC	fraction of a given fish species in an individual's diet (unitless)
HI	hazard index, or ratio of the estimated exposure dose to the RfD for the chemical (unitless)
HI_{mix}	hazard index of a chemical mixture (unitless)
HSDB	Hazardous Substances Data Bank, developed by EPA, available on line through TOXNET

incidence	number of new cases of a disease within a specified time
consumption limits	a daily fish consumption limit, based upon health and toxicity data. They are provided in Chapter 3 of this document. They may also be calculated by the reader using guidance in Chapters 2,4, and 5.
IRIS	Integrated Risk Information System, a data base maintained by EPA, available on line through TOXNET and by subscription through NTIS
latency period	time between induction of a health effect and its manifestation
LEL	same as LOAEL (per IRIS), see below
LOAEL	lowest exposure level at which there are statistically or biologically significant increases in frequency of severity of adverse effects between the exposed population and its appropriate control group.
kg	kilogram, one thousand grams, equivalent to 2.205 pounds (avoirdupois)
mg	milligrams, one one thousandth (10^{-3}) of a gram
mg/kg-day	milligrams exposure per kilogram body weight of the exposed individual per day
modifying factor	a factor used in operationally deriving the RfD from experimental data. It addresses concerns regarding differences in absorption, tolerance to a chemical, or lack of a sensitive endpoint. See Table 5-2

MRL	Minimal Risk Level, from ATSDR. An estimate of daily exposure that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure: acute - 1 to 13 days; intermediate - 14 to 365 days; chronic - over 365 days
MS	meal size (kg/meal)
mutagenic	capable of inducing changes in genetic material (e.g. DNA)
NOAEL	exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its control
NOEL	the same as NOAEL with the exception of the word adverse. NOEL specifies the absence of any effect
NTIS	National Technical Information Service
NTP	National Toxicology Program
OPP	Office of Pesticide Programs at U.S. EPA
oz	ounces
P_j	proportion of a given species in the diet (unitless)
PNS	peripheral nervous system
q_1^*	cancer slope factor, lifetime cancer risk per mg/kg-day
R	incremental risk above background associated with contaminant at given dose ($lifetime^{-1}$)
R_{avg}	mean individual risk in the exposed population (risk/person-lifetime)

Reference Dose (RfD)	estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Units are mg/kg-day.
RfD_m	reference dose of a chemical mixture (mg/kg-day)
risk	the probability of injury, disease, or death under specific circumstances.
RL	maximum acceptable risk level (unitless)
R_{mix}	individual cancer risk from the chemical mixture
SF	cancer slope factor, usually the upper 95 percent confidence limit on the linear term (q_1) in the multi-stage model
SF_m	slope Factor of a chemical mixture
SIZ	size of the exposed population (number of persons)
slope factor	see SF above
SV_c	the screening level concentration for a single contaminant in a given fish species (mg/kg)
SV_n	screening values of a given noncarcinogenic contaminant in a given species of fish (mg/kg)
teratogenic	capable of causing physical defects in the developing embryo or fetus
threshold	dose or exposure below which a significant adverse effect is not expected

uncertainty factors	one of several, generally 10-fold factors, used in operationally deriving the RfD from experimental data. They are intended to account for (1) the variation in sensitivity among the members of the human population (intraspecies variability); (2) the uncertainty in extrapolating animal data to humans; (3) the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure to chronic exposure toxicity; (4) the uncertainty in using LOAEL data rather than NOAEL data; and (5) uncertainty generated by data gaps. See also Table 5-2 in Chapter 5.
weight of evidence	for carcinogens this is a classifications assigned to a chemical by EPA, based on the types of data available regarding carcinogenicity. On a scale of A to E, the classifications reflect the extent to which the available biomedical data support the hypothesis that a substance causes cancer in humans. See EPA (1986a) for additional information.

PART I.

This document is divided into two parts so that readers wishing to use it as a reference source may refer directly to sections containing relevant material without having to refer to background material in other sections. Part I of this document is designed to provide readers with an overview of the critical information used in the calculation of risk-based consumption limits, options for modifying the limits to meet specific local needs, and actual consumption limit tables for the 23 target analytes. Part II of this document contains more detailed information on specific aspects of the risk assessment methodology used to calculate the fish consumption limits and a brief discussion of the toxicity of each of the target analytes.

SECTION 1

INTRODUCTION

1.1 Overview and Objectives

Toxic chemicals from point sources such as industrial or municipal outflow pipes, and non-point sources such as agricultural runoff and atmospheric deposition have contaminated surface waters and their sediments across the United States. In some areas contamination arises from one or a few related chemicals. For example, in the Hudson River in New York, attention has focused on high levels of a group of related chemicals called polychlorinated biphenyls, or PCBs. In other areas a complex mixture of chemicals is present. For example, over 900 different synthetic organic compounds have been found in Puget Sound in Washington State, while nearly 1,000 chemical contaminants have reportedly been found in the Great Lakes.

Many pollutants concentrate in fish tissues by accumulating in fatty tissues or selectively binding to fish muscle tissue (the fillet). Even extremely low concentrations of bioaccumulative pollutants in water or bottom sediments may result in fish tissue concentrations high enough to pose health risks to fish consumers. Lipophilic contaminants, particularly certain organic compounds, tend to accumulate in the fatty tissues of fish. Consequently, fish species with a higher fat content, such as carp, bluefish, some species of salmon, and catfish, may pose greater risks from some contaminants than leaner fish such as bass, sunfish, and yellow perch. Although exposure to some contaminants may be reduced by removing the fat, skin, and viscera before eating, other contaminants, such as methylmercury, accumulate in the fillet, and therefore cannot be removed by trimming. In addition, some fish are consumed whole, or used whole in the preparation of fish stock for soups and other foods. Under these conditions the entire burden of bioaccumulative contaminants contained in the fish would be ingested (U.S. EPA, 1991b).

In addition to the risks borne by the general population due to consumption of contaminated fish, populations eating higher-than-average quantities of fish are at greater risk of having higher body burdens of contaminants. Those at greatest risk include sport and subsistence fishers.[1] Within these populations,

[1] Subsistence fishers are considered in this document to be people who rely on non-commercial fish as a major source of protein.

pregnant women and children may be at greater risk of incurring adverse effects than other members of the populations, due to their proportionally higher consumption rates and/or increased susceptibility to adverse effects.

Fish contaminants vary widely in chemical structure and toxic properties. Potential adverse health effects include cancer, chronic systemic effects, and developmental and reproductive effects. The severity of effects varies with the exposure level and characteristics of the individual, and may range from relatively mild disease states to premature death. Recently, attention has focused on the developmental effects of chemical contaminants because studies conducted over the last two decades have identified many environmental pollutants as causing developmental abnormalities and other adverse reproductive outcomes. For example, in developing a protocol for uniform sport fish consumption advisories across the Great Lakes, the Great Lakes Sport Fish Advisory Task Force used developmental and reproductive toxicity endpoints in calculating their recommended consumption limits.

State, local, and federal agencies and tribal bodies currently use a range of methods to estimate risks to human health from consumption of chemically-contaminated fish. Results of a 1988 survey of such methods, funded by the U.S. Environmental Protection Agency (EPA)[2] and conducted by the American Fisheries Society, identified the need for standardizing the approaches to assessing risks and for developing advisories for contaminated fish. Four key components were identified as critical to the development of a consistent risk-based approach to developing fish consumption advisories: standard practices for sampling and analyzing fish, standardized risk assessment methods, standard procedures for making risk management decisions, and standardized approaches to risk communication.

To address concerns raised by the survey, EPA is developing a series of four documents designed to provide guidance to state, local, regional, and tribal environmental health officials who are responsible for issuing fish advisories for non-commercial fish.[3] The documents are meant to provide guidance only and do not constitute a regulatory requirement. The documents are: *Guidance for Assessing Chemical Contamination Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis (released 1993), Volume 2: Risk Assessment and Fish Consumption Limits, Volume 3: Risk Management, and Volume 4: Risk*

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[2] Throughout this document the abbreviation EPA will be used to represent the U.S. Environmental Protection Agency.

[3] "Fish" specifically refers to non-commercial, sport- and subsistence-caught fresh water and estuarine fish, unless otherwise noted.

Communication. EPA recommends that the four volumes be used together, since no one volume provides all the necessary information to make decisions regarding the issuance of fish consumption advisories.

Some information provided in this document is repeated in more than one section. This was done so that readers wishing to use this document as a reference source may refer directly to sections containing relevant material without having to refer to background material in other sections. For example, the consumption limit tables should be used with an understanding of the uncertainties and assumptions involved in their development; a brief summary of uncertainties and assumptions is provided in Part I and greater detail is provided in Part II.

Volume 2 provides guidance on risk-based consumption limits for the 23 high-priority chemical fish contaminants identified in Volume 1 (See Table 1-1).[4] It represents a refinement of the 1989 EPA publication entitled *Assessing Human Health Risks from Chemically Contaminated Fish and Shellfish: A Guidance Manual* (U.S. EPA, 1989a). The new volume is divided into two parts. Part I of this new volume contains a description of the methods used to calculate consumption limits and ways to modify the limits for specific purposes (e.g., to take multiple contaminants into account). It also contains consumption limit tables (expressed as maximum allowable meals over a given period of time) which were calculated using default values for meal size, consumer body weight, maximum allowable risk level, cancer potencies, and/or chronic reference doses. The tables were developed for two fish-consuming populations: young children, and adults.[5] In addition, consumption limits are provided for methylmercury for women of reproductive age. The information contained in the consumption limit tables may be used directly or modified to better approximate local conditions, as discussed in Section 2.

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[4] The target analytes listed in Table 1-1 were selected as particularly significant fish contaminants by EPA's Office of Water, based upon their occurrence in fish, their potential for bioaccumulation, and their toxicity. The criteria for their selection is discussed in Volume 1, Section 4 of this series.

[5] In future revisions of this document, additional health intake limit tables based on developmental health endpoints will be provided for women of reproductive age and children.

Table 1-1. Target Analytes Examined in This Document[a]

Cadmium
Carbophenothion
Chlordane
Chlorpyrifos
DDT, DDD, DDE
Diazinon
Dicofol
Dieldrin
Dioxin (2,3,7,8-TCDD)
Disulfoton
Endosulfan I,II
Endrin
Ethion
Heptachlor Epoxide
Hexachlorobenzene
Lindane
Methylmercury
Mirex
Oxyfluorfen
PCBs
Selenium
Terbufos
Toxaphene

Source: Volume 1 of this series (U.S. EPA 1993a)

[a] This list may not include all chemical fish contaminants which pose human health risks. In the future, chemicals may be added or deleted from the list as new occurrence data, toxicity data, and environmental fate data become available. See Volume 1 for information on how the target analytes were selected.

Part II contains more detailed technical information including an overview of EPA risk assessment methods used to derive the consumption limit tables,[6] and a discussion of the adverse health effects associated with each of the 23 target analytes. The critical studies and toxicity values (cancer potencies and Reference Doses) used in developing the consumption limit tables and a discussion of uncertainty and assumptions are also provided in Part II.

Risk values for chronic and cancer health effects used in the consumption limit tables and discussed in Section 5 were obtained from the Integrated Risk Information System (IRIS) and other EPA sources.[7] Reference Doses (RfDs) based specifically upon developmental effects have not yet been developed by EPA for most of the target analytes. Because this is an area of interest to many readers, a summary of dose-response data on developmental effects is provided in Section 5 for each target analyte, along with methods for deriving developmental exposure limits. Other recently published toxicity data are also provided. These data provide readers with an opportunity to develop consumption limits as they deem necessary, in addition to the limits offered in Section 3 of this document.[8]

This document does not provide guidance on the evaluation of the overall risk associated with multimedia exposure to chemical contaminants found in fish (e.g., exposure due to other food sources, air, water, and soil). Rather, the focus of this document is exclusively on the risk due to consumption of non-commercial fish from estuarine and fresh water sources. For example, risk from eating *commercially*-caught fish is not included in this guidance. EPA recommends that a comprehensive risk assessment be considered for all confirmed fish contaminants, including an evaluation of all significant exposure pathways.

Risk assessment and risk management of contaminated fish are complex processes due to the many considerations involved in setting fish advisories,

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[6] That is, the four-step risk assessment process: hazard assessment, dose-response evaluation, exposure assessment, and risk characterization.

[7] EPA risk values refer to cancer potency values (q_1^*s) for carcinogenic toxicity and Reference Doses (RfDs) for non-carcinogenic toxicity. These are defined in the Glossary and in Section 4. The values for each of the target analytes is provided in Table 2-2.

[8] Data are not provided on dioxin because it is currently undergoing EPA review. Information on dioxin will be provided in future revisions to this document.

including both the health risks and benefits of fish consumption, the roles of state and federal agencies, and the potential impact of advisories on economic and societal factors. These topics will be discussed in Volume 3 (*Risk Management*), currently under development.

Additional information on risk assessment methods and issues specifically related to fish risk assessment may be obtained from the documents listed in Appendix B. These documents and scientific papers cover a range of topics, from general risk assessment methods, to chemical-specific toxicological data, to identification of chemical contaminant pathways.

1.2 Sources

Information from a wide range of government and academic sources was used in the development of this document. Current approaches developed by states, regional groups such as the Great Lakes Sport Fish Advisory Task Force, and federal agencies including EPA and the U.S. Food and Drug Administration (FDA) were reviewed. Section 6 contains a complete listing of sources cited.

In addition, EPA assembled an Expert Review Group consisting of officials from several EPA offices, FDA, regional groups, and the following states: California, Florida, Michigan, Delaware, Illinois, Minnesota, Missouri, North Dakota, New Jersey, and Wisconsin, to review earlier drafts of this document. A list of the experts and their affiliations is provided in the acknowledgements section at the beginning of this document. The Expert Review Group contributed significant technical information and guidance in the development of this document. Written recommendations made by the experts were incorporated into the final document. Some members were also consulted further on specific issues related to their expertise. In a second round of reviews, this document was circulated to all states, several Native American tribes, and various federal agencies for comment and additional modifications were made. Participation in the review process does not imply concurrence by these individuals with all concepts and methods described in this document.

SECTION 2

DEVELOPMENT AND USE OF RISK-BASED CONSUMPTION LIMITS

2.1. Overview and Section Organization

This section describes the derivation and use of the risk-based consumption limit tables provided in Section 3. Tables were developed for each of the 23 target analytes listed in Table 1-1 and described in further detail in Volume 1 of this series. This section covers:

- Equations used to calculate the consumption limit tables,
- Default values used in developing the consumption limit tables, and
- Modifications to the consumption limit calculations involving different input values, multiple species consumption, and/or multiple contaminant exposure.

Methods for deriving consumption limits for pollutants with carcinogenic and/or noncarcinogenic effects are shown.[1] Methods for calculating consumption limits for multiple contaminants causing the same health effects are also discussed below. Species-specific consumption limits are calculated in kilograms per day and converted to allowable fish meals per 10-day period or month. This approach is taken because consumers tend to think of fish consumption in terms of meals rather than in terms of grams or ounces.

Developing fish consumption limits also requires making assumptions about the edible portions of fish because most contaminants are not evenly distributed throughout the fish. The portion of the fish typically eaten may vary by fish species and/or the dietary habits of fisher populations. Most fishers in the U.S. consume fish fillets. Therefore, it is recommended that contaminant concentrations be measured using skin-on fillets for scaled fish, and skinless fillets for fish that do not have scales (See Volume 1 of this series for further discussion). However, for populations that ingest whole fish, consumption values corresponding to whole fish contaminant concentrations are more

[1] When available data indicate that a target analyte is associated with both carcinogenic and noncarcinogenic health effects, consumption limits based on both types of effects are calculated.

appropriate. Fish consumption patterns are discussed in more detail in Volume 3 of this series.

People may be exposed to one or more fish contaminants through sources or pathways other than non-commercial fish. These include ingestion of contaminated commercially-caught fish, other contaminated food or contaminated water, inhalation of the contaminant, or dermal contact with contaminated material. Caution should be used in setting health safety standards that do not take these other sources into account (See Section 4 for further discussion). Methods for quantifying exposure via sources other than non-commercial fish are not discussed in this series, though Appendix B provides a list of references and government agencies which may be of assistance in quantifying these other sources of exposure.

2.2. Equations Used to Develop Risk-Based Consumption limits

Two equations are required to derive meal consumption limits for either carcinogenic or noncarcinogenic effects. The first equation (Eq. 2.1 for carcinogenic effects or Eq. 2.3 for noncarcinogenic effects) is used to calculate daily consumption limits in units of milligrams of edible fish per kilogram consumer body weight per day (mg/kg-d); the second (Eq. 2.2) is used to convert daily consumption limits to meal consumption limits over a specified period of time.

2.2.1. Calculation of Consumption Limits for Carcinogenic Effects

To calculate consumption limits for carcinogenic effects it is necessary to specify an "acceptable" lifetime risk level (ARL).[2] This document provides consumption limits which were calculated using a range of risk levels from one in ten thousand (10^{-4}) to one in one million (10^{-6}). Equations 2.1 and 2.2 were used to calculate risk-based consumption limits for the 12 target analytes with cancer potency values, based on an assumed 70-year exposure.[3] No subpopulations were identified as being particularly susceptible to the carcinogenic effects of the target analytes. However, readers may wish to calculate consumption limits for specific cohorts (e.g., children, individuals

[2] The appropriate risk level is determined by risk managers; see Volume 3 for further discussion.

[3] A 70 year lifetime is used in keeping with the default value provided in EPA's *Exposure Factors Handbook* (EPA, 1990a). This is a normative value; individuals may actually be exposed for greater or lesser period of time, depending on their lifespan, consumption habits, and residence location.

exposed to other carcinogens) based on their interpretation of the toxicological literature and local conditions.

2.2.1.1. Calculation of Daily Consumption Limits

Equation 2.1 calculates allowable daily consumption of contaminated fish based on a contaminant's carcinogenicity, expressed in terms of kilograms of fish per day:

$$CR_{lim} = \frac{ARL \cdot BW}{q_1^* \cdot C_m} \qquad \text{Equation 2.1}$$

where:

CR_{lim} = Maximum allowable fish consumption rate (kg/day),

ARL = Maximum acceptable individual lifetime risk level (unitless),

BW = Consumer body weight (kg),

q_1^* = Cancer potency, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA ($(mg/kg\text{-}d)^{-1}$), (see Section 4 for a discussion of this value), and

C_m = Measured concentration of contaminant *m* in a given species of fish (mg/kg).

The calculated daily consumption limit (CR_{lim}) represents the amount of fish (in kilograms) expected to generate a risk no greater than the maximum acceptable risk level (ARL) used, based on a lifetime of daily consumption at that consumption limit.

2.2.1.2. Calculation of Meal Consumption Limits

Consumption limits may be more conveniently expressed as the allowable number of fish meals that may be consumed over a given time period. The meal consumption limit is determined in part by the size of the meal consumed. Four meal sizes were used to develop the consumption limit tables for carcinogens in Section 3: 0.114 kg (4 oz), 0.227 kg (8 oz), 0.341 kg (12 oz), and 0.454 kg (16 oz). Note that while all calculations are in units of kilograms, meal sizes are converted to ounces in the tables in Section 3 for ease of risk communication to U.S. consumers. The conversion rate from ounces to kilograms is approximately 1 oz to 0.028 kg, or 1 kg to 35.2 oz. Equation 2.2

can be used to convert the number of allowable kilograms per day (calculated using Equation 2.1) to the number of allowable meals per month:

$$CR_{mm} = \frac{CR_{lim} \cdot dy/mnth}{MS} \qquad \text{Equation 2.2}$$

where:

CR_{mm} = Maximum allowable fish consumption rate (meals/mo),

CR_{lim} = Maximum allowable fish consumption rate (kg/d), and

MS = Meal size (kg fish/meal).

Equation 2.2 can also be modified to calculate meals per day (CR_{md}); this was done to calculate the 10-day consumption limit tables for non-carcinogens in Section 3. Note that this approach does not expressly limit the amount of fish that may be consumed in a given day during the specified time period, so care must be taken to inform consumers of the dangers of eating large amounts of contaminated fish in one sitting when certain acute or developmental toxics may be of concern. For example, consuming the monthly limit in one day could result in exposures for non-carcinogens that are 30 times the RfD (See Section 4.3 for further discussion).

Other consumption rates, such as meals per week, could also be calculated using this equation by substituting, for example, days/week for days/month. In using Equation 2.2 in the table calculations in Section 3, one month was expressed as 365.25 days/12 months.

All meal consumption limits in the tables in Section 3 have been rounded down to the nearest whole number, with the exception of the six meals/year consumption limits, which are expressed as 0.5 meals/month. Meal consumption limits are rounded *down* to make them more protective; rounding up would potentially cause them to exceed maximum acceptable risk levels (ARLs) for carcinogens and/or chronic systemic Reference Doses associated with fish contaminants.

2.2.1.3. Input Parameters

Calculating risk-based consumption limits for carcinogenic effects requires developing appropriate values for the parameters in the equations. The default values used to calculate the consumption limits listed in Section 3 are shown in Table 2-1; a range of values are provided for C_m. Development and modification of these values are discussed in Section 2.3.

Table 2-1. Input Parameters for Risk Equations

Equation Parameter[a]	Values
Maximum acceptable risk level (ARL)	10^{-4} (unitless) 10^{-5} (unitless) 10^{-6} (unitless)
Consumer body weight (BW)	70 kg (general adults 14.5 kg (young children)
Average fish meal size (MS)	3 oz (0.085 kg) (children only) 4 oz (0.114 kg) 8 oz (0.227 kg) 12 oz (0.341 kg) 16 oz (0.454 kg)
Cancer potency (q_1^*)[b] Reference Dose (RfD)	in rate per(mg/kg-d); See Table 2-2 in mg/kg-day; See Table 2-2
Measured contaminant concentration in edible fish tissue (C_m)[c]	in mg/kg; varies with local conditions

[a] Choice of the appropriate acceptable risk level, consumer body weight, and average fish meal size are considered to be risk management decisions. This document provides a range of values; the risk management decision-making process is discussed in Volume 3. Selection or calculation of the appropriate cancer potency and RfD values may be considered toxicological, medical, or risk management decisions. For information regarding these values see Sections 4 and 5 of this document and Volume 3.

[b] Most of the q_1^*s and RfDs were obtained from EPA's Integrated Risk Information System (IRIS, 1993). The RfDs not listed in IRIS were obtained from EPA's Office of Pesticide Programs or the HEAST tables. The q_1^*s and RfDs used are listed in Table 2-2 and discussed in Section 5.

[c] Values for contaminant concentrations must be taken from local sampling and analysis programs as described in Volume 1.

2.2.2. Calculation of Consumption Limits for Noncarcinogenic Effects

Noncarcinogenic health effects caused by consumption of contaminated fish include acute exposure toxicity, chronic exposure health effects (i.e., liver, kidney, neurological, muscular, ocular, reproductive system, respiratory, circulatory system, or other organ toxicities), and adverse developmental effects. Risk-based consumption limit tables for chronic exposure health effects were developed for adults and young children.[4] Section 5 contains a summary of the overall toxicity of the target analytes. In future revisions of this document, additional consumption limit tables for women of reproductive age and children based on developmental health endpoints will be provided. The equations provided in this section may be used by readers to calculate additional or alternative consumption limits, based on their interpretation of toxicological and other literature.

2.2.2.1. Calculation of Daily Consumption Limits

Equation 2.3 is used to calculate the allowable daily consumption (CR_{lim}) of contaminated fish, based on a contaminant's noncarcinogenic health effects, and expressed in terms of kilograms of fish per day:

$$CR_{lim} = \frac{RfD \cdot BW}{C_m} \qquad \text{Equation 2.3}$$

where:

CR_{lim} = Maximum allowable fish consumption rate (kg/day),

RfD = Reference Dose (mg/kg-d),

BW = Consumer body weight (kg), and,

C_m = Measured concentration of contaminant *m* in a given species of fish (mg/kg).

CR_{lim} represents the maximum lifetime daily consumption rate (in kilograms of

[4] Consumption limit tables for women of reproductive age and children were also calculated based on developmental effects of methylmercury.

fish) that would not be expected to cause adverse noncarcinogenic health effects. Most RfDs are based on chronic exposure studies (or subchronic studies used with an additional uncertainty factor). Because the contaminant concentrations required to produce chronic health effects are generally lower than those causing acute health effects, the use of chronic RfDs in developing consumption limits is expected to also protect consumers against acute health effects. They are designed to protect the most sensitive individuals. This may, however, not be the case for developmental toxics (See Section 2.2.3 below).

2.2.2.2. Calculation of Meals Per Month

Equation 2.2, shown above in Section 2.2.1.2, is used to convert daily consumption limits, in kilograms, to meal consumption limits over given time periods, as a function of meal size. Five meal sizes were used to develop the consumption limit tables for noncarcinogenic effects: 3 oz (children only), 4 oz, 8 oz, 12 oz (adults only), and 16 oz (adults only). Monthly and short term (10-day) consumption limits were derived. Monthly consumption limits pertain to seasonal and subsistence fish consumers, while 10-day consumption limits apply to short-term recreational fishers. Note that both sets of tables use the same chronic systemic RfDs; the difference is in the averaging periods (i.e., 10 days versus one month) used in Equation 2.2.[5]

2.2.2.3. Input Parameters

For noncarcinogenic effects, calculating risk-based consumption limits requires developing appropriate values for similar parameters to those required for carcinogenic effects. These are listed in Table 2-1.

2.2.3. Calculation of Consumption Limits for Developmental Effects.

This guidance document considers three groups of fishers in deriving risk-based consumption limits: general adults, women of reproductive age, and young children. Both women of reproductive age and young children are known to be at risk from developmental toxics.[6] It is well-documented that women

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[5] As noted earlier, this approach does not expressly limit the amount of fish that may be consumed in a given day during the specified time period, so care must be taken to inform consumers of the dangers of eating large amounts of contaminated fish in one sitting when certain acute or developmental toxins are of concern.

[6] There is currently very limited information on the potential developmental impact resulting from exposure of men to developmental toxins. However,

exposed to developmental toxic (e.g., methylmercury) may pass on sufficient levels of the contaminants *in utero* or through breast-feeding to induce pre- or post-natal developmental damage in their offspring. Information on developmental toxicity has only recently become available for many chemical contaminants. Consequently, the IRIS database, the source of most of the chronic RfDs used to calculated consumption limits, does not contain detailed developmental toxicity data for all target analytes. Consumption limits specifically designed to address developmental health effects in women of reproductive age and children have been calculated for methylmercury (See Section 3). In addition, the RfD used for PCBs is considered protective against developmental toxicity, based on the data available on Aroclor 1016 (See the discussion of PCBs in Section 5). New data are being reviewed by EPA and will be incorporated in future versions of this document.

Readers are referred to Sections 4 and 5 which contain discussions of developmental toxicity. Developmental study data, sources of additional toxicity data, and a methodology for calculating exposure limits are provided in Section 5 so that readers may evaluate available information and make informed decisions regarding developmental toxicity and consumption limits. Exposure limits for developmental and other health endpoints may be calculated by readers, as deemed necessary, using methods described in Section 5.

2.3. Default Values and Alternative Values For Calculating Consumption Limits

The consumption limit tables provided in Section 3 are based on default values for consumer body weights and average meal sizes. These values may not be valid for some recreational and subsistence fisher populations. Readers are encouraged to modify these variables, if necessary, to better fit local conditions relating to consumer body weight, risk level of concern, meal size, new toxicological data, and/or the presence of multiple contaminants. This section describes the default input values shown in Table 2-1 and provides additional input values and multipliers for use in modifying and/or recalculating the consumption limit tables.

Seven variables are involved in calculating the values in the consumption limit tables (See Equations 2.1 to 2.3):

- Maximum acceptable risk level (ARL),
- Cancer potency (q_1^*),
- Chronic Reference Dose (RfD),
- Consumer body weight (BW),

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some information on this is provided in Sections 4 and 5.

- Fish meal size (MS),
- Contaminant concentration in edible fish tissue (C_m), and
- Maximum allowable consumption rate (CR_{lim}).

Blank table templates are provided at the end of this section for use in developing new consumption limit tables based on changes in input parameters.

2.3.1. Maximum Acceptable Risk Level (ARL)

The consumption limit tables shown in Section 3 for target analytes with carcinogenic effects were calculated for maximum individual acceptable risk levels (ARLs) of 10^{-4} to 10^{-6}. Note that the variable ARL appears in the numerator of Equation 2.1, the equation for calculating the daily consumption limit for carcinogens. Since ARL appears in multiples of 10, one may derive new meal consumption limits from the existing tables by multiplying or dividing the existing meal consumption limits by factors of 10, as appropriate. *Equally, changing the ARL by a factor of 10 would cause the same meal consumption limits to be valid for chemical concentrations 10 times higher or 10 times lower than those associated with the original ARL. For example:*

- To go from an ARL of 10^{-4} to an ARL of 10^{-3}, shift the meal consumption limit values for the ARL of 10^{-4} to chemical concentrations 10 times *greater* than the original (e.g., if the original meal consumption limit is 12 8-oz meals per month at a contaminant concentration of *0.6 mg/kg* for an ARL of 10^{-4}, then the new meal consumption limit for an ARL of 10^{-3} would be 12 8-oz meals per month at a contaminant concentration of *6 mg/kg*. This increases the estimated individual lifetime risk by a factor of 10.

- To go from an ARL of 10^{-6} to an ARL of 10^{-7}, shift the meal consumption values for the ARL of 10^{-6} to chemical concentrations 10 times *lower* than the original (e.g., if the original meal consumption limit is 12 8-oz meals per month at a contaminant concentration of *0.006 mg/kg* for an ARL of 10^{-6}, then the new meal consumption limit for an ARL of 10^{-7} would be 12 8-oz meals per month at a contaminant concentration of *0.0006 mg/kg*. This decreases the estimated individual lifetime risk by a factor of 10.

EXAMPLE: Modified Risk Level (ARL)

The consumption limit table for general adults for the non-carcinogenic effects of chlordane was taken from Section 3 and modified to include consumption limits for risk levels of 10^{-3} (one in 1000) and 10^{-7} (one in 10,000,000) for an

8-oz meal size (shown in bold). Consumption limits for other meal sizes have been deleted for clarity. Table 3-10a is shown below.

2.3.2. Chronic Reference Doses and Cancer Potencies (RfDs and q_1^*s)

Table 2-2 contains the risk values used in the development of the consumption limit tables shown in Section 3. All of the q_1^*s and RfDs were obtained from EPA data bases, primarily from IRIS (1993). Preference was given to IRIS values because they represent consensus within EPA. When IRIS values were not available, RfDs from other EPA sources were used (See Section 5).

EPA evaluates dose-response data as they become available. Because toxicological data is continually being generated, there may be data not yet incorporated into the risk values. This is especially relevant for developmental toxicity, neurotoxicity, and immunotoxicity, which are the subject of much current research. To address this, a summary discussion of the toxicity data has been provided in Section 5 for each target analyte; the summaries include a discussion of acute, chronic, developmental, carcinogenic,and genetic toxicity, and special susceptibilities. The summaries contain a brief synopsis of the toxicity data current through 1993, based on a review of summary documents and data bases. Readers are urged to review this information for those target analytes of interest in their geographic areas. A method for estimating acceptable exposure levels from the new data is provided in Section 5; the methods follow the basic dose-response approach recommended by EPA for calculation of RfDs (discussed in Sections 4 and 5). This information is provided to enable readers to use new dose-response data to develop consumption limits if they feel the data warrant such an approach. This may be particularly useful when there are concerns regarding the exposure of pregnant and lactating women and children to developmental contaminants.

2.3.3. Consumer Body Weight (BW)

The consumption limit tables in Section 3 are based on non-commercial fish consumers of two body weights: 70 kg (156 pounds) and 14.5 kg (32 pounds). Seventy kg corresponds to the average body weight of male and female adults in the U.S. (EPA, 1990a). The 14.5 kg body weight corresponds to that of a young child of three to four years (EPA, 1990a). As Equation 2.3 shows, consumption limits are linearly related to body weight. That is, the higher the body weight assumed for the population, the higher the consumption limits. EPA's *Exposure Factors Handbook* (EPA, 1990a) provides additional specific body weight information which can be used to adjust the body weight component of Equation 2.3. The values can also be used as to develop a set of multipliers to directly adjust consumption limits for body weight variations (See below).

Table 3–10a. Monthly Consumption for Carcinogenic Health Endpoints

Chemical Name:	Chlordane
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	1.3 per mg/kg–d
Detection Limit:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)							
	4	8					12	16
		ARL						
		10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}		
<0.00006		**UNLIM**	UNLIM	UNLIM	UNLIM	**UNLIM**		
0.00006		**UNLIM**	UNLIM	UNLIM	UNLIM	**12**		
0.00008		**UNLIM**	UNLIM	UNLIM	UNLIM	**9**		
0.0001		**UNLIM**	UNLIM	UNLIM	UNLIM	**7**		
0.0002		**UNLIM**	UNLIM	UNLIM	UNLIM	**3**		
0.0004		**UNLIM**	UNLIM	UNLIM	UNLIM	**1**		
0.0006		**UNLIM**	UNLIM	UNLIM	12	**1**		
0.0008		**UNLIM**	UNLIM	UNLIM	9	**0.5**		
0.001		**UNLIM**	UNLIM	UNLIM	7	**0.5**		
0.002		**UNLIM**	UNLIM	UNLIM	3	**NONE**		
0.004		**UNLIM**	UNLIM	UNLIM	1	**NONE**		
0.006		**UNLIM**	UNLIM	12	1	**NONE**		
0.008		**UNLIM**	UNLIM	9	0.5	**NONE**		
0.01		**UNLIM**	UNLIM	7	0.5	**NONE**		
0.02		**UNLIM**	UNLIM	3	NONE	**NONE**		
0.04		**UNLIM**	UNLIM	1	NONE	**NONE**		
0.06		**UNLIM**	12	1	NONE	**NONE**		
0.08		**UNLIM**	9	0.5	NONE	**NONE**		
0.1		**UNLIM**	7	0.5	NONE	**NONE**		
0.2		**UNLIM**	3	NONE	NONE	**NONE**		
0.4		**UNLIM**	1	NONE	NONE	**NONE**		
0.6		**12**	1	NONE	NONE	**NONE**		
0.8		**9**	0.5	NONE	NONE	**NONE**		
1		**7**	0.5	NONE	NONE	**NONE**		
2		**3**	NONE	NONE	NONE	**NONE**		
4		**1**	NONE	NONE	NONE	**NONE**		
6		**1**	NONE	NONE	NONE	**NONE**		
8		**0.5**	NONE	NONE	NONE	**NONE**		
10		**0.5**	NONE	NONE	NONE	**NONE**		
>10		**NONE**	NONE	NONE	NONE	**NONE**		

An 8–oz meal size corresponds to 0.227 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Note that some values may be below detection limits.
All values were rounded down to the nearest whole meal size.
Note nonlinear scale of concentration values.
ARL = Acceptable Risk Level

Table 2-2. Risk Values Used in Risk-Based Consumption Limit Tables in Section 3

Target Analyte	Chronic RfD (mg/kg-day)[a]	q_1^* (per mg/kg-day)[a]
Cadmium	1×10^{-3}	--
Carbophenothion	1.3×10^{-4}[b]	--
Chlordane	6×10^{-5}	1.3
Chlorpyrifos	3×10^{-3}	---
DDT, DDD, DDE	5×10^{-4}	0.34
Diazinon	9×10^{-5}[b]	--
Dicofol	1×10^{-3}[b]	0.4[b,c]
Dieldrin	5×10^{-5}	16
Dioxin (2,3,7,8-TCDD)	--	$1.56 \times 10^{+5}$
Disulfoton	4×10^{-5}	--
Endosulfan	5×10^{-5}	--
Endrin	3×10^{-4}	--
Ethion	5×10^{-4}	--
Heptachlor epoxide	1.3×10^{-5}	9.1
Hexachlorobenzene	8×10^{-4}	1.6
Lindane	3×10^{-4}	1.3[d]
Methylmercury (Chronic Systemic)[e]	3×10^{-4}	--
Methylmercury (Developmental)[f]	6×10^{-5}[g]	--
Mirex	2×10^{-4}	1.8[e]
Oxyfluorfen	3×10^{-3}	0.13
PCBs	2×10^{-5}[h]	7.7[d]
Selenium	5×10^{-3}	--
Terbufos	5×10^{-5}[b]	--
Toxaphene	2.5×10^{-4}[b]	1.1

[a] All risk values cited are from the Integrated Risk Information System (IRIS, 1993) unless noted. All risk numbers provided in this table are subject to change as new toxicological data and methodology become available.
[b] Developed by EPA Office of Pesticide Programs.
[c] The q_1^* for dicofol and DDD, DDT and/or DDE combined is 0.34 per mg/kg-d (IRIS, 1993)
[d] Developed by EPA and listed in the Health Effects Assessment Summary Tables (HEAST, 1992)
[e] Used in calculations for the general adult population
[f] Used in calculations for women of reproductive age and children.
[g] Source: EPA (1993a). Developed by EPA's Office of Water. See Section 5 on methylmercury.
[h] The RfD for PCBs is based on Aroclor 1254 (IRIS, 1993); the q_1^* for PCBs is based on Aroclor 1260 (IRIS, 1993).

Table 2-3 provides a range of average body weights (based on age and sex) for the U.S., and their associated multipliers. Values shown in bold represent those used in the calculation of the consumption limit tables in Section 3. A *multiplier* is provided for each age group which represents the number by which the meal consumption limits in the *general adult population* tables may be multiplied in order to calculate new meal consumption limits using an alternative body weight.

2.3.3.1. Derivation of Multipliers for Body Weight Adjustment

Body weight multipliers represent the ratio of the alternative body weight to the standard 70 kg body weight. Body weight multipliers were calculated as shown:

$$Multiplier = \frac{Alternate\ Consumer\ Body\ Weight}{General\ Adult\ Body\ Weight}$$

EXAMPLE: Calculating Multiplier for Body Weight

To calculate the multiplier for a 9 to 12 year old with an average body weight of 36 kg (See Table 2.3), the equation is:

$$Multiplier = \frac{36\ kg}{70\ kg} = 0.51\ (unitless)$$

where 0.51 represents the ratio between the child body weight (36 kg) and the general adult body weight (70 kg). In this document, a body weight of 70 kg was used for all adults, including women of reproductive age, to calculate the consumption limits shown in Section 3. Readers may wish to modify some or all of these consumption limits using alternative body weight values, based on the health endpoint of concern. For example, in cases where certain developmental toxics are of concern, exposure of women of childbearing age could be assessed separately. As described in Section 4, a body weight value of 64 kg (143 pounds) can be used to represent the body weight for women of reproductive age, based on the arithmetic mean of the average weights of women of three age groups (18-25, 26-35, and 36-45) given in the *Exposure Factors Handbook* (EPA, 1990a; see Table 2-3). A more protective body weight value would be to use the lower 95th percentile body weight of women age 18 to 25 years (Blindauer, 1994). Readers are encouraged to use local information when available to determine appropriate body weights for calculating exposure limits.

Table 2-3. Average Body Weights and Associated Multipliers

Age Group (yrs)[b]	Average Male Body Weight (kg)	Average Female Body Weight (kg)	Average Body Weight for Males and Females Combined (kg)	Multiplier[a]
< 3	11.9	11.2	11.6	0.17
3 to 6	17.6	17.1	17.4	0.25
0 to 6	**14.8**	**14.2**	**14.5**	0.21
6 to 9	25.3	24.6	25.0	0.36
9 to 12	35.7	36.2	36.0	0.51
12 to 15	50.5	50.7	50.6	0.72
15 to 18	64.9	57.4	61.2	0.87
18 to 25	73.7	60.6	67.2	0.96
25 to 35	78.7	64.2	71.5	1.0
35 to 45	80.8	67.1	74.0	1.1
45 to 55	81.0	67.9	74.5	1.1
55 to 65	78.8	67.9	73.4	1.0
65 to 75	74.8	66.6	70.7	1.0
18 to 45	-	64	-	0.91
18 to 75	**78.1**	**65.4**	**71.8 (70)[c]**	**1.0**

[a] The multiplier is multiplied by the consumption limits associated with 70 kg general adult fish consumers to obtain new consumption limits using the alternative body weight (See text). The multiplier represents the alternate body weight divided by the general adult body weight.

[b] Numbers in bold represent the default values used to calculate the consumption limit tables.

[c] Per recommendations in the *Exposure Factors Handbook*, the body weight value of 71.8 kg for the general population was rounded to one significant digit, or 70 kg (EPA, 1990a).

To derive modified consumption limits using alternate values for body weight, multiply the existing consumption limits (in meals per month) found in the tables for the **general 70 kg fisher population** by the multiplier associated with the new body weight:

$$New\ CR_{mm} = CR_{mm_{70\text{-}kg\ BW}} \cdot Multiplier_{BW}$$

where:

CR_{mm} = Maximum allowable fish consumption rate (meals/mo),

$CR_{mm\text{-}70\ kg\ BW}$ = Maximum allowable fish consumption rate of a 70-kg fish consumer (meals/mo),

BW = Consumer body weight (kg), and

$Multiplier_{BW}$ = Body weight multiplier (unitless).

If the resultant meal frequency value is not a whole number, *round down* to the nearest whole number.[7]

EXAMPLE: Modified Body Weight

To modify Table 3-9 (which shows the monthly consumption limits for chronic systemic health effects in general adults from exposure to chlordane) to represent consumption limits for 9 to 12-year olds weighing an average of 36 kg, multiply each value in the consumption limit table by 0.51:

$$New\ CR_{mm} = CR_{mm_{70\text{-}kg\ BW}} \cdot 0.51$$

Table 3-9 has been modified to represent consumption limits for 36-kg consumers, shown below as Table 3-9a. For example, while general adults

[7] Rounding up would make the advisory less protective. It is also important to note that rounding down the modified CR_{lim} could lead to unnecessarily conservative meal consumption limits, since the original CR_{lim} values for general adults have already been rounded down once. Readers may wish to derive more accurate estimates by recalculating meal consumption limits using Equations 2.1 to 2.3 instead of using a multiplier (See Section 2.3.4).

Table 3–9a. Monthly Consumption for Chronic Systemic Health Endpoints

Chemical Name:	Chlordane
Population:	Children
Body Weight:	36
Reference Dose:	6E–05 mg/kg–d
Detection Limit	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	UNLIM	7
0.03	UNLIM	UNLIM	6	4
0.04	UNLIM	7	4	3
0.05	UNLIM	5	3	2
0.06	UNLIM	4	3	2
0.07	8	4	2	2
0.08	7	3	2	1
0.09	6	3	2	1
0.1	5	2	1	1
0.2	2	1	0.5	0.5
0.3	1	0.5	0.5	NONE
0.4	1	0.5	NONE	NONE
0.5	1	0.5	NONE	NONE
0.6	0.5	NONE	NONE	NONE
0.7	0.5	NONE	NONE	NONE
0.8	0.5	NONE	NONE	NONE
0.9	0.5	NONE	NONE	NONE
1	0.5	NONE	NONE	NONE
2	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.

may be able to safely eat nine 8-oz fish meals contaminated with 0.06 mg chlordane/kg fish per month, 9 to 12-year olds would only be able to safely eat four meals per month at this contaminant level (9 • 0.51 = 4.59, rounded down to 4) to achieve the same daily contaminant exposure in mg/kg-day.

Scaling to a different body weight may cause the contaminant concentrations of concern to change substantially. Note, for example, that Table 3-9a only includes meal consumption limits of eight meals per month and below, since all meal frequencies listed in the original table were effectively halved to derive the new meal frequencies for 36-kg consumers. Section 2.3.5 describes the methods used to add meal frequency values to concentration ranges that fall under unlimited ("UNLIM") or no ("NONE") consumption in the original table for the 70-kg consumer, but no longer do in the modified table.[8]

2.3.4. Meal Size

Meal size is defined as the amount of fish (in kilograms) consumed at one sitting. Four average meal sizes were used for developing consumption limits for the general adult population. Three were used for children under four. Note that while children tend to eat smaller portions than adults, they may consume significantly more fish per unit of body weight. Women of reproductive age (considered separately for methylmercury consumption limits) were assumed to eat the same amount of fish per meal as other adults.

EPA has identified a value of eight ounces (227 grams) of cooked fish fillet per 70 kilogram consumer body weight as an average meal size for the general adult non-commercial fish consuming population and for women of reproductive age.[9] This meal size, however, does not represent higher end exposures, where persons consume more than average in a given meal. These larger meal sizes are particularly important to consider in cases where acute or developmental effects from fish contamination are of concern. Therefore, the consumption limit tables in Section 3 provide meal limits based on a range of

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[8] For the purposes of this document, unlimited safe fish consumption (represented by "UNLIM" in the tables) has been defined as an intake limit of more than 17 fish meals per month, or four fish meals per week for the monthly tables, and more than one meal per day for the 10-day tables. The definition of no safe fish consumption (represented by "NONE" in the tables) is a health intake limit of less than one meal in two months for the monthly tables, and less than one meal per 10 days for the 10-day table. These definitions do not represent EPA recommendations.

[9] See Section 4.4.2.3 for rationale and references.

meal sizes from 4 oz to 16 oz. For children younger than four years, the EPA has estimated the average fish meal size to be 3 ounces (85 grams) of cooked fish fillet. Meal sizes of 3, 4, and 8 ounces are used in Section 3 for children under four. Discussion of the development of these values is found in Section 4.

Readers may wish to develop fish consumption limits using other meal sizes, obtained from data on local fish consumption patterns and/or other fish consumption surveys as appropriate (See Volume 3 of this series). Table 2-4 provides other meal sizes and their associated multipliers. To obtain modified consumption limits using alternate values for meal size, multiply the existing consumption limits found in the tables for the *8-oz meal size* by the multiplier associated with the new meal size:

$$New\ CR_{mm} = CR_{mm_{8\text{-}oz\ MS}} \cdot Multiplier_{MS}$$

where variables are as defined above. If the resultant meal frequency value is not a whole number, *round down* to the nearest whole number (See Footnote 8).

EXAMPLE: Modified Meal Size

To modify Table 3-9 to develop values for a 24-oz meal size, multiply the consumption limits for 8-oz meals in the table by 1/3, or 0.33:

$$New\ CR_{mm} = CR_{mm_{8\text{-}oz\ MS}} \cdot 0.33$$

Table 3-9 has been modified to represent consumption limits for general adults consuming 24 oz (1 1/2 lb or 0.680 kg) fish meals, shown below as Table 3-9b. This shows that, for example, while a 70-kg adult could consume nine 8-oz fish meals contaminated with 0.06 mg chlordane/kg fish, he or she could only consume three 24-oz meals per month (9 • 1/3 = 3).

Scaling to a different meal size may cause the concentrations of concern to change substantially. Note, for example, that Table 3-9b only includes values for meal consumption limits of four meals per month and below for 24 oz meals, since all meal frequencies listed in the original table (Table 3-9) were divided by 3 to derive the new meal frequencies. Section 2.3.5 describes the

Table 2-4. Alternative Meal Sizes and Associated Multipliers

Meal Size (oz)[a]	Multiplier[b]
1	8
2	4
3	**2.67**
4	**2.0**
5	1.6
6	1.33
7	1.14
8	**1.0**
9	0.89
10	0.80
11	0.73
12	**0.67**
13	0.62
14	0.57
15	0.53
16	**0.5**
24	0.33
32	0.25

[a] Bolded values are those used in the consumption limit tables in Section 3.
[b] The multiplier is multiplied by the consumption limits associated with eight ounce meals to obtain new consumption limits using the alternative meal size.

Table 3–9b. Monthly Consumption for Chronic Systemic Health Endpoints

Chemical Name:	Chlordane
Population:	General
Body Weight:	70 kg
Reference Dose:	6E–05 mg/kg–d
Detection Limit	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)				
	4	8	12	16	24
<0.02	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	UNLIM	14	UNLIM
0.03	UNLIM	UNLIM	12	9	UNLIM
0.04	UNLIM	14	9	7	4
0.05	UNLIM	11	7	5	3
0.06	UNLIM	9	6	4	3
0.07	16	8	5	4	2
0.08	14	7	4	3	2
0.09	12	6	4	3	2
0.1	11	5	3	2	1
0.2	5	2	1	1	0.5
0.3	3	1	1	0.5	NONE
0.4	2	1	0.5	0.5	NONE
0.5	2	1	0.5	0.5	NONE
0.6	1	0.5	0.5	NONE	NONE
0.7	1	0.5	0.5	NONE	NONE
0.8	1	0.5	NONE	NONE	NONE
0.9	1	0.5	NONE	NONE	NONE
1	1	0.5	NONE	NONE	NONE
2	0.5	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE	NONE

UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.

methods used to add meal frequency values to concentration ranges that fall under unlimited ("UNLIM") or no ("NONE") consumption in the original table for the 8-oz meal size, but no longer do in the modified table.

In addition, if specific meal consumption limits are desired for consumers ages four to adult, modifications can be made for both body weight and meal size using the following equation:

$$New\ CR_{mm} = CR_{mm_{70\ kg\ BW,8\text{-}oz\ MS}} \cdot Multiplier_{BW} \cdot Multiplier_{MS}$$

where the parameters are as defined above.

EXAMPLE: Modified Body Weight and Meal Size

To modify Table 3-9 for a 3-oz meal size for 3 to 6 year olds with an average body weight of 17.4 kg, multiply the values for the 8-oz meal size by 0.25 (the body weight multiplier; see Table 2-3) and 2.67 (the meal size multiplier; see Table 2-4):

$$New\ CR_{mm} = CR_{mm_{70\ kg\ BW,8\text{-}oz\ MS}} \cdot 0.25 \cdot 2.67$$

In this example, the new consumption limits are equivalent to 2/3 of the old consumption limits. Table 3-9 has been modified to represent consumption limits for 17.4-kg children consuming 3-oz (0.085 kg) fish meals, shown below as Table 3-9c. For clarity, only the meal frequencies for a 3-oz meal size have been calculated. This shows that, for example, while a 70-kg adult could consume nine 8-oz fish meals contaminated with 0.06 mg chlordane/kg fish, a 17.4 kg child could only consume six *3-oz* meals per month at the same contamination level (9 • 0.25 • 2.67 = 6). Again, as noted above, readers will need to use the methods described in Section 2.3.5 to add meal frequency values to concentration ranges that fall under unlimited ("UNLIM") or no ("NONE") consumption in the original table for general adults, but no longer do in the modified table.

2.3.5. Meal Frequency (CR_{lim})

Readers may wish to add meal frequency values to the consumption limit tables if 1) other modifications to the tables shift the concentrations of concern so that some values need to be added (See above), 2) multiple modifications to the tables are required, justifying recalculation of the tables, and/or, 3) different definitions for unlimited and no consumption are desired for other reasons.

Table 3–9c. Monthly Consumption for Chronic Systemic Health Endpoints

Chemical Name:	Chlordane
Population:	Children
Body Weight:	17.4 kg
Reference Dose:	6E–05 mg/kg–d
Detection Limit	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			
	2	3	4	8
<0.04		UNLIM		
0.04		9		
0.05		7		
0.06		6		
0.07		5		
0.08		4		
0.09		4		
0.1		3		
0.2		1		
0.3		0.5		
0.4		0.5		
0.5		0.5		
>0.5		NONE		

A meal size of 3 oz corresponds to 0.085 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.

Recalculating meal frequencies requires the use of Equations 2.1 to 2.3 (See Section 2.2). These equations are provided here for convenience.

Equation 2.1 is used to calculate daily consumption limits (in kg fish/day) for carcinogens:

$$CR_{lim} = \frac{ARL \cdot BW}{q_1^* \cdot C_m} \qquad \text{Equation 2.1}$$

where:

CR_{lim} = Maximum allowable fish consumption rate (kg/day),

ARL = Maximum acceptable risk level (unitless),

BW = Consumer body weight (kg),

q_1^* = Cancer potency, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA ($(mg/kg\text{-}d)^{-1}$), and

C_m = Measured concentration of contaminant *m* in a given species of fish (mg/kg).

Equation 2.3 is used to calculate daily consumption limits (in kg fish/day) for noncarcinogens:

$$CR_{lim} = \frac{RfD \cdot BW}{C_m} \qquad \text{Equation 2.3}$$

where:

CR_{lim} = Maximum allowable fish consumption rate (kg/day),

RfD = Reference Dose (mg/kg-d),

BW = Consumer body weight (kg), and,

C_m = Measured concentration of contaminant *m* in a given species of fish (mg/kg).

Daily consumption rates (in kg fish/day) calculated in Equations 2.1 and 2.3 are then converted to meals per month using Equation 2.2:

$$CR_{mm} = \frac{CR_{lim} \cdot dy/mnth}{MS} \qquad \text{Equation 2.2}$$

where parameters are defined as above. The resultant meal consumption limits calculated are then placed at the point in the table where the meal size (and risk level, if a carcinogen) and the chemical concentration used in the equations intersect (See Section 3 for illustration).

EXAMPLE: Calculating Meal Consumption limits

The monthly meal consumption limits shown in Table 3-9 include a limit for a contaminant concentration of 0.07 mg chlordane/kg fish and a meal size of 4 oz (0.114 kg), based on a chronic systemic RfD of 6 x 10^{-5} mg/kg-d, and a consumer body weight of 70 kg. Using these values for the parameters in Equation 2.3 yields a maximum daily consumption rate of 0.060 kg fish/day:

$$CR_{lim} = \frac{6 \times 10^{-5}\ mg/kg\text{-}d \cdot 70\ kg}{0.07\ mg/kg} = 0.060\ kg\ fish/d$$

With a meal size of 0.114 kg (4 oz), a consumption rate of 0.060 kg fish/day, and a time period of one month (expressed as 365.25 days/12 months), Equation 2.2 yields a meal consumption limit of 16 meals per month, as shown in Table 3-9, below:

$$CR_{mm} = \frac{0.060\ kg/d \cdot \frac{365.25\ d/yr}{12\ mo/yr}}{0.114\ kg/meal} = 16\ meals/mo$$

All meal consumption limit modifications may be done in this manner by substituting the appropriate values into Equations 2.1 to 2.3. Note that while meal sizes are given in ounces in the tables in Section 3, they need to be calculated in *kilograms* in Equations 2.1 to 2.3. The conversion rate from ounces to kilograms is approximately 1 oz to 0.028 kg, or 1 kg to 35.2 oz.

Table 3–9. Monthly Consumption for Chronic Systemic Health Endpoints

Chemical Name:	Chlordane
Population:	General
Body Weight:	70 kg
Reference Dose:	6E–05 mg/kg–d
Detection Limit	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	UNLIM	14
0.03	UNLIM	UNLIM	12	9
0.04	UNLIM	14	9	7
0.05	UNLIM	11	7	5
0.06	UNLIM	9	6	4
0.07	16	8	5	4
0.08	14	7	4	3
0.09	12	6	4	3
0.1	11	5	3	2
0.2	5	2	1	1
0.3	3	1	1	0.5
0.4	2	1	0.5	0.5
0.5	2	1	0.5	0.5
0.6	1	0.5	0.5	NONE
0.7	1	0.5	0.5	NONE
0.8	1	0.5	NONE	NONE
0.9	1	0.5	NONE	NONE
1	1	0.5	NONE	NONE
2	0.5	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.

2.4. Modification of Consumption limits for Multiple Species, Single Contaminant Exposure

Equations 2.1 and 2.3 may be modified to calculate consumption limits for exposure to a single contaminant through consumption of several fish species. This section describes the modifications required to do so.

Individuals often eat several species of fish in their diets. Equations 2.1 and 2.3, however, are based on contaminant concentrations in single species of fish. Where multiple species of contaminated fish are consumed by a single individual, such limits may not be sufficiently protective. If several fish species are contaminated with the same chemical, then doses from each of these species must first be summed across all species eaten, in proportion to the amount which is eaten. This is described by Equation 2.4:

$$C_{tm} = \sum_{j=1}^{n} C_{mj} \cdot P_j \qquad \text{Equation 2.4}$$

where:

C_{tm} = Total concentration of chemical *m* in an individual's fish diet,

C_{mj} = Concentration of chemical *m* in species *j* (mg/kg), and,

P_j = Proportion of species *j* in the diet (unitless).

Note that this equation requires that the risk assessor know or be able to estimate the proportion of each fish species in the exposed individual's diet. Equation 2.4 yields the weighted average contaminant concentration across all fish species consumed (C_{tm}), which then may be used in modified versions of Equations 2.1 to 2.3 to calculate overall and species-specific risk-based consumption limits (See below).

2.4.1. Carcinogenic Effects

The equation to calculate an overall daily consumption limit based on exposure to a single carcinogen in a multiple species diet is very similar to Equation 2.1. However, in place of C_m, which indicates the average chemical concentration in one species, Equation 2.5 uses the equation for C_{tm}, the weighted average chemical concentration across all of the species consumed:

$$CR_{lim} = \frac{ARL \cdot BW}{\sum_{j=1}^{n} (C_{mj} \cdot P_j) \cdot q_1^*}$$ Equation 2.5

where:

CR_{lim} = Maximum allowable fish consumption rate (kg/day),

ARL = Maximum acceptable lifetime risk level (unitless),

BW = consumer body weight (kg),

C_{mj} = Concentration of chemical *m* in species *j* (mg/kg),

P_j = Proportion of a given species in the diet (unitless), and,

q_1^* = Cancer potency, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA $((mg/kg\text{-}d)^{-1})$.

The daily consumption limit for each species is then calculated as:

$$CR_j = CR_{lim} \cdot P_j$$ Equation 2.6

where:

CR_j = Consumption rate of fish species *j* (kg/day),

CR_{lim} = Maximum allowable fish consumption rate (kg/day), and

P_j = Proportion of a given species in the diet (unitless).

Meal consumption limits may then be calculated for each species as before, using Equation 2.2 (See Section 2.2), with CR_j substituted for CR_{lim} in the equation. Note that Equation 2.6 may be used before or after Equation 2.2, with the same results.

2.4.2. Noncarcinogenic Effects

For noncarcinogenic effects, the equation to calculate consumption limits based on exposure to a single noncarcinogenic chemical in a multiple species diet is similar to Equation 2.3 for a single species. However, in place of C_m, which indicates the chemical concentration in one species, Equation 2.7 uses the equation for C_{tm}, the weighted average chemical concentration across all of the species consumed:

$$CR_{lim} = \frac{RfD \cdot BW}{\sum_{j=1}^{n} (C_{mj} \cdot P_j)} \qquad \text{Equation 2.7}$$

where the parameters are as defined above. The consumption limit for each species is then calculated using Equation 2.6. Meal consumption limits for each species may then be calculated as before, using Equation 2.2.

EXAMPLE: Consumption Limits for Multiple Species, Single Contaminant Exposure

The combined results from a sampling and analysis program and a local fish consumption survey determine that local fishers eat a diet of 30 percent catfish contaminated with 0.006 mg/kg chlordane, and 70 percent trout contaminated with 0.008 mg/kg chlordane. The RfD for chlordane reported in IRIS is 0.00006 mg/kg-d (IRIS, 1993). Since chlordane causes both chronic and carcinogenic effects, consumption limits must be calculated for both health endpoints. The q_1^* for chlordane reported in IRIS is 1.3 per mg/kg-d (IRIS, 1993). The average body weight of a general adult is estimated to be 70 kg.

Carcinogenic Effects: Using a risk level of 10^{-5} and the values specified above, Equation 2.5 yields a daily consumption rate of 0.073 mg/kg, based on carcinogenic endpoints:

$$CR_{lim} = \frac{10^{-5} \cdot 70\ kg}{(0.006\ mg/kg \cdot 0.3 + 0.008\ mg/kg \cdot 0.7) \cdot 1.3\ per\ mg/kg\text{-}d} = 0.073$$

Equation 2.2 is used as before to calculate a meal consumption limit, based on a meal size of 8 oz (0.227 kg):

$$CR_{mm} = \frac{0.073\ kg/d \cdot \frac{365.25}{12}\ d/mo}{0.227\ kg} = 9.8 \approx 9$$

Equation 2.2 yields a meal consumption limit of nine 8-oz meals per month, or three 8-oz meals per 10 days, based on chlordane's carcinogenicity. Equation 2.6 indicates that two 8-oz catfish meals and six 8-oz trout meals per month may be consumed without increased risk of developing cancer:

$$CR_{catfish} = 9\ meals/mo \cdot 0.3 = 2.7 \approx 2\ meals/mo$$

$$CR_{trout} = 9\ meals/mo \cdot 0.7 = 6.3 \approx 6\ meals/mo$$

Note that in both cases the meal consumption limits were rounded down. This is a conservative approach. One might also *round up* the number of meals of the species with the *lower* contaminant concentration, and *round down* the number of meals of the species with the *higher* contaminant concentration, so that the total number of fish meals per month equals that found in Equation 2.5. In this case, since catfish were less contaminated than trout, the consumption limit would be three 8-oz catfish meals and six 8-oz trout meals per month. This approach is based upon the proportion of each type of fish eaten. If the actual proportion differs from that used in the equation, the resulting risks may be higher or lower than the targeted risk level (e.g., 10^{-5}).

Noncarcinogenic Effects: Equation 2.7 is used to calculate the daily consumption limit based on chlordane's chronic health effects, using the RfD rather than the q_1^*.

$$CR_{lim} = \frac{6 \times 10^{-5}\ mg/kg\text{-}d \cdot 70\ kg}{0.006\ mg/kg \cdot 0.3 + 0.008\ mg/kg \cdot 0.7} = 0.570\ kg/day$$

As with carcinogenic effects, Equation 2.2 is used to convert the daily consumption limit of 0.570 kg fish to a meal consumption limit:

$$CR_{mm} = \frac{0.570\ kg/d \cdot \frac{365.25}{12}\ d/mo}{0.227\ kg} = 76.4 \approx 76$$

This analysis indicates that 0.57 kg/d is equivalent to 76 8-oz fish meals per month, or over two 8-oz fish meals per day under this mixed-species diet. This is categorized as unlimited consumption ("UNLIM") in the consumption limit tables in Section 3. Thus, based on the above results, risk managers might choose to issue a consumption advisory for general adults of two (or three) 8-oz catfish meals and six 8-oz trout meals per month based on chlordane's carcinogenic effects, the more sensitive of the two health endpoints, or elect to base their advisories on non-carcinogenic effects. In addition, they may also review the toxicity data and develop exposure limits based on their interpretation of the toxicity data.

2.5. Modification of Consumption Limits for Multiple Contaminant Exposures

Equations 2.5 and 2.7 discussed in Section 2.4 can be further modified to develop consumption limits for multiple chemical exposures across single or multiple species. Section 5 and Volume 3 provide additional information on exposure to multiple chemical contaminants.

Individuals who ingest chemically contaminated fish may be exposed to a number of different chemicals simultaneously. This could occur when: 1) a single fish species is contaminated with several different chemicals, 2) an individual consumes a mixture of species in his or her diet, each contaminated with a different chemical, or, 3) some combination of the above circumstances occurs.

Possible toxic interactions in mixtures of chemicals are usually placed in one of three categories:

- Antagonistic, where the chemical mixture exhibits less toxicity than the chemicals considered individually,
- Synergistic, where the chemical mixture is more toxic than the sum of the individual toxicities of the chemicals in the mixture, and
- Additive, where the toxicity of the chemical mixture is equal to the sum of the toxicities of the individual chemicals in the mixture.

Using available data is especially important in cases where mixtures exhibit synergistic interactions, thereby increasing toxicity. Very little data are available on the toxic interactions between multiple chemicals, however, and no quantitative data on interactions between any of the target analytes considered in this document were located. Some qualitative information is provided in Section 5.

In cases where all of the chemicals in a mixture induce the same health effect by similar modes of action (e.g., cholinesterase inhibition), contaminants may be assumed to contribute additively to risk (EPA, 1986d), unless specific data indicate otherwise. Chemicals in a particular class (e.g., organochlorine or organophosphate pesticides) usually have similar mechanisms of toxicity and produce similar effects. Effects of chemicals and chemical groups are discussed in more detail in Section 5. For mixtures of chemicals that cause similar endpoints, consumption limits are derived by summing the contaminants from all fish species consumed, as discussed below.

Some chemical mixtures may contain chemicals that cause dissimilar health effects. Methods currently do not exist for combining dissimilar health effects to characterize overall health concerns from chemical mixtures. Instead, the risks from these contaminants need to be characterized and presented separately. It is important to review the overall toxicity of a contaminant in evaluating combined risks because most contaminants are capable of causing multiple effects in numerous organ systems at elevated exposures.

2.5.1. Carcinogenic Effects

Cancer evaluations and q_1^*s for most carcinogens are based on animal studies, which are not generally assumed to predict the site of cancer in humans. Consequently, carcinogenic effects are not usually categorized by the cancer site observed in animal studies. Rather, carcinogenic effects are generally assumed to be additive, unless data derived from human studies show them to be otherwise. Carcinogenic effects for the 12 carcinogens considered in this guidance series are assumed to be additive.

Equation 2.8 can be used to calculate daily consumption limits for chemical mixtures of carcinogens in single or multiple fish species. It is similar to Equation 2.1, with the summation of all species and all chemicals substituted for C_m in the denominator:

$$CR_{lim} = \frac{ARL \cdot BW}{\sum_{m=1}^{x}\left(\sum_{j=1}^{n} C_{mj} \cdot P_j\right) \cdot q_1^*{}_m} \qquad \text{Equation 2.8}$$

where:

CR_{lim} = Maximum allowable fish consumption rate (kg/day),

ARL = Maximum acceptable lifetime risk level (unitless),

BW = Consumer body weight (kg),

C_{mj} = Concentration of chemical *m* in species *j* (mg/kg),

P_j = Proportion of a given species in the diet (unitless), and,

q_1^* = Cancer potency, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA ($(mg/kg\text{-}d)^{-1}$),

Meal consumption limits for mixtures of carcinogens are then calculated using Equation 2.2, as above. When only one fish species is involved, Equation 2.8 may be simplified to Equation 2.9, shown below:

$$CR_{lim} = \frac{ARL \cdot BW}{\sum_{m=1}^{x} C_m \cdot q_1^*{}_m} \qquad \text{Equation 2.9}$$

where the variables are as defined above.

2.5.2. Noncarcinogenic Effects

Equation 2.10, used to calculate daily consumption limits for noncarcinogenic chemical mixtures in single or multiple fish species, is similar to Equation 2.3, with the summation of all species and all chemicals assumed to act additively substituted for C_m in the denominator, and their respective RfDs in the numerator:

$$CR_{lim} = \sum_{m=1}^{x} \left(\frac{RfD_m}{\sum_{j=1}^{n} (C_{mj} \cdot P_j)} \right) \cdot BW \qquad \text{Equation 2.10}$$

where the parameters are defined as above. Meal consumption limits are then calculated using Equation 2.2, as above. Again, when only one fish species is involved, Equation 2.10 can be simplified to Equation 2.11, shown below:

$$CR_{lim} = \sum_{m=1}^{x} \left(\frac{RfD_m}{C_m} \right) \cdot BW \qquad \text{Equation 2.11}$$

where the variables are as defined above. Note that Equations 2.10 and 2.11 may **not** be used for contaminants causing dissimilar health effects.

EXAMPLE: Consumption Limits for Single Species, Multiple Contaminant Exposure

A single fish species is contaminated with 0.04 mg chlordane/kg and 0.01 mg heptachlor epoxide/kg. A maximum acceptable risk level of 10^{-5} and a general adult body weight of 70 kg are used. Because chlordane and heptachlor epoxide cause both carcinogenic and chronic systemic health effects, both health endpoints must be considered in establishing consumption limits for these chemicals.

Carcinogenic:

The q_1^* for chlordane reported in IRIS is 1.3 per mg/kg-d (IRIS, 1993). The q_1^* for heptachlor epoxide reported in IRIS is 9.1 per mg/kg-d (IRIS, 1993). Equation 2.9 is used to calculate daily consumption limits based on the combined carcinogenic effects of both contaminants:

$$CR_{lim} = \frac{10^{-5} \cdot 70}{(0.04 \cdot 1.3) + (0.01 \cdot 9.1)} = 0.005 \ kg/d$$

A daily consumption limit of 0.005 kg fish per day is calculated. Using Equation 2.2, this daily consumption limit is converted to a meal consumption limit of one 4-oz meal per month (or six 8-oz meals per year).

Noncarcinogenic:

Chlordane and heptachlor[10] are both organochlorine pesticides and cause many similar noncarcinogenic effects. Adverse liver effects formed the basis of the RfDs for both chemicals (IRIS, 1993). A combined daily consumption limit based on an RfD of 6×10^{-5} mg/kg-d for chlordane and 1.3×10^{-5} mg/kg-d for heptachlor was calculated using Equation 2.11:

$$CR_{lim} = \left(\frac{6 \ x \ 10^{-5} \ mg/kg\text{-}d}{0.04 \ mg/kg} + \frac{1.3 \ x \ 10^{-5} \ mg/kg\text{-}d}{0.01 \ mg/kg} \right) \cdot 70 \ kg = 0.2 \ kg/d$$

Equation 2.11 yields a daily consumption rate of 0.2 kg fish per day, at the contaminant concentrations described above. Using Equation 2.2, a meal consumption limit of 26 meals per month is calculated. This meal frequency falls under unlimited consumption ("UNLIM") in the consumption limit tables in Section 3.

Therefore, based on the carcinogenic and chronic systemic consumption limits calculated for combined heptachlor epoxide and chlordane contamination, a risk manager may choose to advise 1) limiting fish consumption to six 8-oz meals

[10] Heptachlor epoxide is a metabolite of heptachlor, a pesticide. When heptachlor is released into the environment, it quickly breaks down into heptachlor epoxide. Therefore, the toxicity values used in this document are for heptachlor epoxide, not heptachlor (See Chapter 5).

per year, based on the combined carcinogenic effects, or 2) unlimited consumption, based on non-carcinogenic effects.[11]

2.5.3. Species-Specific Consumption Limits in a Multiple Species Diet

To calculate the risk-based consumption limits for each species in a multiple species diet the following equation is used for both carcinogenic and non-carcinogenic toxicity:

$$CR_j = CR_{lim} \cdot P_j \qquad \text{Equation 2.6}$$

where the variables are as defined above. CR_{lim} is calculated using Equations 2.8 or 2.10, for carcinogenic and non-carcinogenic toxicity respectively. As with the consumption limits for single chemicals, these consumption limits are only valid if the assumed mix of species in the diet is correct, and if the contaminant concentrations in each species are accurate.

EXAMPLE: Consumption Limits for Multiple Contaminant, Multiple Species Exposure

Chlorpyrifos and carbophenothion both cause cholinesterase inhibition, so are considered together when developing meal consumption limits. The RfD for chlorpyrifos reported in IRIS is 0.003 mg/kg-d (IRIS, 1993), while the RfD for carbophenothion is 0.00013 mg/kg-d (IRIS, 1993).

A local fish consumption survey reveals that adult fishers consume trout and catfish at a ratio of 70:30, respectively. A sampling and analysis program reports chlorpyrifos and carbophenothion contamination in both species. Trout are contaminated with 4.0 mg/kg chlorpyrifos/kg fillet and 0.3 mg carbophenothion/kg fillet. Catfish are contaminated with 6.0 mg chlorpyrifos/kg fillet and 0.8 mg carbophenothion/kg fillet. Given a general adult body weight of 70 kg, a risk-based consumption limit of 0.065 kg fish per day is calculated using Equation 2.10:

$$CR_{lim} = \left(\frac{0.003}{(4.0 \cdot 0.7) + (6.0 \cdot 0.3)} + \frac{0.00013}{(0.3 \cdot 0.7) + (0.8 \cdot 0.3)} \right) \cdot 70 = 0.065 \ kg/$$

[11] In addition, risk assessors or risk managers may also elect to use a third health endpoint (e.g., developmental toxicity), based on their review of the toxicological data.

Using Equation 2.2, a meal consumption limit of eight 8-oz meals per month is derived. Note that if chlorpyrifos and carbophenothion did not cause the same health endpoint, then separate meal consumption limits would have to be calculated for each as described in Section 2.4.2, with the more protective meal consumption limit usually serving as the basis for a fish consumption advisory (See Section 2.5.4).

Equation 2.6 is used to determine meal consumption limits for trout and catfish, based on a diet of 70 percent trout and 30 percent catfish:

$$CR_{trout} = 8\ 8\text{-}oz\ meals/mo \cdot 0.7 = 5.6 \approx 5\ 8\text{-}oz\ meals/mo$$

$$CR_{catfish} = 8\ 8\text{-}oz\ meals/mo \cdot 0.3 = 2.4 \approx 2\ 8\text{-}oz\ meals/mo$$

According to Equation 2.6, a general adult may safely consume five 8-oz meals of trout per month and two 8-oz meals of catfish per month. Again, as mentioned in Section 2.4.2, rounding down both species-specific consumption limits is a conservative approach. One might also *round up* the number of meals of the species with the *lower* contaminant concentration, and *round down* the number of meals of the species with the *higher* contaminant concentration, so that the total number of fish meals per month equals that found in Equation 2.10. In this case, since trout were less contaminated than catfish, the species-specific consumption limit would be six 8-oz trout meals and two 8-oz catfish meals per month.

2.6. Choice of Consumption Limits

Where chemicals found in a given species cause dissimilar health effects, dose addition is not often justified scientifically; if dose addition is used in these cases, it must be supported by biological plausibility (EPA, 1986d). Thus, in most cases where chemicals cause different effects, readers are advised to use the consumption limits for the contaminant that results in the most protective fish consumption advisory for the population of concern. This approach may result in different advisories for each subpopulation of concern, since different subpopulations may have varying health effects of concern. It is important to compare the consumption limits calculated for all chemicals found in a given species and choose the most appropriate consumption limits for each consumer population. This selection may be considered a risk management decision or a medical/toxicological decision.

If, for example, local sampling and analysis programs and fish consumption surveys determine that consumers are exposed to all four of the contaminants

discussed in the above examples (chlordane, heptachlor epoxide, chlorpyrifos and carbophenothion), then risk assessors could consider a number of separate fish consumption limits for the chemical mixture:

- A consumption limit could be based on the combined carcinogenic effects of chlordane and heptachlor epoxide, as described in the first example above,

- A consumption limit could be based on chronic liver damage caused by exposure to the chlordane and heptachlor, as shown in the first example above,

- A consumption limit could be developed for the chronic health effect (cholinesterase inhibition) caused by exposure to both chlorpyrifos and carbophenothion, as shown in the second example above, and

- Consumption limits could be based on new study data reviewed by readers (e.g., xenoestrogenic effects of organochlorines, or developmental effects), using the equations provided in this document.[12]

Readers might then base fish consumption advisories for this particular chemical mixture on the most appropriate of the consumption limits for each population of concern. Decisions regarding selection and implementation of consumption limits will be discussed in Volume 3 of this series.

Most fish contaminants have the potential to cause multiple adverse health effects, given sufficiently-high exposure levels. Readers are advised to examine the chemical profiles in Section 5 to determine the most appropriate health endpoints on which to base fish consumption limits. Many of the chronic RfDs for organophosphates, for example, are currently based on cholinesterase inhibition as the critical health endpoint of concern. However, the EPA's Scientific Advisory Board recently raised concerns about using cholinesterase inhibition as a critical endpoint in the absence of clinical symptoms (EPA, 1993q; see Section 5 for further discussion). For those who wish to calculate alternative exposure limits for these or other fish contaminants for use in developing alternative consumption limits, Section 5 provides a summary of current EPA methods for doing so and sources of additional guidance.

[12] Intake limits based on developmental or other effects can be calculated using the same equations as are used for chronic health endpoints throughout Section 2.

Table __–__. Monthly Consumption for Chronic Systemic Health Endpoints

Chemical Name:		
Population:		
Body Weight:		kg
Reference Dose:		mg/kg–d
Detection Limit		mg/kg

Risk–Based Consumption Limit (meals per month)				
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			

Table __-__. Intake Limits for Carcinogenic Health Endpoints

Chemical Name:		
Population:		
Body Weight:		kg
Cancer Potency Factor:		per mg/kg-d
Detection Limit:		mg/kg

Risk-Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}

SECTION 3

RISK-BASED CONSUMPTION LIMIT TABLES

3.1. Overview and Section Organization

This section provides consumption limit tables for chronic and carcinogenic health endpoints for the general adult population, and chronic health endpoints for young children for each of the 23 chemical analytes listed in Section 1. In addition, consumption limit tables based on developmental effects associated with exposure to methylmercury are included for women of reproductive age and children. The consumption limits in these tables were calculated using Equations 2.1 to 2.3 and the default values for each of the variables described in Sections 2.2 and 2.3.

Variables involved in calculating the consumption limits include fish meal size, consumer body weight, contaminant concentration, and maximum acceptable risk level (for carcinogenic health endpoints).[1] Default values for these variables are listed in Section 2 and described further in Section 4.

Current EPA risk values (cancer potency factors and RfDs) were also used in the consumption limit calculations, as described in Section 2.2 and Section 5. Because there are new toxicity data for some target analytes not reflected in the current RfDs, readers are encouraged to review Section 5.6, which contains a summary of toxicity data for the target analytes. Methods for using this information to generate additional consumption limits are discussed in Section 5.3 and 5.4.

Most target analytes are known to cause multiple effects at elevated exposure levels, according to the results of animal studies. However, because the levels of fish contaminants typically ingested by non-commercial fish consumers are lower than those used in animal studies, consumers may experience only one or a few of the known chronic effects, and/or only the more susceptible

[1] Three maximum acceptable risk levels are offered as options in the consumption limit tables. Selection of the most appropriate risk level is a risk management decision to be made at the state, local or tribal level and is discussed in Volume 3.

members of the population may develop the health endpoints of concern. For example, analytes which cause developmental toxicity pose risk to children and women who are having or are expecting to have children (See Section 5 for discussion). Readers are advised to consider these data in reviewing the consumption limit tables and the toxicity discussions in Section 5. Alternatively, some effects are of concern to all exposed individuals. For example, women of reproductive age do not necessarily develop cancer or chronic exposure health effects at different rates than others in the general population. Consequently, the consumption limit tables for carcinogenic and chronic exposure toxicity for the general population are also applicable to this subgroup.[2]

Monthly consumption limits were developed for carcinogenic health endpoints, while ten-day and monthly consumption limit tables were derived for chronic exposure health endpoints. Both the 10-day and the monthly consumption limit tables are based on the same chronic reference doses because there are not currently reference doses for acute health endpoints available from the EPA RfD/RfC Workgroup (See Section 5). Ten-day consumption limits for chronic exposure health endpoints apply to short-term recreational and subsistence fishers, while monthly consumption limits pertain to both seasonal (e.g., three-month) and year-round non-commercial fish consumers.

Ten-day consumption limit tables for chronic health endpoints were developed for both adults and children, while monthly consumption limit tables were developed for general adults only. Monthly consumption limit tables were not calculated for children because, for example, the lower limit of allowable consumption (i.e., six meals per year) represents sixty times the RfD, based on the methodology used in this document (See Section 4 for discussion). This was not considered appropriate. If it is anticipated that children's exposure will occur over an extended period of time, readers may use the ten-day limits for longer periods by adding time increments as appropriate. Alternatively, readers may wish to calculate consumption limits for children based on developmental toxicity data discussed in Chapter 5 for some of the target analytes. Chapter 5 also contains a description of a methodology which can be used to derive risk-based consumption limits for developmental and other toxicities.

Each consumption table lists, by chemical and fisher population, the maximum fish meals per unit time that may be safely eaten by the population of concern. Limits are given for a range of fish meal sizes, population members (adults and children), and contaminant levels. In addition, for carcinogens, limits are

[2] Note that women of reproductive age are defined as a separate population only for health intake limits based on developmental health effects.

provided for a range of maximum acceptable risk levels. Readers may use these tables by: 1) determining the chemical concentration found in local sampling and analysis programs, 2) determining the meal size (and risk level, for carcinogens) they wish to use, 3) locating the point where the parameters intersect, and, 4) reading the value for maximum safe number of meals per month that may be eaten for each contaminant, based on its reference dose and/or cancer potency value. All consumption limits have been rounded down to the nearest integer, with the exception of the limits of six meals per year, which are expressed as 0.5 meals per month in the tables.

Some of the contaminant concentrations in the tables are below current laboratory detection limits. Because of improvements in technology, however, chemical detection limits regularly decrease. The concentrations which are currently below the detection limits are provided so that risk managers may use them once detection is possible. Current detection limits are listed at the top of each of the consumption tables.

For the purposes of this document, unlimited safe fish consumption (represented by "UNLIM" in the tables) has been defined as a consumption limit of more than 17 fish meals per month (four fish meals per week) for the monthly consumption limit tables, and more than one meal per day for the 10-day tables.[3] The definition of no safe fish consumption used in this document (represented by "NONE" in the tables) is a consumption limit of less than one meal in two months for the monthly tables, and less than one meal per 10 days for the 10-day tables.[4] These definitions do not represent EPA recommendations. Rather, it is the responsibility of risk managers to define "unlimited" and "no" fish consumption, based on a variety of considerations, including adverse health effects and the consumption patterns of the populations of interest. Note that the chemical concentrations listed are only those that fall in between these two parameters, and that they are not listed in a linear fashion. Directions for calculating other meal frequencies not found in the tables are given in Section 2.

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[3] i.e., in the case of the monthly consumption limits, where risk calculations indicate that more than 17 meals per month may be eaten without incurring undue risk of cancer or developing adverse chronic health effects, risk managers may choose to not advise restricting consumption of non-commercial fish.

[4] i.e., under the definition of no consumption for the monthly tables, where risk calculations indicate that six fish meals per year may not be safely eaten, risk managers may choose to advise zero consumption of contaminated non-commercial fish.

Specific guidance regarding the use of these limits in a fish advisory program will be provided in *Volume 3: Risk Management*. Readers are encouraged to review this and the other documents in the series regarding selection of consumption limits for their fish advisory programs. Fish advisories involve many factors that are not represented in these tables, including societal, economic, nutritional, and cultural impacts. These factors are discussed in Volume 3.

3.2. Consumption Limit Tables

Table 3-1 provides a directory of the consumption limits given in Section 3. Readers using the tables as a basis for fish consumption advisories should note that the values given in the tables are valid **only** for single contaminants in single species diets. Section 2 describes the use of the tables to calculate consumption limits for multiple contaminants and multiple species diets.

Table 3–1. Tables Contained in Section 3							
Chemical Contaminant	Location of Toxicity Data (Section no.)[a]	Table Number					
		General Population 10–Day[d]	Women of Childbearing Age 10–Day[e]	General Population Monthly[d]	Women of Childbearing Age Monthly[e]	General Population Carcinogenic	Children 10–Day[d]
Cadmium	5.6.21	3–2		3–3			3–4
Carbofenothion	5.6.12	3–5		3–6			3–7
Chlordane	5.6.1	3–8		3–9		3–10	3–11
Chlorpyrifos	5.6.13	3–12		3–13			3–14
DDT, DDD, DDE	5.6.2	3–15		3–16		3–17	3–18
Diazinon	5.6.14	3–19		3–20			3–21
Dicofol	5.6.3	3–22		3–23		3–24	3–25
Dieldrin	5.6.4	3–26		3–27		3–28	3–29
Dioxin	5.6.20					3–30	
Disulfoton	5.6.15	3–31		3–32			3–33
Endosulfan I,II	5.6.5	3–34		3–35			3–36
Endrin	5.6.6	3–37		3–38			3–39
Ethion	5.6.16	3–40		3–41			3–42
Heptachlor Epoxide	5.6.7	3–43		3–44		3–45	3–46
Hexachlorobenzene	5.6.8	3–47		3–48		3–49	3–50
Lindane	5.6.9	3–51		3–52		3–53	3–54
Methylmercury	5.6.22	3–55	3–56	3–57	3–58		3–59
Mirex	5.6.10	3–60		3–61		3–62	3–63
Oxyfluorfen	5.6.18	3–64		3–65		3–66	3–67
PCBs[b]	5.6.19	3–68		3–69		3–70	3–71
Selenium	5.6.23	3–72		3–73			3–74
Terbufos	5.6.17	3–75		3–76			3–77
Toxaphene	5.6.11	3–78		3–79		3–80	3–81

[a] Section 5 describes the studies used by EPA to develop the q_1^*s and RfDs used in these tables.
[b] Intake limits for carcinogenicity of PCBs are based on Aroclor 1260. Chronic toxicity for PCBs is based on Aroclor 1254.
[d] Based on non–carcinogenic toxicity (i.e., chronic RfDs)
[e] Based on developmental toxicity
Shaded cells represent variables for which no health intake limits have been developed.

Table 3–2. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Cadmium
Population:	General
Body Weight:	70 kg
Reference Dose:	0.001 mg/kg–d
Detection Limit:	0.005 mg/kg

Risk–Based Consumption Limit (meals per 10 days)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			
	4	8	12	16
<0.2	UNLIM	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	10	7
0.3	UNLIM	10	6	5
0.4	UNLIM	7	5	3
0.5	UNLIM	6	4	3
0.6	10	5	3	2
0.7	8	4	2	2
0.8	7	3	2	1
0.9	6	3	2	1
1	6	3	2	1
2	3	1	1	NONE
3	2	1	NONE	NONE
4	1	NONE	NONE	NONE
5	1	NONE	NONE	NONE
6	1	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–3. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Cadmium
Population:	General
Body Weight:	70 kg
Reference Dose:	0.001 mg/kg–d
Detection Limit	0.005 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.3	UNLIM	UNLIM	UNLIM	UNLIM
0.3	UNLIM	UNLIM	UNLIM	15
0.4	UNLIM	UNLIM	15	11
0.5	UNLIM	UNLIM	12	9
0.6	UNLIM	15	10	7
0.7	UNLIM	13	8	6
0.8	UNLIM	11	7	5
0.9	UNLIM	10	6	5
1	UNLIM	9	6	4
2	9	4	3	2
3	6	3	2	1
4	4	2	1	1
5	3	1	1	0.5
6	3	1	1	0.5
7	2	1	0.5	0.5
8	2	1	0.5	0.5
9	2	1	0.5	0.5
10	1	0.5	0.5	NONE
20	0.5	NONE	NONE	NONE
30	0.5	NONE	NONE	NONE
40	0.5	NONE	NONE	NONE
>40	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–4. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Cadmium
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	0.001 mg/kg–d
Detection Limits:	0.005 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days)		
	Meal Size (oz)		
	3	4	8
<0.06	UNLIM	UNLIM	UNLIM
0.06	UNLIM	UNLIM	10
0.07	UNLIM	UNLIM	9
0.08	UNLIM	UNLIM	7
0.09	UNLIM	UNLIM	7
0.1	UNLIM	UNLIM	6
0.2	8	6	3
0.3	5	4	2
0.4	4	3	1
0.5	3	2	1
0.6	2	2	1
0.7	2	1	NONE
0.8	2	1	NONE
0.9	1	1	NONE
1	1	1	NONE
2	NONE	NONE	NONE
3	NONE	NONE	NONE
>3	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–5. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Carbophenothion
Population:	General
Body Weight:	70 kg
Reference Dose:	1E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days)			
	Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	UNLIM	10
0.03	UNLIM	UNLIM	8	6
0.04	UNLIM	10	6	5
0.05	UNLIM	8	5	4
0.06	UNLIM	6	4	3
0.07	UNLIM	5	3	2
0.08	9	5	3	2
0.09	8	4	2	2
0.1	7	4	2	2
0.2	3	2	1	1
0.3	2	1	NONE	NONE
0.4	1	1	NONE	NONE
0.5	1	NONE	NONE	NONE
0.6	1	NONE	NONE	NONE
0.7	1	NONE	NONE	NONE
0.8	NONE	NONE	NONE	NONE
0.9	NONE	NONE	NONE	NONE
1	NONE	NONE	NONE	NONE
>1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–6. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Carbophenothion
Population:	General
Body Weight:	70 kg
Reference Dose:	1E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month)			
	Meal Size (oz)			
	4	8	12	16
<0.04	UNLIM	UNLIM	UNLIM	UNLIM
0.04	UNLIM	UNLIM	UNLIM	15
0.05	UNLIM	UNLIM	16	12
0.06	UNLIM	UNLIM	13	10
0.07	UNLIM	17	11	8
0.08	UNLIM	15	10	7
0.09	UNLIM	13	9	6
0.1	UNLIM	12	8	6
0.2	13	6	4	3
0.3	8	4	2	2
0.4	6	3	2	1
0.5	4	2	1	1
0.6	4	2	1	1
0.7	3	1	1	0.5
0.8	3	1	1	0.5
0.9	2	1	0.5	0.5
1	2	1	0.5	0.5
2	1	0.5	NONE	NONE
3	0.5	NONE	NONE	NONE
4	0.5	NONE	NONE	NONE
>4	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–7. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Carbophenothion
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	1E–04 mg/kg–d
Detection Limits:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.008	UNLIM	UNLIM	UNLIM
0.008	UNLIM	UNLIM	10
0.009	UNLIM	UNLIM	9
0.01	UNLIM	UNLIM	8
0.02	UNLIM	8	4
0.03	7	5	2
0.04	5	4	2
0.05	4	3	1
0.06	3	2	1
0.07	3	2	1
0.08	2	2	1
0.09	2	1	NONE
0.1	2	1	NONE
0.2	1	NONE	NONE
0.3	NONE	NONE	NONE
0.4	NONE	NONE	NONE
>0.4	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–8. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Chlordane
Population:	General
Body Weight:	70 kg
Reference Dose:	6E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.009	UNLIM	UNLIM	UNLIM	UNLIM
0.009	UNLIM	UNLIM	UNLIM	10
0.01	UNLIM	UNLIM	UNLIM	9
0.02	UNLIM	9	6	4
0.03	UNLIM	6	4	3
0.04	9	4	3	2
0.05	7	3	2	1
0.06	6	3	2	1
0.07	5	2	1	1
0.08	4	2	1	1
0.09	4	2	1	1
0.1	3	1	1	NONE
0.2	1	NONE	NONE	NONE
0.3	1	NONE	NONE	NONE
0.4	NONE	NONE	NONE	NONE
0.5	NONE	NONE	NONE	NONE
0.6	NONE	NONE	NONE	NONE
0.7	NONE	NONE	NONE	NONE
>0.7	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–9. Monthly Consumption Limits for Chronic Systemic *Health Endpoints*

Chemical Name:	Chlordane
Population:	General
Body Weight:	70 kg
Reference Dose:	6E–05 mg/kg–d
Detection Limit	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	UNLIM	14
0.03	UNLIM	UNLIM	12	9
0.04	UNLIM	14	9	7
0.05	UNLIM	11	7	5
0.06	UNLIM	9	6	4
0.07	16	8	5	4
0.08	14	7	4	3
0.09	12	6	4	3
0.1	11	5	3	2
0.2	5	2	1	1
0.3	3	1	1	0.5
0.4	2	1	0.5	0.5
0.5	2	1	0.5	0.5
0.6	1	0.5	0.5	NONE
0.7	1	0.5	0.5	NONE
0.8	1	0.5	NONE	NONE
0.9	1	0.5	NONE	NONE
1	1	0.5	NONE	NONE
2	0.5	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–10. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name: Chlordane
Population: General
Body Weight: 70 kg
Cancer Potency Factor: 1.3 per mg/kg–d
Detection Limit: 1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	9
0.0006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	8	UNLIM	UNLIM	6
0.0008	UNLIM	UNLIM	17	UNLIM	UNLIM	9	UNLIM	UNLIM	6	UNLIM	UNLIM	4
0.001	UNLIM	UNLIM	14	UNLIM	UNLIM	7	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.002	UNLIM	UNLIM	7	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	UNLIM	1
0.004	UNLIM	UNLIM	3	UNLIM	UNLIM	1	UNLIM	12	1	UNLIM	9	0.5
0.006	UNLIM	UNLIM	2	UNLIM	12	1	UNLIM	8	0.5	UNLIM	6	0.5
0.008	UNLIM	17	1	UNLIM	9	0.5	UNLIM	6	0.5	UNLIM	4	NONE
0.01	UNLIM	14	1	UNLIM	7	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.02	UNLIM	7	0.5	UNLIM	3	NONE	UNLIM	2	NONE	UNLIM	1	NONE
0.04	UNLIM	3	NONE	UNLIM	1	NONE	12	1	NONE	9	0.5	NONE
0.06	UNLIM	2	NONE	12	1	NONE	8	0.5	NONE	6	0.5	NONE
0.08	17	1	NONE	9	0.5	NONE	6	0.5	NONE	4	NONE	NONE
0.1	14	1	NONE	7	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.2	7	0.5	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
0.4	3	NONE	NONE	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE
0.6	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.8	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
1	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
2	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
All values were rounded down to the nearest whole meal size.
Note nonlinear scale of concentration values.
ARL = Acceptable Risk Level

Table 3–11. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Chlordane
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	6E–05 mg/kg–d
Detection Limits:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.004	UNLIM	UNLIM	UNLIM
0.004	UNLIM	UNLIM	9
0.005	UNLIM	UNLIM	7
0.006	UNLIM	UNLIM	6
0.007	UNLIM	UNLIM	5
0.008	UNLIM	9	4
0.009	UNLIM	8	4
0.01	10	7	3
0.02	5	3	1
0.03	3	2	1
0.04	2	1	NONE
0.05	2	1	NONE
0.06	1	1	NONE
0.07	1	1	NONE
0.08	1	NONE	NONE
0.09	1	NONE	NONE
0.1	1	NONE	NONE
0.2	NONE	NONE	NONE
>0.2	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–12. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Chlorpyrifos
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–03 mg/kg–d
Detection Limit:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.5	UNLIM	UNLIM	UNLIM	UNLIM
0.5	UNLIM	UNLIM	UNLIM	9
0.6	UNLIM	UNLIM	10	7
0.7	UNLIM	UNLIM	8	6
0.8	UNLIM	UNLIM	7	5
0.9	UNLIM	10	6	5
1	UNLIM	9	6	4
2	9	4	3	2
3	6	3	2	1
4	4	2	1	1
5	3	1	1	NONE
6	3	1	1	NONE
7	2	1	NONE	NONE
8	2	1	NONE	NONE
9	2	1	NONE	NONE
10	1	NONE	NONE	NONE
20	NONE	NONE	NONE	NONE
30	NONE	NONE	NONE	NONE
>30	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–13. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Chlorpyrifos
Population:	General
Body Weight:	70
Reference Dose:	3E–03 mg/kg–d
Detection Limit:	3E–03 mg/kg

Risk–Based Consumption Limit (meals per month)				
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (kg)			
	4	8	12	16
<0.8	UNLIM	UNLIM	UNLIM	UNLIM
0.8	UNLIM	UNLIM	UNLIM	17
0.9	UNLIM	UNLIM	UNLIM	15
1	UNLIM	UNLIM	UNLIM	14
2	UNLIM	14	9	7
3	UNLIM	9	6	4
4	14	7	4	3
5	11	5	3	2
6	9	4	3	2
7	8	4	2	2
8	7	3	2	1
9	6	3	2	1
10	5	2	1	1
20	2	1	NONE	NONE
30	1	NONE	NONE	NONE
40	1	NONE	NONE	NONE
50	1	NONE	NONE	NONE
>50	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–14. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Chlorpyrifos
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	3E–03 mg/kg–d
Detection Limits:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.2	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	9
0.3	UNLIM	UNLIM	6
0.4	UNLIM	9	4
0.5	10	7	3
0.6	8	6	3
0.7	7	5	2
0.8	6	4	2
0.9	5	4	2
1	5	3	1
2	2	1	NONE
3	1	1	NONE
4	1	NONE	NONE
5	1	NONE	NONE
6	NONE	NONE	NONE
7	NONE	NONE	NONE
8	NONE	NONE	NONE
9	NONE	NONE	NONE
10	NONE	NONE	NONE
>10	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–15. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	DDT/DDE/DDD
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.08	UNLIM	UNLIM	UNLIM	UNLIM
0.08	UNLIM	UNLIM	UNLIM	9
0.09	UNLIM	UNLIM	UNLIM	8
0.1	UNLIM	UNLIM	10	7
0.2	UNLIM	7	5	3
0.3	10	5	3	2
0.4	7	3	2	1
0.5	6	3	2	1
0.6	5	2	1	1
0.7	4	2	1	1
0.8	3	1	1	NONE
0.9	3	1	1	NONE
1	3	1	1	NONE
2	1	NONE	NONE	NONE
3	1	NONE	NONE	NONE
4	NONE	NONE	NONE	NONE
5	NONE	NONE	NONE	NONE
6	NONE	NONE	NONE	NONE
>6	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–16. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	DDT/DDE/DDD
Fisher Population:	General
Fisher Body Weight:	70 kg
Reference Dose:	5E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.2	UNLIM	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	15	11
0.3	UNLIM	15	10	7
0.4	UNLIM	11	7	5
0.5	UNLIM	9	6	4
0.6	15	7	5	3
0.7	13	6	4	3
0.8	11	5	3	2
0.9	10	5	3	2
1	9	4	3	2
2	4	2	1	1
3	3	1	1	0.5
4	2	1	0.5	0.5
5	1	0.5	0.5	NONE
6	1	0.5	0.5	NONE
7	1	0.5	NONE	NONE
8	1	0.5	NONE	NONE
9	1	0.5	NONE	NONE
10	0.5	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–17. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	DDT/DDE/DDD
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	3E–01 per mg/kg–d
Detection Limits:	1E–04 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	17
0.001	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	13
0.002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	13	UNLIM	UNLIM	9	UNLIM	UNLIM	6
0.004	UNLIM	UNLIM	13	UNLIM	UNLIM	6	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.006	UNLIM	UNLIM	9	UNLIM	UNLIM	4	UNLIM	UNLIM	3	UNLIM	UNLIM	2
0.008	UNLIM	UNLIM	6	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	17	1
0.01	UNLIM	UNLIM	5	UNLIM	UNLIM	2	UNLIM	UNLIM	1	UNLIM	13	1
0.02	UNLIM	UNLIM	2	UNLIM	13	1	UNLIM	9	0.5	UNLIM	6	0.5
0.04	UNLIM	13	1	UNLIM	6	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.06	UNLIM	9	0.5	UNLIM	4	NONE	UNLIM	3	NONE	UNLIM	2	NONE
0.08	UNLIM	6	NONE	UNLIM	3	NONE	UNLIM	2	NONE	17	1	NONE
0.1	UNLIM	5	NONE	UNLIM	2	NONE	UNLIM	1	NONE	13	1	NONE
0.2	UNLIM	2	NONE	13	1	NONE	9	0.5	NONE	6	0.5	NONE
0.4	13	1	NONE	6	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.6	9	0.5	NONE	4	NONE	NONE	3	NONE	NONE	2	NONE	NONE
0.8	6	NONE	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
1	5	NONE	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
2	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
4	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
6	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>6	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–18. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	DDT/DDE/DDD
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	5E–04
Detection Limits:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.03	UNLIM	UNLIM	UNLIM
0.03	UNLIM	UNLIM	10
0.04	UNLIM	UNLIM	7
0.05	UNLIM	UNLIM	6
0.06	UNLIM	10	5
0.07	UNLIM	9	4
0.08	10	7	3
0.09	9	7	3
0.1	8	6	3
0.2	4	3	1
0.3	2	2	1
0.4	2	1	NONE
0.5	1	1	NONE
0.6	1	1	NONE
0.7	1	NONE	NONE
0.8	1	NONE	NONE
0.9	NONE	NONE	NONE
1	NONE	NONE	NONE
>1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–19. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Diazinon
Population:	General
Body Weight:	70 kg
Reference Dose:	9E–05 mg/kg–d
Detection Limit:	5E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days)			
	Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	9	6
0.03	UNLIM	9	6	4
0.04	UNLIM	6	4	3
0.05	UNLIM	5	3	2
0.06	9	4	3	2
0.07	7	3	2	1
0.08	6	3	2	1
0.09	6	3	2	1
0.1	5	2	1	1
0.2	2	1	NONE	NONE
0.3	1	NONE	NONE	NONE
0.4	1	NONE	NONE	NONE
0.5	1	NONE	NONE	NONE
0.6	NONE	NONE	NONE	NONE
0.7	NONE	NONE	NONE	NONE
0.8	NONE	NONE	NONE	NONE
0.9	NONE	NONE	NONE	NONE
1	NONE	NONE	NONE	NONE
>1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–20. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Diazinon
Population:	General
Body Weight:	70 kg
Reference Dose:	9E–05 mg/kg–d
Detection Limit:	5E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.03	UNLIM	UNLIM	UNLIM	UNLIM
0.03	UNLIM	UNLIM	UNLIM	14
0.04	UNLIM	UNLIM	14	10
0.05	UNLIM	16	11	8
0.06	UNLIM	14	9	7
0.07	UNLIM	12	8	6
0.08	UNLIM	10	7	5
0.09	UNLIM	9	6	4
0.1	16	8	5	4
0.2	8	4	2	2
0.3	5	2	1	1
0.4	4	2	1	1
0.5	3	1	1	0.5
0.6	2	1	0.5	0.5
0.7	2	1	0.5	0.5
0.8	2	1	0.5	0.5
0.9	1	0.5	0.5	NONE
1	1	0.5	0.5	NONE
2	0.5	NONE	NONE	NONE
3	0.5	NONE	NONE	NONE
>3	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–21. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Diazinon
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	9E–05 mg/kg–d
Detection Limits:	5E–02 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.006	UNLIM	UNLIM	UNLIM
0.006	UNLIM	UNLIM	9
0.007	UNLIM	UNLIM	8
0.008	UNLIM	UNLIM	7
0.009	UNLIM	UNLIM	6
0.01	UNLIM	UNLIM	5
0.02	7	5	2
0.03	5	3	1
0.04	3	2	1
0.05	3	2	1
0.06	2	1	NONE
0.07	2	1	NONE
0.08	1	1	NONE
0.09	1	1	NONE
0.1	1	1	NONE
0.2	NONE	NONE	NONE
0.3	NONE	NONE	NONE
>0.3	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–22. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Dicofol
Population:	General
Body Weight:	70 kg
Reference Dose:	1E–03 mg/kg–d
Detection Limit:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.2	UNLIM	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	10	7
0.3	UNLIM	10	6	5
0.4	UNLIM	7	5	3
0.5	UNLIM	6	4	3
0.6	10	5	3	2
0.7	8	4	2	2
0.8	7	3	2	1
0.9	6	3	2	1
1	6	3	2	1
2	3	1	1	NONE
3	2	1	NONE	NONE
4	1	NONE	NONE	NONE
5	1	NONE	NONE	NONE
6	1	NONE	NONE	NONE
7	NONE	NONE	NONE	NONE
8	NONE	NONE	NONE	NONE
9	NONE	NONE	NONE	NONE
10	NONE	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–23. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Dicofol
Population:	General
Body Weight:	70 kg
Reference Dose:	1E–03 mg/kg–d
Detection Limit:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.3	UNLIM	UNLIM	UNLIM	UNLIM
0.3	UNLIM	UNLIM	UNLIM	15
0.4	UNLIM	UNLIM	15	11
0.5	UNLIM	UNLIM	12	9
0.6	UNLIM	15	10	7
0.7	UNLIM	13	8	6
0.8	UNLIM	11	7	5
0.9	UNLIM	10	6	5
1	UNLIM	9	6	4
2	9	4	3	2
3	6	3	2	1
4	4	2	1	1
5	3	1	1	0.5
6	3	1	1	0.5
7	2	1	0.5	0.5
8	2	1	0.5	0.5
9	2	1	0.5	0.5
10	1	0.5	0.5	NONE
20	0.5	NONE	NONE	NONE
30	0.5	NONE	NONE	NONE
40	0.5	NONE	NONE	NONE
>40	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–24. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Dicofol
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:*	3E–01 per mg/kg–d
Detection Limit:	3E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	17
0.001	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	13
0.002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	13	UNLIM	UNLIM	9	UNLIM	UNLIM	6
0.004	UNLIM	UNLIM	13	UNLIM	UNLIM	6	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.006	UNLIM	UNLIM	9	UNLIM	UNLIM	4	UNLIM	UNLIM	3	UNLIM	UNLIM	2
0.008	UNLIM	UNLIM	6	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	17	1
0.01	UNLIM	UNLIM	5	UNLIM	UNLIM	2	UNLIM	UNLIM	1	UNLIM	13	1
0.02	UNLIM	UNLIM	2	UNLIM	13	1	UNLIM	9	0.5	UNLIM	6	0.5
0.04	UNLIM	13	1	UNLIM	6	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.06	UNLIM	9	0.5	UNLIM	4	NONE	UNLIM	3	NONE	UNLIM	2	NONE
0.08	UNLIM	6	NONE	UNLIM	3	NONE	UNLIM	2	NONE	17	1	NONE
0.1	UNLIM	5	NONE	UNLIM	2	NONE	UNLIM	1	NONE	13	1	NONE
0.2	UNLIM	2	NONE	13	1	NONE	9	0.5	NONE	6	0.5	NONE
0.4	13	1	NONE	6	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.6	9	0.5	NONE	4	NONE	NONE	3	NONE	NONE	2	NONE	NONE
0.8	6	NONE	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
1	5	NONE	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
2	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
4	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
6	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>6	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

* The cancer status for dicofol is under review by the Agency, and no cancer potency is currently available. EPA recommends using a cancer potency of 0.34 per mg/kg–d when dicofol appears with DDT, DDD, and/or DDE; this table reflects this cancer potency of 0.34 per mg/kg–d.
Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–25. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Dicofol
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	1E–03 mg/kg–d
Detection Limits:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.06	UNLIM	UNLIM	UNLIM
0.06	UNLIM	UNLIM	10
0.07	UNLIM	UNLIM	9
0.08	UNLIM	UNLIM	7
0.09	UNLIM	UNLIM	7
0.1	UNLIM	UNLIM	6
0.2	8	6	3
0.3	5	4	2
0.4	4	3	1
0.5	3	2	1
0.6	2	2	1
0.7	2	1	NONE
0.8	2	1	NONE
0.9	1	1	NONE
1	1	1	NONE
2	NONE	NONE	NONE
3	NONE	NONE	NONE
>3	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–26. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Dieldrin
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.008	UNLIM	UNLIM	UNLIM	UNLIM
0.008	UNLIM	UNLIM	UNLIM	9
0.009	UNLIM	UNLIM	UNLIM	8
0.01	UNLIM	UNLIM	10	7
0.02	UNLIM	7	5	3
0.03	10	5	3	2
0.04	7	3	2	1
0.05	6	3	2	1
0.06	5	2	1	1
0.07	4	2	1	1
0.08	3	1	1	NONE
0.09	3	1	1	NONE
0.1	3	1	1	NONE
0.2	1	NONE	NONE	NONE
0.3	1	NONE	NONE	NONE
0.4	NONE	NONE	NONE	NONE
0.5	NONE	NONE	NONE	NONE
0.6	NONE	NONE	NONE	NONE
>0.6	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
References for RfDs are found in Part II, Section 5.
References for estimated threshold values are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–27. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Dieldrin
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	15	11
0.03	UNLIM	15	10	7
0.04	UNLIM	11	7	5
0.05	UNLIM	9	6	4
0.06	15	7	5	3
0.07	12	6	4	3
0.08	11	5	3	2
0.09	10	5	3	2
0.1	9	4	3	2
0.2	4	2	1	1
0.3	3	1	1	0.5
0.4	2	1	0.5	0.5
0.5	1	0.5	0.5	NONE
0.6	1	0.5	0.5	NONE
0.7	1	0.5	NONE	NONE
0.8	1	0.5	NONE	NONE
0.9	1	0.5	NONE	NONE
1	0.5	NONE	NONE	NONE
>1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–28. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Dieldrin
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	2E+01 per mg/kg–d
Detection Limit:	1E–04 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.00002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.00002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	14
0.00004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	14	UNLIM	UNLIM	9	UNLIM	UNLIM	7
0.00006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	9	UNLIM	UNLIM	6	UNLIM	UNLIM	4
0.00008	UNLIM	UNLIM	14	UNLIM	UNLIM	7	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.0001	UNLIM	UNLIM	11	UNLIM	UNLIM	5	UNLIM	UNLIM	3	UNLIM	UNLIM	2
0.0002	UNLIM	UNLIM	5	UNLIM	UNLIM	2	UNLIM	UNLIM	1	UNLIM	14	1
0.0004	UNLIM	UNLIM	2	UNLIM	14	1	UNLIM	9	0.5	UNLIM	7	0.5
0.0006	UNLIM	UNLIM	1	UNLIM	9	0.5	UNLIM	6	0.5	UNLIM	4	NONE
0.0008	UNLIM	14	1	UNLIM	7	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.001	UNLIM	11	1	UNLIM	5	0.5	UNLIM	3	NONE	UNLIM	2	NONE
0.002	UNLIM	5	0.5	UNLIM	2	NONE	UNLIM	1	NONE	14	1	NONE
0.004	UNLIM	2	NONE	14	1	NONE	9	0.5	NONE	7	0.5	NONE
0.006	UNLIM	1	NONE	9	0.5	NONE	6	0.5	NONE	4	NONE	NONE
0.008	14	1	NONE	7	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.01	11	1	NONE	5	0.5	NONE	3	NONE	NONE	2	NONE	NONE
0.02	5	0.5	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
0.04	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.06	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
0.08	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
0.1	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
0.2	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>0.2	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–29. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Dieldrin
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limits:	1E–04 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.003	UNLIM	UNLIM	UNLIM
0.003	UNLIM	UNLIM	10
0.004	UNLIM	UNLIM	7
0.005	UNLIM	UNLIM	6
0.006	UNLIM	10	5
0.007	UNLIM	9	4
0.008	10	7	3
0.009	9	7	3
0.01	8	6	3
0.02	4	3	1
0.03	2	2	1
0.04	2	1	NONE
0.05	1	1	NONE
0.06	1	1	NONE
0.07	1	NONE	NONE
0.08	1	NONE	NONE
0.09	NONE	NONE	NONE
0.1	NONE	NONE	NONE
>0.1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3-30. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Dioxin
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	2E+05 per mg/kg-d
Detection Limit:	7E-07 mg/kg

Risk-Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.000000001	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.000000001	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.000000002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	15
0.000000004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	15	UNLIM	UNLIM	10	UNLIM	UNLIM	7
0.000000006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	10	UNLIM	UNLIM	6	UNLIM	UNLIM	5
0.000000008	UNLIM	UNLIM	14	UNLIM	UNLIM	7	UNLIM	UNLIM	5	UNLIM	UNLIM	3
0.00000001	UNLIM	UNLIM	11	UNLIM	UNLIM	6	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.00000002	UNLIM	UNLIM	5	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	15	1
0.00000004	UNLIM	UNLIM	2	UNLIM	15	1	UNLIM	10	1	UNLIM	7	0.5
0.00000006	UNLIM	UNLIM	1	UNLIM	10	1	UNLIM	6	0.5	UNLIM	5	0.5
0.00000008	UNLIM	14	1	UNLIM	7	0.5	UNLIM	5	0.5	UNLIM	3	NONE
0.0000001	UNLIM	11	1	UNLIM	6	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.0000002	UNLIM	5	0.5	UNLIM	3	NONE	UNLIM	2	NONE	15	1	NONE
0.0000004	UNLIM	2	NONE	15	1	NONE	10	1	NONE	7	0.5	NONE
0.0000006	UNLIM	1	NONE	10	1	NONE	6	0.5	NONE	5	0.5	NONE
0.0000008	14	1	NONE	7	0.5	NONE	5	0.5	NONE	3	NONE	NONE
0.000001	11	1	NONE	6	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.000002	5	0.5	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
0.000004	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE
0.000006	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.000008	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
0.00001	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
0.00002	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>0.00002	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–31. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Disulfoton
Population:	General
Body Weight:	70 kg
Reference Dose:	4E–05 mg/kg–d
Detection Limit:	N/A

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.006	UNLIM	UNLIM	UNLIM	UNLIM
0.006	UNLIM	UNLIM	UNLIM	10
0.007	UNLIM	UNLIM	UNLIM	8
0.008	UNLIM	UNLIM	10	7
0.009	UNLIM	UNLIM	9	6
0.01	UNLIM	UNLIM	8	6
0.02	UNLIM	6	4	3
0.03	8	4	2	2
0.04	6	3	2	1
0.05	4	2	1	1
0.06	4	2	1	1
0.07	3	1	1	NONE
0.08	3	1	1	NONE
0.09	2	1	NONE	NONE
0.1	2	1	NONE	NONE
0.2	1	NONE	NONE	NONE
0.3	NONE	NONE	NONE	NONE
0.4	NONE	NONE	NONE	NONE
>0.4	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
N/A = not available
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–32. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Disulfoton
Population:	General
Body Weight:	70 kg
Reference Dose:	4E–05 mg/kg–d
Detection Limit:	N/A

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month)			
	Meal Size (kg)			
	0.114	0.227	0.341	0.454
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	12	9
0.03	UNLIM	12	8	6
0.04	UNLIM	9	6	4
0.05	14	7	4	3
0.06	12	6	4	3
0.07	10	5	3	2
0.08	9	4	3	2
0.09	8	4	2	2
0.1	7	3	2	1
0.2	3	1	1	0.5
0.3	2	1	0.5	0.5
0.4	1	0.5	0.5	NONE
0.5	1	0.5	NONE	NONE
0.6	1	0.5	NONE	NONE
0.7	1	0.5	NONE	NONE
0.8	0.5	NONE	NONE	NONE
0.9	0.5	NONE	NONE	NONE
1	0.5	NONE	NONE	NONE
>1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
N/A = not available
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–33. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Disulfoton
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	4E–05 mg/kg–d
Detection Limits:	N/A

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.003	UNLIM	UNLIM	UNLIM
0.003	UNLIM	UNLIM	8
0.004	UNLIM	UNLIM	6
0.005	UNLIM	10	5
0.006	UNLIM	8	4
0.007	9	7	3
0.008	8	6	3
0.009	7	5	2
0.01	6	5	2
0.02	3	2	1
0.03	2	1	NONE
0.04	1	1	NONE
0.05	1	1	NONE
0.06	1	NONE	NONE
0.07	NONE	NONE	NONE
0.08	NONE	NONE	NONE
0.09	NONE	NONE	NONE
0.1	NONE	NONE	NONE
>0.1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
N/A = not available
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–34. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Endosulfan
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	0.005–0.07 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days)			
	Meal Size (oz)			
	4	8	12	16
<0.008	UNLIM	UNLIM	UNLIM	UNLIM
0.008	UNLIM	UNLIM	UNLIM	9
0.009	UNLIM	UNLIM	UNLIM	8
0.01	UNLIM	UNLIM	10	7
0.02	UNLIM	7	5	3
0.03	10	5	3	2
0.04	7	3	2	1
0.05	6	3	2	1
0.06	5	2	1	1
0.07	4	2	1	1
0.08	3	1	1	NONE
0.09	3	1	1	NONE
0.1	3	1	1	NONE
0.2	1	NONE	NONE	NONE
0.3	1	NONE	NONE	NONE
0.4	NONE	NONE	NONE	NONE
0.5	NONE	NONE	NONE	NONE
0.6	NONE	NONE	NONE	NONE
>0.6	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–35. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Endosulfan
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	0.005–0.07 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month)			
	Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	15	11
0.03	UNLIM	15	10	7
0.04	UNLIM	11	7	5
0.05	UNLIM	9	6	4
0.06	15	7	5	3
0.07	13	6	4	3
0.08	11	5	3	2
0.09	10	5	3	2
0.1	9	4	3	2
0.2	4	2	1	1
0.3	3	1	1	0.5
0.4	2	1	0.5	0.5
0.5	1	0.5	0.5	NONE
0.6	1	0.5	0.5	NONE
0.7	1	0.5	NONE	NONE
0.8	1	0.5	NONE	NONE
0.9	1	0.5	NONE	NONE
1	0.5	NONE	NONE	NONE
>1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–36. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Endosulfan
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	0.005–0.07 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.003	UNLIM	UNLIM	UNLIM
0.003	UNLIM	UNLIM	10
0.004	UNLIM	UNLIM	7
0.005	UNLIM	UNLIM	6
0.006	UNLIM	10	5
0.007	UNLIM	9	4
0.008	10	7	3
0.009	9	7	3
0.01	8	6	3
0.02	4	3	1
0.03	2	2	1
0.04	2	1	NONE
0.05	1	1	NONE
0.06	1	1	NONE
0.07	1	NONE	NONE
0.08	1	NONE	NONE
0.09	NONE	NONE	NONE
0.1	NONE	NONE	NONE
>0.1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–37. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Endrin
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.05	UNLIM	UNLIM	UNLIM	UNLIM
0.05	UNLIM	UNLIM	UNLIM	9
0.06	UNLIM	UNLIM	UNLIM	7
0.07	UNLIM	UNLIM	8	6
0.08	UNLIM	UNLIM	7	5
0.09	UNLIM	10	6	5
0.1	UNLIM	9	6	4
0.2	9	4	3	2
0.3	6	3	2	1
0.4	4	2	1	1
0.5	3	1	1	NONE
0.6	3	1	1	NONE
0.7	2	1	NONE	NONE
0.8	2	1	NONE	NONE
0.9	2	1	NONE	NONE
1	1	NONE	NONE	NONE
2	NONE	NONE	NONE	NONE
3	NONE	NONE	NONE	NONE
<3	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–38. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Endrin
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.08	UNLIM	UNLIM	UNLIM	UNLIM
0.08	UNLIM	UNLIM	UNLIM	17
0.09	UNLIM	UNLIM	UNLIM	15
0.1	UNLIM	UNLIM	UNLIM	14
0.2	UNLIM	14	9	7
0.3	UNLIM	9	6	4
0.4	14	7	4	3
0.5	11	5	3	2
0.6	9	4	3	2
0.7	8	4	2	2
0.8	7	3	2	1
0.9	6	3	2	1
1	5	2	1	1
2	2	1	0.5	0.5
3	1	0.5	0.5	NONE
4	1	0.5	NONE	NONE
5	1	0.5	NONE	NONE
6	0.5	NONE	NONE	NONE
7	0.5	NONE	NONE	NONE
8	0.5	NONE	NONE	NONE
9	0.5	NONE	NONE	NONE
10	0.5	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–39. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Endrin
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limits:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.02	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	9
0.03	UNLIM	UNLIM	6
0.04	UNLIM	9	4
0.05	10	7	3
0.06	8	6	3
0.07	7	5	2
0.08	6	4	2
0.09	5	4	2
0.1	5	3	1
0.2	2	1	NONE
0.3	1	1	NONE
0.4	1	NONE	NONE
0.5	1	NONE	NONE
0.6	NONE	NONE	NONE
0.7	NONE	NONE	NONE
0.8	NONE	NONE	NONE
0.9	NONE	NONE	NONE
1.0	NONE	NONE	NONE
>1.0	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–40. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Ethion
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–04 mg/kg–d
Detection Limit:	2E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.08	UNLIM	UNLIM	UNLIM	UNLIM
0.08	UNLIM	UNLIM	UNLIM	9
0.09	UNLIM	UNLIM	UNLIM	8
0.1	UNLIM	UNLIM	10	7
0.2	UNLIM	7	5	3
0.3	10	5	3	2
0.4	7	3	2	1
0.5	6	3	2	1
0.6	5	2	1	1
0.7	4	2	1	1
0.8	3	1	1	NONE
0.9	3	1	1	NONE
1	3	1	1	NONE
2	1	NONE	NONE	NONE
3	1	NONE	NONE	NONE
4	NONE	NONE	NONE	NONE
5	NONE	NONE	NONE	NONE
6	NONE	NONE	NONE	NONE
>6	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–41. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Ethion
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–04 mg/kg–d
Detection Limit:	2E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.2	UNLIM	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	15	11
0.3	UNLIM	15	10	7
0.4	UNLIM	11	7	5
0.5	UNLIM	9	6	4
0.6	15	7	5	3
0.7	13	6	4	3
0.8	11	5	3	2
0.9	10	5	3	2
1	9	4	3	2
2	4	2	1	1
3	3	1	1	0.5
4	2	1	0.5	0.5
5	1	0.5	0.5	NONE
6	1	0.5	0.5	NONE
7	1	0.5	NONE	NONE
8	1	0.5	NONE	NONE
9	1	0.5	NONE	NONE
10	0.5	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–42. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Ethion
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	5E–04 mg/kg–d
Detection Limits:	2E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.03	UNLIM	UNLIM	UNLIM
0.03	UNLIM	UNLIM	10
0.04	UNLIM	UNLIM	7
0.05	UNLIM	UNLIM	6
0.06	UNLIM	10	5
0.07	UNLIM	9	4
0.08	10	7	3
0.09	9	7	3
0.1	8	6	3
0.2	4	3	1
0.3	2	2	1
0.4	2	1	NONE
0.5	1	1	NONE
0.6	1	1	NONE
0.7	1	NONE	NONE
0.8	1	NONE	NONE
0.9	NONE	NONE	NONE
1	NONE	NONE	NONE
>1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–43. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Heptachlor Epoxide
Population:	General
Body Weight:	70 kg
Reference Dose:	1E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.002	UNLIM	UNLIM	UNLIM	UNLIM
0.002	UNLIM	UNLIM	UNLIM	10
0.003	UNLIM	UNLIM	8	6
0.004	UNLIM	10	6	5
0.005	UNLIM	8	5	4
0.006	UNLIM	6	4	3
0.007	UNLIM	5	3	2
0.008	9	5	3	2
0.009	8	4	2	2
0.01	7	4	2	2
0.02	3	2	1	1
0.03	2	1	NONE	NONE
0.04	1	1	NONE	NONE
0.05	1	NONE	NONE	NONE
0.06	1	NONE	NONE	NONE
0.07	1	NONE	NONE	NONE
0.08	NONE	NONE	NONE	NONE
0.09	NONE	NONE	NONE	NONE
0.1	NONE	NONE	NONE	NONE
>0.1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–44. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Heptachlor Epoxide
Population:	General
Body Weight:	70 kg
Reference Dose:	1E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month)			
	Meal Size (oz)			
	4	8	12	16
<0.004	UNLIM	UNLIM	UNLIM	UNLIM
0.004	UNLIM	UNLIM	UNLIM	15
0.005	UNLIM	UNLIM	16	12
0.006	UNLIM	UNLIM	13	10
0.007	UNLIM	17	11	8
0.008	UNLIM	15	10	7
0.009	UNLIM	13	9	6
0.01	UNLIM	12	8	6
0.02	12	6	4	3
0.03	8	4	2	2
0.04	6	3	2	1
0.05	4	2	1	1
0.06	4	2	1	1
0.07	3	1	1	0.5
0.08	3	1	1	0.5
0.09	2	1	0.5	0.5
0.1	2	1	0.5	0.5
0.2	1	0.5	NONE	NONE
0.3	0.5	NONE	NONE	NONE
0.4	0.5	NONE	NONE	NONE
>0.4	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–45. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Heptachlor Epoxide
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	9E+00 per mg/kg–d
Detection Limit:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.00004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.00004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	17	UNLIM	UNLIM	12
0.00006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	17	UNLIM	UNLIM	11	UNLIM	UNLIM	8
0.00008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	8	UNLIM	UNLIM	6
0.0001	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	10	UNLIM	UNLIM	6	UNLIM	UNLIM	5
0.0002	UNLIM	UNLIM	10	UNLIM	UNLIM	5	UNLIM	UNLIM	3	UNLIM	UNLIM	2
0.0004	UNLIM	UNLIM	5	UNLIM	UNLIM	2	UNLIM	17	1	UNLIM	12	1
0.0006	UNLIM	UNLIM	3	UNLIM	17	1	UNLIM	11	1	UNLIM	8	0.5
0.0008	UNLIM	UNLIM	2	UNLIM	12	1	UNLIM	8	0.5	UNLIM	6	0.5
0.001	UNLIM	UNLIM	2	UNLIM	10	1	UNLIM	6	0.5	UNLIM	5	0.5
0.002	UNLIM	10	1	UNLIM	5	0.5	UNLIM	3	NONE	UNLIM	2	NONE
0.004	UNLIM	5	0.5	UNLIM	2	NONE	17	1	NONE	12	1	NONE
0.006	UNLIM	3	NONE	17	1	NONE	11	1	NONE	8	0.5	NONE
0.008	UNLIM	2	NONE	12	1	NONE	8	0.5	NONE	6	0.5	NONE
0.01	UNLIM	2	NONE	10	1	NONE	6	0.5	NONE	5	0.5	NONE
0.02	10	1	NONE	5	0.5	NONE	3	NONE	NONE	2	NONE	NONE
0.04	5	0.5	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
0.06	3	NONE	NONE	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE
0.08	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.1	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.2	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
0.4	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>0.4	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–46. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Heptachlor Epoxide
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	1E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.0008	UNLIM	UNLIM	UNLIM
0.0008	UNLIM	UNLIM	10
0.0009	UNLIM	UNLIM	9
0.001	UNLIM	UNLIM	8
0.002	UNLIM	8	4
0.003	7	5	2
0.004	5	4	2
0.005	4	3	1
0.006	3	2	1
0.007	3	2	1
0.008	2	2	1
0.009	2	1	NONE
0.01	2	1	NONE
0.02	1	NONE	NONE
0.03	NONE	NONE	NONE
0.04	NONE	NONE	NONE
>0.04	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–47. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Hexachlorobenzene
Population:	General
Body Weight:	70 kg
Reference Dose:	8E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.2	UNLIM	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	8	6
0.3	UNLIM	8	5	4
0.4	UNLIM	6	4	3
0.5	9	4	3	2
0.6	8	4	2	2
0.7	7	3	2	1
0.8	6	3	2	1
0.9	5	2	1	1
1	4	2	1	1
2	2	1	NONE	NONE
3	1	NONE	NONE	NONE
4	1	NONE	NONE	NONE
5	NONE	NONE	NONE	NONE
6	NONE	NONE	NONE	NONE
7	NONE	NONE	NONE	NONE
8	NONE	NONE	NONE	NONE
9	NONE	NONE	NONE	NONE
>9	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–48. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Hexachlorobenzene
Population:	General
Body Weight:	70 kg
Reference Dose:	8E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month)			
	Meal Size (oz)			
	4	8	12	16
<0.3	UNLIM	UNLIM	UNLIM	UNLIM
0.3	UNLIM	UNLIM	16	12
0.4	UNLIM	UNLIM	12	9
0.5	UNLIM	15	9	7
0.6	UNLIM	12	8	6
0.7	UNLIM	10	7	5
0.8	UNLIM	9	6	4
0.9	16	8	5	4
1	14	7	4	3
2	7	3	2	1
3	4	2	1	1
4	3	1	1	0.5
5	2	1	0.5	0.5
6	2	1	0.5	0.5
7	2	1	0.5	0.5
8	1	0.5	0.5	NONE
9	1	0.5	0.5	NONE
10	1	0.5	NONE	NONE
20	0.5	NONE	NONE	NONE
>20	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–49. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Hexachlorobenzene
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	2E+00 per mg/kg–d
Detection Limit:	1E–04 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	14
0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	14	UNLIM	UNLIM	9	UNLIM	UNLIM	7
0.0006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	9	UNLIM	UNLIM	6	UNLIM	UNLIM	4
0.0008	UNLIM	UNLIM	14	UNLIM	UNLIM	7	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.001	UNLIM	UNLIM	11	UNLIM	UNLIM	5	UNLIM	UNLIM	3	UNLIM	UNLIM	2
0.002	UNLIM	UNLIM	5	UNLIM	UNLIM	2	UNLIM	UNLIM	1	UNLIM	14	1
0.004	UNLIM	UNLIM	2	UNLIM	14	1	UNLIM	9	0.5	UNLIM	7	0.5
0.006	UNLIM	UNLIM	1	UNLIM	9	0.5	UNLIM	6	0.5	UNLIM	4	NONE
0.008	UNLIM	14	1	UNLIM	7	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.01	UNLIM	11	1	UNLIM	5	0.5	UNLIM	3	NONE	UNLIM	2	NONE
0.02	UNLIM	5	0.5	UNLIM	2	NONE	UNLIM	1	NONE	14	1	NONE
0.04	UNLIM	2	NONE	14	1	NONE	9	0.5	NONE	7	0.5	NONE
0.06	UNLIM	1	NONE	9	0.5	NONE	6	0.5	NONE	4	NONE	NONE
0.08	14	1	NONE	7	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.1	11	1	NONE	5	0.5	NONE	3	NONE	NONE	2	NONE	NONE
0.2	5	0.5	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
0.4	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.6	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
0.8	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
1	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
2	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–50. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Hexachlorobenzene
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	8E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.05	UNLIM	UNLIM	UNLIM
0.05	UNLIM	UNLIM	10
0.06	UNLIM	UNLIM	8
0.07	UNLIM	UNLIM	7
0.08	UNLIM	UNLIM	6
0.09	UNLIM	UNLIM	5
0.1	UNLIM	10	5
0.2	6	5	2
0.3	4	3	1
0.4	3	2	1
0.5	2	2	1
0.6	2	1	NONE
0.7	1	1	NONE
0.8	1	1	NONE
0.9	1	1	NONE
1	1	1	NONE
2	NONE	NONE	NONE
>2	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–51. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Lindane
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.05	UNLIM	UNLIM	UNLIM	UNLIM
0.05	UNLIM	UNLIM	UNLIM	9
0.06	UNLIM	UNLIM	UNLIM	7
0.07	UNLIM	UNLIM	8	6
0.08	UNLIM	UNLIM	7	5
0.09	UNLIM	10	6	5
0.1	UNLIM	9	6	4
0.2	9	4	3	2
0.3	6	3	2	1
0.4	4	2	1	1
0.5	3	1	1	NONE
0.6	3	1	1	NONE
0.7	2	1	NONE	NONE
0.8	2	1	NONE	NONE
0.9	2	1	NONE	NONE
1	1	NONE	NONE	NONE
2	NONE	NONE	NONE	NONE
3	NONE	NONE	NONE	NONE
>3	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–52. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Lindane
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month)			
	Meal Size (oz)			
	4	8	12	16
<0.08	UNLIM	UNLIM	UNLIM	UNLIM
0.08	UNLIM	UNLIM	UNLIM	17
0.09	UNLIM	UNLIM	UNLIM	15
0.1	UNLIM	UNLIM	UNLIM	14
0.2	UNLIM	14	9	7
0.3	UNLIM	9	6	4
0.4	14	7	4	3
0.5	11	5	3	2
0.6	9	4	3	2
0.7	8	4	2	2
0.8	7	3	2	1
0.9	6	3	2	1
1	5	2	1	1
2	2	1	0.5	0.5
3	1	0.5	0.5	NONE
4	1	0.5	NONE	NONE
5	1	0.5	NONE	NONE
6	0.5	NONE	NONE	NONE
7	0.5	NONE	NONE	NONE
8	0.5	NONE	NONE	NONE
9	0.5	NONE	NONE	NONE
10	0.5	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–53. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Lindane
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	1E+00 per mg/kg–d
Detection Limit:	1E–04 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	18.05002	UNLIM	UNLIM	12	UNLIM	UNLIM	9
0.0006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	8	UNLIM	UNLIM	6
0.0008	UNLIM	UNLIM	17	UNLIM	UNLIM	9	UNLIM	UNLIM	6	UNLIM	UNLIM	4
0.001	UNLIM	UNLIM	14	UNLIM	UNLIM	7	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.002	UNLIM	UNLIM	7	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	UNLIM	1
0.004	UNLIM	UNLIM	3	UNLIM	UNLIM	1	UNLIM	12	1	UNLIM	9	0.5
0.006	UNLIM	UNLIM	2	UNLIM	12	1	UNLIM	8	0.5	UNLIM	6	0.5
0.008	UNLIM	17	1	UNLIM	9	0.5	UNLIM	6	0.5	UNLIM	4	NONE
0.01	UNLIM	14	1	UNLIM	7	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.02	UNLIM	7	0.5	UNLIM	3	NONE	UNLIM	2	NONE	UNLIM	1	NONE
0.04	UNLIM	3	NONE	UNLIM	1	NONE	12	1	NONE	9	0.5	NONE
0.06	UNLIM	2	NONE	12	1	NONE	8	0.5	NONE	6	0.5	NONE
0.08	17	1	NONE	9	0.5	NONE	6	0.5	NONE	4	NONE	NONE
0.1	14	1	NONE	7	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.2	7	0.5	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
0.4	3	NONE	NONE	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE
0.6	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.8	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
1	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
2	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–54. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Lindane
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limits:	1E–04 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.02	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	9
0.03	UNLIM	UNLIM	6
0.04	UNLIM	9	4
0.05	10	7	3
0.06	8	6	3
0.07	7	5	2
0.08	6	4	2
0.09	5	4	2
0.1	5	3	1
0.2	2	1	NONE
0.3	1	1	NONE
0.4	1	NONE	NONE
0.5	1	NONE	NONE
0.6	NONE	NONE	NONE
0.7	NONE	NONE	NONE
0.8	NONE	NONE	NONE
0.9	NONE	NONE	NONE
1.0	NONE	NONE	NONE
>1.0	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–55. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Methylmercury
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	1E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.05	UNLIM	UNLIM	UNLIM	UNLIM
0.05	UNLIM	UNLIM	UNLIM	9
0.06	UNLIM	UNLIM	UNLIM	7
0.07	UNLIM	UNLIM	8	6
0.08	UNLIM	UNLIM	7	5
0.09	UNLIM	10	6	5
0.1	UNLIM	9	6	4
0.2	9	4	3	2
0.3	6	3	2	1
0.4	4	2	1	1
0.5	3	1	1	NONE
0.6	3	1	1	NONE
0.7	2	1	NONE	NONE
0.8	2	1	NONE	NONE
0.9	2	1	NONE	NONE
1	1	NONE	NONE	NONE
<1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.
A dose–response variable of 3×10^{-4} mg/kg–d may be appropriate for adult males (See Section 5.6).

Table 3–56. 10–Day Consumption Limits for Developmental Health Endpoints

Chemical Name:	Methylmercury
Population:	Women of Child–Bearing Age
Body Weight:	70 kg
Interim Dose–Response Variable:	6E–05 mg/kg–d
Detection Limit:	1E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.009	UNLIM	UNLIM	UNLIM	UNLIM
0.009	UNLIM	UNLIM	UNLIM	10
0.01	UNLIM	UNLIM	UNLIM	9
0.02	UNLIM	9	6	4
0.03	UNLIM	6	4	3
0.04	9	4	3	2
0.05	7	3	2	1
0.06	6	3	2	1
0.07	5	2	1	1
0.08	4	2	1	1
0.09	4	2	1	1
0.1	3	1	1	NONE
0.2	1	NONE	NONE	NONE
0.3	1	NONE	NONE	NONE
0.4	NONE	NONE	NONE	NONE
>0.4	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–57. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Methylmercury
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	1E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.08	UNLIM	UNLIM	UNLIM	UNLIM
0.08	UNLIM	UNLIM	UNLIM	17
0.09	UNLIM	UNLIM	UNLIM	15
0.1	UNLIM	UNLIM	UNLIM	14
0.2	UNLIM	14	9	7
0.3	UNLIM	9	6	4
0.4	14	7	4	3
0.5	11	5	3	2
0.6	9	4	3	2
0.7	8	4	2	2
0.8	7	3	2	1
0.9	6	3	2	1
1	5	2	1	1
2	2	1	0.5	0.5
3	1	0.5	0.5	NONE
4	1	0.5	NONE	NONE
5	1	0.5	NONE	NONE
6	0.5	NONE	NONE	NONE
7	0.5	NONE	NONE	NONE
8	0.5	NONE	NONE	NONE
9	0.5	NONE	NONE	NONE
10	0.5	NONE	NONE	NONE
>10	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
A dose–response variable of 3×10^{-4} mg/kg–d may be appropriate for adult males (See Section 5.6).

Table 3–58. Monthly Consumption Limits for Developmental Health Endpoints

Chemical Name:	Methylmercury
Population:	Women of Child–Bearing Age
Body Weight:	70 kg
Interim Dose–Response Variable:	6E–05 mg/kg–d
Detection Limit:	1E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	UNLIM	14
0.03	UNLIM	UNLIM	12	9
0.04	UNLIM	14	9	7
0.05	UNLIM	11	7	5
0.06	UNLIM	9	6	4
0.07	16	8	5	4
0.08	14	7	4	3
0.09	12	6	4	3
0.1	11	5	3	2
0.2	5	2	1	1
0.3	3	1	1	0.5
0.4	2	1	0.5	0.5
0.5	2	1	0.5	0.5
0.6	1	0.5	0.5	NONE
0.7	1	0.5	0.5	NONE
0.8	1	0.5	NONE	NONE
0.9	1	0.5	NONE	NONE
1	1	0.5	NONE	NONE
2	0.5	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for the interim dose–response variable are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Monthly limits are based on the total dose allowable over a one–month period
When this dose is delivered in less than one month (e.g., in a few large meals),
note that the daily dose exceeds the interim dose–response variable (see Section 4.3).
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.

Table 3–59. 10–Day Consumption Limits for Developmental Health Endpoints

Chemical Name:	Methylmercury
Population:	Children
Body Weight:	14.5 kg
Interim Dose–Response Variable:	6E–05 mg/kg–d
Detection Limit:	1E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.004	UNLIM	UNLIM	UNLIM
0.004	UNLIM	UNLIM	9
0.005	UNLIM	UNLIM	7
0.006	UNLIM	UNLIM	6
0.007	UNLIM	UNLIM	5
0.008	UNLIM	9	4
0.009	UNLIM	8	4
0.01	10	7	3
0.02	5	3	1
0.03	3	2	1
0.04	2	1	NONE
0.05	2	1	NONE
0.06	1	1	NONE
0.07	1	1	NONE
0.08	1	NONE	NONE
0.09	1	NONE	NONE
0.1	1	NONE	NONE
>0.1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for the dose–response variable are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period
When this dose is delivered in less than 10 days (e.g., in a single meal),
note that the daily dose exceeds the dose–response variable (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–60. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Mirex
Population:	General
Body Weight:	70 kg
Reference Dose:	2E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.03	UNLIM	UNLIM	UNLIM	UNLIM
0.03	UNLIM	UNLIM	UNLIM	10
0.04	UNLIM	UNLIM	10	7
0.05	UNLIM	UNLIM	8	6
0.06	UNLIM	10	6	5
0.07	UNLIM	8	5	4
0.08	UNLIM	7	5	3
0.09	UNLIM	6	4	3
0.1	UNLIM	6	4	3
0.2	6	3	2	1
0.3	4	2	1	1
0.4	3	1	1	NONE
0.5	2	1	NONE	NONE
0.6	2	1	NONE	NONE
0.7	1	NONE	NONE	NONE
0.8	1	NONE	NONE	NONE
0.9	1	NONE	NONE	NONE
1	1	NONE	NONE	NONE
2	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–61. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Mirex
Population:	General
Body Weight:	70 kg
Reference Dose:	2E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.06	UNLIM	UNLIM	UNLIM	UNLIM
0.06	UNLIM	UNLIM	UNLIM	15
0.07	UNLIM	UNLIM	17	13
0.08	UNLIM	UNLIM	15	11
0.09	UNLIM	UNLIM	13	10
0.1	UNLIM	UNLIM	12	9
0.2	UNLIM	9	6	4
0.3	12	6	4	3
0.4	9	4	3	2
0.5	7	3	2	1
0.6	6	3	2	1
0.7	5	2	1	1
0.8	4	2	1	1
0.9	4	2	1	1
1	3	1	1	0.5
2	1	0.5	0.5	NONE
3	1	0.5	NONE	NONE
4	0.5	NONE	NONE	NONE
5	0.5	NONE	NONE	NONE
6	0.5	NONE	NONE	NONE
7	0.5	NONE	NONE	NONE
>7	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–62. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Mirex
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	2E+00 per mg/kg–d
Detection Limit	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0002	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	17	UNLIM	UNLIM	13
0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	13	UNLIM	UNLIM	8	UNLIM	UNLIM	6
0.0006	UNLIM	UNLIM	17	UNLIM	UNLIM	8	UNLIM	UNLIM	5	UNLIM	UNLIM	4
0.0008	UNLIM	UNLIM	12	UNLIM	UNLIM	6	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.001	UNLIM	UNLIM	10	UNLIM	UNLIM	5	UNLIM	UNLIM	3	UNLIM	UNLIM	2
0.002	UNLIM	UNLIM	5	UNLIM	UNLIM	2	UNLIM	17	1	UNLIM	13	1
0.004	UNLIM	UNLIM	2	UNLIM	13	1	UNLIM	8	0.5	UNLIM	6	0.5
0.006	UNLIM	17	1	UNLIM	8	0.5	UNLIM	5	0.5	UNLIM	4	NONE
0.008	UNLIM	12	1	UNLIM	6	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.01	UNLIM	10	1	UNLIM	5	0.5	UNLIM	3	NONE	UNLIM	2	NONE
0.02	UNLIM	5	0.5	UNLIM	2	NONE	17	1	NONE	13	1	NONE
0.04	UNLIM	2	NONE	13	1	NONE	8	0.5	NONE	6	0.5	NONE
0.06	17	1	NONE	8	0.5	NONE	5	0.5	NONE	4	NONE	NONE
0.08	12	1	NONE	6	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.1	10	1	NONE	5	0.5	NONE	3	NONE	NONE	2	NONE	NONE
0.2	5	0.5	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
0.4	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.6	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
0.8	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
1	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
2	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–63. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Mirex
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	2E–04 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.02	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	6
0.03	UNLIM	8	4
0.04	8	6	3
0.05	6	5	2
0.06	5	4	2
0.07	4	3	1
0.08	4	3	1
0.09	3	2	1
0.1	3	2	1
0.2	1	1	NONE
0.3	1	NONE	NONE
0.4	NONE	NONE	NONE
0.5	NONE	NONE	NONE
0.6	NONE	NONE	NONE
>0.6	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–64. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Oxyfluorfen
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–03 mg/kg–d
Detection Limit:	N/A

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.5	UNLIM	UNLIM	UNLIM	UNLIM
0.5	UNLIM	UNLIM	UNLIM	9
0.6	UNLIM	UNLIM	10	7
0.7	UNLIM	UNLIM	8	6
0.8	UNLIM	UNLIM	7	5
0.9	UNLIM	10	6	5
1	UNLIM	9	6	4
2	9	4	3	2
3	6	3	2	1
4	4	2	1	1
5	3	1	1	NONE
6	3	1	1	NONE
7	2	1	NONE	NONE
8	2	1	NONE	NONE
9	2	1	NONE	NONE
10	1	NONE	NONE	NONE
20	NONE	NONE	NONE	NONE
30	NONE	NONE	NONE	NONE
>30	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
N/A = not available
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–65. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Oxyfluorfen
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–03 mg/kg–d
Detection Limit:	N/A

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.8	UNLIM	UNLIM	UNLIM	UNLIM
0.8	UNLIM	UNLIM	UNLIM	17
0.9	UNLIM	UNLIM	UNLIM	15
1	UNLIM	UNLIM	UNLIM	14
2	UNLIM	14	9	7
3	UNLIM	9	6	4
4	14	7	4	3
5	11	5	3	2
6	9	4	3	2
7	8	4	2	2
8	7	3	2	1
9	6	3	2	1
10	5	2	1	1
20	2	1	0.5	0.5
30	1	0.5	0.5	NONE
40	1	0.5	NONE	NONE
50	1	0.5	NONE	NONE
60	0.5	NONE	NONE	NONE
70	0.5	NONE	NONE	NONE
80	0.5	NONE	NONE	NONE
90	0.5	NONE	NONE	NONE
100	0.5	NONE	NONE	NONE
>100	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
N/A = not available
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3-66. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Oxyfluorofen
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	1E-01 per mg/kg-d
Detection Limit:	N/A

Risk-Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	9
0.006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	8	UNLIM	UNLIM	6
0.008	UNLIM	UNLIM	17	UNLIM	UNLIM	9	UNLIM	UNLIM	6	UNLIM	UNLIM	4
0.01	UNLIM	UNLIM	14	UNLIM	UNLIM	7	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.02	UNLIM	UNLIM	7	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	UNLIM	1
0.04	UNLIM	UNLIM	3	UNLIM	UNLIM	1	UNLIM	12	1	UNLIM	9	0.5
0.06	UNLIM	UNLIM	2	UNLIM	12	1	UNLIM	8	0.5	UNLIM	6	0.5
0.08	UNLIM	17	1	UNLIM	9	0.5	UNLIM	6	0.5	UNLIM	4	NONE
0.1	UNLIM	14	1	UNLIM	7	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.2	UNLIM	7	0.5	UNLIM	3	NONE	UNLIM	2	NONE	UNLIM	1	NONE
0.4	UNLIM	3	NONE	UNLIM	1	NONE	12	1	NONE	9	0.5	NONE
0.6	UNLIM	2	NONE	12	1	NONE	8	0.5	NONE	6	0.5	NONE
0.8	17	1	NONE	9	0.5	NONE	6	0.5	NONE	4	NONE	NONE
1	14	1	NONE	7	0.5	NONE	4	NONE	NONE	3	NONE	NONE
2	7	0.5	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
4	3	NONE	NONE	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE
6	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
8	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
10	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
20	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>20	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
N/A = not available
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–67. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Oxyfluorfen
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	3E–03 mg/kg–d
Detection Limit:	N/A

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.2	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	9
0.3	UNLIM	UNLIM	6
0.4	UNLIM	9	4
0.5	10	7	3
0.6	8	6	3
0.7	7	5	2
0.8	6	4	2
0.9	5	4	2
1	5	3	1
2	2	1	NONE
3	1	1	NONE
4	1	NONE	NONE
5	1	NONE	NONE
6	NONE	NONE	NONE
7	NONE	NONE	NONE
8	NONE	NONE	NONE
9	NONE	NONE	NONE
10	NONE	NONE	NONE
>10	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
N/A = not available
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–68. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	PCBs (Aroclor 1254)
Population:	General
Body Weight:	70 kg
Reference Dose:	2E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.003	UNLIM	UNLIM	UNLIM	UNLIM
0.003	UNLIM	UNLIM	UNLIM	10
0.004	UNLIM	UNLIM	10	7
0.005	UNLIM	UNLIM	8	6
0.006	UNLIM	10	6	5
0.007	UNLIM	8	5	4
0.008	UNLIM	7	5	3
0.009	UNLIM	6	4	3
0.01	UNLIM	6	4	3
0.02	6	3	2	1
0.03	4	2	1	1
0.04	3	1	1	NONE
0.05	2	1	NONE	NONE
0.06	2	1	NONE	NONE
0.07	1	NONE	NONE	NONE
0.08	1	NONE	NONE	NONE
0.09	1	NONE	NONE	NONE
0.1	1	NONE	NONE	NONE
0.2	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–69. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	PCBs (Aroclor 1254)
Population:	General
Body Weight:	70 kg
Reference Dose:	2E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program	Meal Size (oz)			
	4	8	12	16
<0.006	UNLIM	UNLIM	UNLIM	UNLIM
0.006	UNLIM	UNLIM	UNLIM	15
0.007	UNLIM	UNLIM	17	13
0.008	UNLIM	UNLIM	15	11
0.009	UNLIM	UNLIM	13	10
0.01	UNLIM	UNLIM	12	9
0.02	UNLIM	9	6	4
0.03	12	6	4	3
0.04	9	4	3	2
0.05	7	3	2	1
0.06	6	3	2	1
0.07	5	2	1	1
0.08	4	2	1	1
0.09	4	2	1	1
0.1	3	1	1	0.5
0.2	1	0.5	0.5	NONE
0.3	1	0.5	NONE	NONE
0.4	0.5	NONE	NONE	NONE
0.5	0.5	NONE	NONE	NONE
0.6	0.5	NONE	NONE	NONE
0.7	0.5	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–70. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	PCBs (Aroclor 1260)
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	8E+00 per mg/kg–d
Detection Limit:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL*			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.00004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.00004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	15
0.00006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	13	UNLIM	UNLIM	10
0.00008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	15	UNLIM	UNLIM	10	UNLIM	UNLIM	7
0.0001	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	12	UNLIM	UNLIM	8	UNLIM	UNLIM	6
0.0002	UNLIM	UNLIM	12	UNLIM	UNLIM	6	UNLIM	UNLIM	4	UNLIM	UNLIM	3
0.0004	UNLIM	UNLIM	6	UNLIM	UNLIM	3	UNLIM	UNLIM	2	UNLIM	15	1
0.0006	UNLIM	UNLIM	4	UNLIM	UNLIM	2	UNLIM	13	1	UNLIM	10	1
0.0008	UNLIM	UNLIM	3	UNLIM	15	1	UNLIM	10	1	UNLIM	7	0.5
0.001	UNLIM	UNLIM	2	UNLIM	12	1	UNLIM	8	0.5	UNLIM	6	0.5
0.002	UNLIM	12	1	UNLIM	6	0.5	UNLIM	4	NONE	UNLIM	3	NONE
0.004	UNLIM	6	0.5	UNLIM	3	NONE	UNLIM	2	NONE	15	1	NONE
0.006	UNLIM	4	NONE	UNLIM	2	NONE	13	1	NONE	10	1	NONE
0.008	UNLIM	3	NONE	15	1	NONE	10	1	NONE	7	0.5	NONE
0.01	UNLIM	2	NONE	12	1	NONE	8	0.5	NONE	6	0.5	NONE
0.02	12	1	NONE	6	0.5	NONE	4	NONE	NONE	3	NONE	NONE
0.04	6	0.5	NONE	3	NONE	NONE	2	NONE	NONE	1	NONE	NONE
0.06	4	NONE	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
0.08	3	NONE	NONE	1	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE
0.1	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.2	1	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
0.4	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>0.4	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–71. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	PCBs (Aroclor 1254)
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	2E–05 mg/kg–d
Detection Limit:	1E–03 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.002	UNLIM	UNLIM	UNLIM
0.004	8	6	3
0.005	6	5	2
0.006	5	4	2
0.007	4	3	1
0.008	4	3	1
0.009	3	2	1
0.01	3	2	1
0.02	1	1	NONE
0.03	1	NONE	NONE
0.04	NONE	NONE	NONE
0.05	NONE	NONE	NONE
0.06	NONE	NONE	NONE
>0.06	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–72 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Selenium
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–03 mg/kg–d
Detection Limit:	2E–02 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)			
	4	8	12	16
<0.8	UNLIM	UNLIM	UNLIM	UNLIM
0.8	UNLIM	UNLIM	UNLIM	9
0.9	UNLIM	UNLIM	UNLIM	8
1	UNLIM	UNLIM	10	7
2	UNLIM	7	5	3
3	10	5	3	2
4	7	3	2	1
5	6	3	2	1
6	5	2	1	1
7	4	2	1	1
8	3	1	1	NONE
9	3	1	1	NONE
10	3	1	1	NONE
20	1	NONE	NONE	NONE
30	1	NONE	NONE	NONE
40	NONE	NONE	NONE	NONE
50	NONE	NONE	NONE	NONE
60	NONE	NONE	NONE	NONE
>60	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–73. Monthly Consumption Limits for *Chronic Systemic Health Endpoints*

Chemical Name:	Selenium
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–03 mg/kg–d
Detection Limit:	2E–02 mg/kg

Risk–Based Consumption Limit (meals per month)				
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			
	4	8	12	16
<2	UNLIM	UNLIM	UNLIM	UNLIM
2	UNLIM	UNLIM	15	11
3	UNLIM	15	10	7
4	UNLIM	11	7	5
5	UNLIM	9	6	4
6	15	7	5	3
7	13	6	4	3
8	11	5	3	2
9	10	5	3	2
10	9	4	3	2
20	4	2	1	1
30	3	1	1	0.5
40	2	1	0.5	0.5
50	1	0.5	0.5	NONE
60	1	0.5	0.5	NONE
70	1	0.5	NONE	NONE
80	1	0.5	NONE	NONE
90	1	0.5	NONE	NONE
100	0.5	NONE	NONE	NONE
>100	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–74. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Selenium
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	5E–03 mg/kg–d
Detection Limits:	2E–02 mg/kg

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.2	UNLIM	UNLIM	UNLIM
0.2	UNLIM	UNLIM	UNLIM
0.3	UNLIM	UNLIM	10
0.4	UNLIM	UNLIM	7
0.5	UNLIM	UNLIM	6
0.6	UNLIM	10	5
0.7	UNLIM	9	4
0.8	10	7	3
0.9	9	7	3
1	8	6	3
2	4	3	1
3	2	2	1
4	2	1	NONE
5	1	1	NONE
6	1	1	NONE
7	1	NONE	NONE
8	1	NONE	NONE
9	NONE	NONE	NONE
10	NONE	NONE	NONE
>10	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–75. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Terbufos
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	N/A

Risk–Based Consumption Limit (meals per 10 days)				
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			
	4	8	12	16
<0.008	UNLIM	UNLIM	UNLIM	UNLIM
0.008	UNLIM	UNLIM	UNLIM	9
0.009	UNLIM	UNLIM	UNLIM	8
0.01	UNLIM	UNLIM	10	7
0.02	UNLIM	7	5	3
0.03	10	5	3	2
0.04	7	3	2	1
0.05	6	3	2	1
0.06	5	2	1	1
0.07	4	2	1	1
0.08	3	1	1	NONE
0.09	3	1	1	NONE
0.1	3	1	1	NONE
0.2	1	NONE	NONE	NONE
0.3	1	NONE	NONE	NONE
0.4	NONE	NONE	NONE	NONE
0.5	NONE	NONE	NONE	NONE
0.6	NONE	NONE	NONE	NONE
>0.6	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
N/A = not available
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–76. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Terbufos
Population:	General
Body Weight:	70 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limit:	N/A

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.02	UNLIM	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	15	11
0.03	UNLIM	15	10	7
0.04	UNLIM	11	7	5
0.05	UNLIM	9	6	4
0.06	15	7	5	3
0.07	13	6	4	3
0.08	11	5	3	2
0.09	10	5	3	2
0.1	9	4	3	2
0.2	4	2	1	4
0.3	3	1	1	0.5
0.4	2	1	0.5	0.5
0.5	1	0.5	0.5	NONE
0.6	1	0.5	0.5	NONE
0.7	1	0.5	NONE	NONE
0.8	1	0.5	NONE	NONE
0.9	1	0.5	NONE	NONE
1	0.5	NONE	NONE	NONE
>1	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
N/A = not available
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–77. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Terbufos
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	5E–05 mg/kg–d
Detection Limits:	N/A

Risk–Based Consumption Limit (meals per 10 days)			
Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)		
	3	4	8
<0.003	UNLIM	UNLIM	UNLIM
0.003	UNLIM	UNLIM	10
0.004	UNLIM	UNLIM	7
0.005	UNLIM	UNLIM	6
0.006	UNLIM	10	5
0.007	UNLIM	9	4
0.008	10	7	3
0.009	9	7	3
0.01	8	6	3
0.02	4	3	1
0.03	2	2	1
0.04	2	1	NONE
0.05	1	1	NONE
0.06	1	1	NONE
0.07	1	NONE	NONE
0.08	1	NONE	NONE
0.09	NONE	NONE	NONE
0.1	NONE	NONE	NONE
>0.1	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
N/A = not available
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–78. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Toxaphene
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	3E–03 mg/kg

Risk–Based Consumption Limit (meals per 10 days)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)			
	4	8	12	16
<0.04	UNLIM	UNLIM	UNLIM	UNLIM
0.04	UNLIM	UNLIM	UNLIM	9
0.05	UNLIM	UNLIM	10	7
0.06	UNLIM	UNLIM	8	6
0.07	UNLIM	UNLIM	7	5
0.08	UNLIM	9	6	4
0.09	UNLIM	8	5	4
0.1	UNLIM	7	5	3
0.2	7	3	2	1
0.3	5	2	1	1
0.4	3	1	1	NONE
0.5	3	1	1	NONE
0.6	2	1	NONE	NONE
0.7	2	1	NONE	NONE
0.8	1	NONE	NONE	NONE
0.9	1	NONE	NONE	NONE
1	1	NONE	NONE	NONE
2	NONE	NONE	NONE	NONE
3	NONE	NONE	NONE	NONE
>3	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 1 meal per day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period (based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–79. Monthly Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Toxaphene
Population:	General
Body Weight:	70 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limit:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per month) Meal Size (oz)			
	4	8	12	16
<0.07	UNLIM	UNLIM	UNLIM	UNLIM
0.07	UNLIM	UNLIM	UNLIM	16
0.08	UNLIM	UNLIM	UNLIM	14
0.09	UNLIM	UNLIM	17	13
0.1	UNLIM	UNLIM	15	11
0.2	UNLIM	11	7	5
0.3	15	7	5	3
0.4	11	5	3	2
0.5	9	4	3	2
0.6	7	3	2	1
0.7	6	3	2	1
0.8	5	2	1	1
0.9	5	2	1	1
1	4	2	1	1
2	2	1	0.5	0.5
3	1	0.5	0.5	NONE
4	1	0.5	NONE	NONE
5	0.5	NONE	NONE	NONE
6	0.5	NONE	NONE	NONE
7	0.5	NONE	NONE	NONE
8	0.5	NONE	NONE	NONE
9	0.5	NONE	NONE	NONE
>9	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Monthly limits are based on the total dose allowable over a one–month period (based on the RfD). When this dose is delivered in less than one month (e.g., in a few large meals), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

Table 3–80. Monthly Consumption Limits for Carcinogenic Health Endpoints

Chemical Name:	Toxaphene
Population:	General
Body Weight:	70 kg
Cancer Potency Factor:	1E+00 per mg/kg–d
Detection Limit:	3E–03 mg/kg

Risk–Based Consumption Limit (meals per month)

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Meal Size (oz)											
	4			8			12			16		
	ARL			ARL			ARL			ARL		
	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}	10^{-4}	10^{-5}	10^{-6}
<0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM
0.0004	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	14	UNLIM	UNLIM	10
0.0006	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	14	UNLIM	UNLIM	9	UNLIM	UNLIM	7
0.0008	UNLIM	UNLIM	UNLIM	UNLIM	UNLIM	10	UNLIM	UNLIM	7	UNLIM	UNLIM	5
0.001	UNLIM	UNLIM	16	UNLIM	UNLIM	8	UNLIM	UNLIM	5	UNLIM	UNLIM	4
0.002	UNLIM	UNLIM	8	UNLIM	UNLIM	4	UNLIM	UNLIM	2	UNLIM	UNLIM	2
0.004	UNLIM	UNLIM	4	UNLIM	UNLIM	2	UNLIM	14	1	UNLIM	10	1
0.006	UNLIM	UNLIM	2	UNLIM	14	1	UNLIM	9	0.5	UNLIM	7	0.5
0.008	UNLIM	UNLIM	2	UNLIM	10	1	UNLIM	7	0.5	UNLIM	5	0.5
0.01	UNLIM	16	1	UNLIM	8	0.5	UNLIM	5	0.5	UNLIM	4	NONE
0.02	UNLIM	8	0.5	UNLIM	4	NONE	UNLIM	2	NONE	UNLIM	2	NONE
0.04	UNLIM	4	NONE	UNLIM	2	NONE	14	1	NONE	10	1	NONE
0.06	UNLIM	2	NONE	14	1	NONE	9	0.5	NONE	7	0.5	NONE
0.08	UNLIM	2	NONE	10	1	NONE	7	0.5	NONE	5	0.5	NONE
0.1	16	1	NONE	8	0.5	NONE	5	0.5	NONE	4	NONE	NONE
0.2	8	0.5	NONE	4	NONE	NONE	2	NONE	NONE	2	NONE	NONE
0.4	4	NONE	NONE	2	NONE	NONE	1	NONE	NONE	1	NONE	NONE
0.6	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
0.8	2	NONE	NONE	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE
1	1	NONE	NONE	0.5	NONE	NONE	0.5	NONE	NONE	NONE	NONE	NONE
2	0.5	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
>2	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE

Meal sizes of 4, 8, 12, and 16 oz. correspond to 0.114, 0.227, 0.341, and 0.454 kg.
UNLIM = Unlimited consumption; more than 4 meals per week (17/month).
NONE = No consumption; less than six meals per year.
0.5 meals per month represents six meals per year.
References for cancer potency factors are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
All values were rounded down to the nearest whole meal size.
* ARL = Acceptable Risk Level

Table 3–81. 10–Day Consumption Limits for Chronic Systemic Health Endpoints

Chemical Name:	Toxaphene
Population:	Children
Body Weight:	14.5 kg
Reference Dose:	3E–04 mg/kg–d
Detection Limits:	3E–03 mg/kg

Chemical Concentration Found in Sampling and Analysis Program (mg/kg)	Risk–Based Consumption Limit (meals per 10 days) Meal Size (oz)		
	3	4	8
<0.005	UNLIM	UNLIM	UNLIM
0.008	UNLIM	UNLIM	UNLIM
0.009	UNLIM	UNLIM	UNLIM
0.01	UNLIM	UNLIM	UNLIM
0.02	UNLIM	UNLIM	7
0.03	UNLIM	10	5
0.04	10	7	3
0.05	8	6	3
0.06	7	5	2
0.07	6	4	2
0.08	5	3	1
0.09	4	3	1
0.1	4	3	1
0.2	2	1	NONE
0.3	1	1	NONE
0.4	1	NONE	NONE
0.5	NONE	NONE	NONE
0.6	NONE	NONE	NONE
0.7	NONE	NONE	NONE
0.8	NONE	NONE	NONE
>0.8	NONE	NONE	NONE

Meal sizes of 3, 4, and 8 oz. correspond to 0.085, 0.114, and 0.227 kg.
UNLIM = Unlimited consumption; more than 1 meal/day.
NONE = No consumption; less than one meal per 10 days.
References for RfDs are found in Part II, Section 5.
Instructions for modifying the variables in this table are found in Section 2.3.
Note that some values may be below detection limits.
Note nonlinear scale of concentration values.
Ten–day limits are based on the total dose allowable over a 10–day period based on the RfD). When this dose is delivered in less than 10 days (e.g., in a single meal), note that the daily dose exceeds the RfD (see Section 4.3).
All values were rounded down to the nearest whole meal size.

PART II.

This section of the guidance document provides an overview of the basic EPA methodology used to carry out a risk assessment for contaminated non-commercial fish consumption. Section 4 focuses on those aspects relevant to evaluating risk and setting guidelines for fish, and provides more detail on the methods used to calculate consumption limits. Section 5 contains summaries of toxicological data for the 23 target analytes and methods for estimating exposure limits for developmental and chronic exposure effects. Section 6 lists the references used in this document. Appendix A provides further information on genotoxicity and mutagenicity, while Appendix B provides a list of additional sources of information.

SECTION 4

RISK ASSESSMENT METHODS

4.1 Introduction

The presentation of risk assessment methods in Section 4 follows the format of the risk assessment process recommended by EPA for cancer and non-cancer toxicity:

- Hazard identification,
- Dose-response assessment,
- Exposure assessment, and
- Risk characterization (EPA, 1986a, c; IRIS, 1993).

EPA methods follow the outline developed in the National Academy of Sciences (NAS) report entitled *Risk Assessment in the Federal Government: Managing the Process* (NAS, 1983; see Figure 4-1). According to NAS,

> "risk assessment can be divided into four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. A risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate." (NAS, 1983)

Readers may wish to consult the new NAS document, entitled *Science and Judgement in Risk Assessment*, which provides an update and expansion of the 1983 work (NAS, 1994).

Hazard identification is the first step in the risk assessment process. It consists of a review of biological, chemical, and exposure information bearing on the potential for an agent to pose a specific hazard (Preuss and Erlich, 1986). Hazard identification involves gathering and evaluating data on the types of health effects which are associated with chemicals of concern under specific exposure conditions (e.g., chronic, acute, airborne, or foodborne; EPA, 1985).[1]

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[1] Some groups within EPA which conduct primarily chemical-specific evaluations do not incorporate considerations of occurrence or exposure into their hazard identification process.

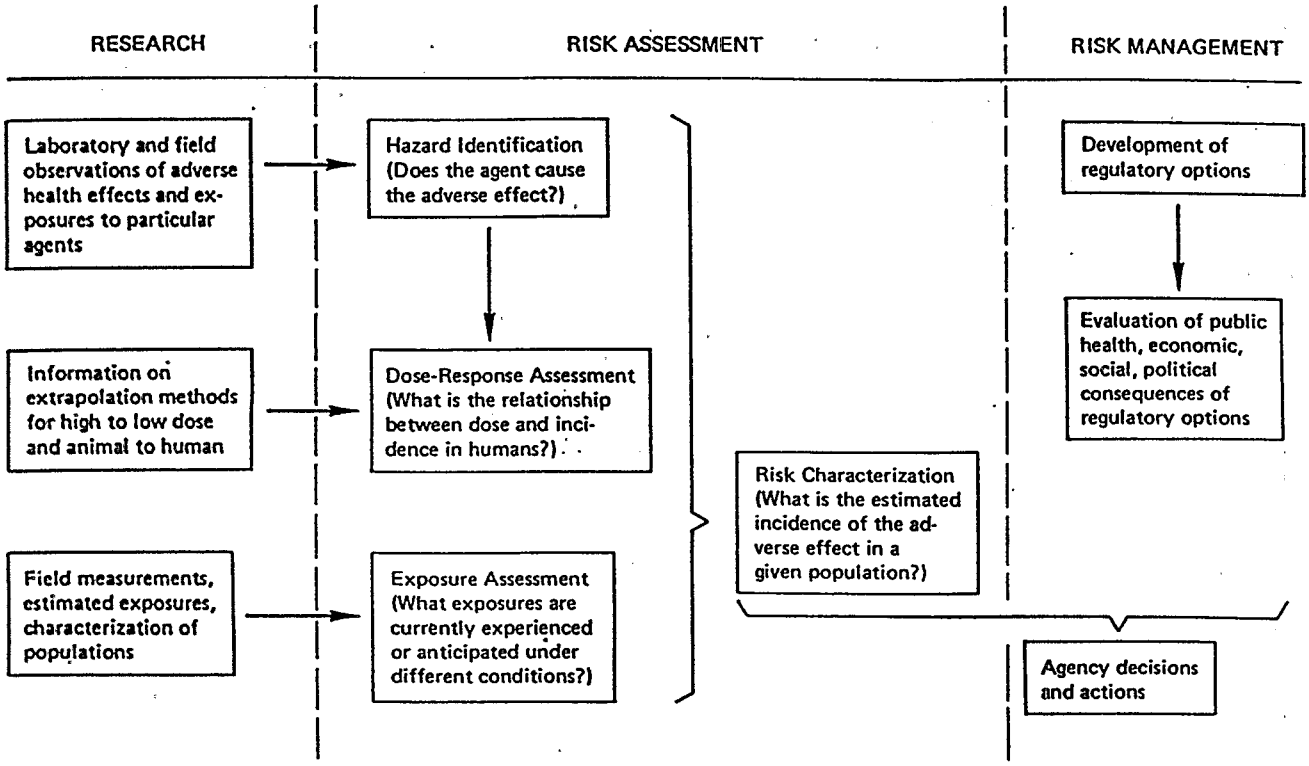

Figure 4-1. Elements of Risk Assessment and Risk Management (NAS, 1983)

Section 4.2 provides an overview and summary of the hazard identification process and specific information on hazard identification for non-commercial fish chemical contaminants. It does not provide detailed guidance on hazard identification since EPA's Office of Water has already completed the hazard identification step with respect to fish contaminants. This work was undertaken to identify the fish contamination target analytes of concern, as described in *Volume 1: Fish Sampling and Analysis* (EPA, 1993a) in this guidance series. This process included an evaluation of information regarding toxicity, occurrence, persistence, and other factors. The methods for selecting the highest priority chemicals as target analytes are described in Volume 1 and summarized briefly in Section 4.2.1. of this document.

The second step in the risk assessment process is the evaluation of the dose-response dynamics for chemicals of concern (See Section 4.3). The dose-response dynamic expresses the relationship between exposure and health effects. To evaluate this relationship, the results of human and animal studies are reviewed; the dose-response evaluation may focus on specific types of effects (e.g., developmental, carcinogenic) or be designed to encompass all adverse effects which could occur under any plausible scenario.

The third step in the risk assessment process is exposure assessment (See Section 4.4). Individual exposure assessments use data on chemical residues in fish and human consumption patterns to estimate exposure for hypothetical individuals. Population exposure assessments consider the distributions of exposure in a population. Exposure assessments are then combined with dose-response data to determine risk.

The final step in risk assessment is risk characterization (See Section 4.5), which provides an estimate of the overall individual or population risks. Risk characterization can be used by risk managers to prioritize resource allocation and identify specific at-risk populations; it is also used to establish regulations or guidelines, and to estimate individual or population risk. In this document, risk characterization involves developing the risk-based consumption limits provided in Section 3. When risk characterization is used to estimate individual or population risk, it serves to provide the risk manager with necessary information regarding the probable nature and distribution of health risks associated with various contaminants and contaminant levels. This aspect of risk characterization is discussed in more detail in Volume 3 of this series. An overview of the methods which would be used when chemical concentrations exceed screening values is also provided in Volume 1 (EPA, 1993a).

The importance of describing and, when possible, quantifying the uncertainties and assumptions inherent in risk assessment has been long recognized, though not consistently practiced (Habicht, 1992). Uncertainty analysis is particularly

critical in risk characterization and must be performed throughout the risk assessment process in order to adequately characterize assumptions in this last step of the process. Consequently, a description of various sources of uncertainty and a discussion of assumptions is provided for each of the four activities which comprise risk assessment.

4.1.1. Other Information Sources

This document contains only an overview of risk assessment as it applies to fish advisories. For readers who wish to obtain more detail, EPA has issued several guidelines for conducting specific portions of the risk assessment process, which address the following areas:

- Exposure assessment (EPA, 1992a),
- Carcinogenicity risk assessment (EPA, 1986a),
- Mutagenicity risk assessment (EPA, 1986c),
- Developmental toxicity risk assessment (EPA, 1991a),
- Assessment of female and male reproductive risk (EPA, 1988a; 1988b),
- Health risk assessment of chemical mixtures (EPA, 1986d), and
- Exposure factors (EPA, 1990a).

These guidelines were developed by EPA to ensure consistency and quality among Agency risk assessments. EPA's Risk Assessment Forum is in the process of developing quantitative guidelines on dose-response assessment of systemic toxicants. One approach used to estimate Reference Doses for chronic exposure toxicity is presented in the Background Documents for the Integrated Risk Information System (IRIS). It is also found in many EPA publications and has been summarized in recent papers which discuss risk assessment within EPA (s.f., Barnes and Dourson, 1988; Abernathy and Roberts, 1994). Relevant sections of each of the above guidelines were consulted in developing this section, along with other resources cited throughout the section. Additional references are listed in Section 6 and Appendix B.

4.2. Hazard Identification

Hazard identification assesses the likelihood that exposure to specific chemicals under defined exposure conditions will pose a threat to human health. Hazard identification is often used effectively to determine whether a chemical or groups of chemicals occurring in specific exposure situation require action. It has been narrowly defined for some applications to provide only chemical specific hazard data (NAS, 1983). However, in the new NAS document, *Science and Judgement in Risk Assessment*, the use of an iterative approach

to evaluating risk is emphasized which entails the use of relatively inexpensive screening techniques to determine when to proceed to more in-depth evaluations (NAS, 1994). This is analogous, in practice, to what is already frequently done at the state and local level. The early stages of risk assessment often include consideration of the existence or likelihood of exposure in order to determine whether further work on a chemical should be pursued. At the state, local and tribal levels, administrators and risk managers concurrently evaluate both the hazard and the occurrence of chemicals to assess whether sufficient risk exists to justify an investment of time and resources in further action. Their needs for information to guide further action are, therefore, different from that of a federal agency, which may evaluate hazards independently of exposure considerations.

A preliminary risk evaluation typically precedes an in-depth risk assessment because most states, localities, and tribal bodies do not have the resources to conduct detailed risk analyses in the absence of information indicating that health risks may occur. As a result of this practical need for information, hazard identification is discussed in this section in a manner designed to enable readers to make preliminary decisions regarding further action on fish advisories. This approach is similar to the screening methodology used for the identification of the 23 target analytes addressed in this guidance series and is discussed in *Volume 1: Sampling and Analysis* in this series (EPA, 1993a).

Although hazard identification is essentially a screening process, it may entail a complex evaluation of the exposure scenarios and toxicological and biological properties of contaminants (e.g., bioavailability, degradation, existence of breakdown products and metabolites). Hazard identification ranges in scope from the use of existing summary data (e.g., IRIS, or ATSDR Toxicological Profiles) to a detailed evaluation of each aspect of exposure and risk; the depth of analysis is usually determined by time and resource availability. For example, an evaluation of a contaminant's toxicological properties may include an analysis of all health endpoints likely to occur in the exposure scenarios of concern. Recent EPA guidance (Habicht, 1992) describes hazard identification as:

> "a qualitative description based on factors such as the kind and quality of data on humans or laboratory animals, the availability of ancillary information (e.g., structure-activity analysis, genetic toxicity, pharmacokinetics) from other studies, and the weight-of-evidence from all of these data sources. "

Under some circumstances extensive data collection may be undertaken. For example, to evaluate carcinogenic risk, EPA has recommended the following information be reviewed in a hazard identification: physical-chemical properties,

routes and patterns of exposure, structure-activity relationships, metabolic and pharmacokinetic properties, toxicological effects (including subchronic and chronic effects, interactions with other chemicals, pathophysiological reactions, and time-to-response analysis), short-term tests (including mutagenicity and DNA damage assessment), long-term animal studies, human studies, and weight-of-evidence (EPA, 1986a). At the state, local, and tribal level, this type of in-depth analysis is rarely carried out for each health endpoint of a chemical hazard, due to the time and resources required. Alternatively, data bases, such as IRIS and the Hazardous Substances Data Bank (HSDB) which summarize health endpoints and associated risk values, are inexpensively, readily available, and often consulted in the development of a hazard profile.

4.2.1. Approach for Fish Contaminants

The hazard identification step in risk assessment of chemically-contaminated fish has been refined by EPA through careful review of the chemical characteristics considered to be critical parameters in determining human health risk. These parameters are:

- High persistence in the aquatic environment,
- High bioaccumulation potential,
- Known sources of contaminant in areas of interest,
- High potential toxicity to humans, and
- High concentrations of contaminants in previous samples of fish or shellfish from areas of interest (EPA, 1989a).

These characteristics are described in detail in *Volume 1: Fish Sampling and Analysis* in this series. Additional information on persistence and bioaccumulation potential may be obtained from EPA documents such as the *Technical Support Document for Water Quality-Based Toxics Control* from the Office of Water (EPA, 1991b), which contains a brief description of the bioaccumulation characteristics considered for the development of reference ambient concentrations (RAC). Readers may also wish to consult the open literature (s.f., Lyman et al., 1982, Callahan et al., 1979).

4.2.1.1. Toxicological Data

The toxicity of a chemical to humans can be evaluated based on its acute (short-term) exposure toxicity and/or chronic (long-term) exposure toxicity. The chronic toxicity of a chemical is usually of primary concern for environmental toxics; however, the varied consumption patterns of fish consumers complicate the analysis of fish contaminants. Section 4.3 contains a discussion of this issue. There are a number of data bases which contain risk values for various types of chronic toxicity (e.g., carcinogenicity, liver toxicity, and

neurotoxicity). IRIS is a widely-accepted data source due to the extensive review conducted on the risk values contained in the data base. EPA's Health Effects Assessment Summary Tables (HEAST) are also a frequently-used risk data base (HEAST, 1992). Other relevant data bases include HSDB, the National Cancer Institute's Chemical Carcinogenesis Research Information System (CCRIS), EPA's GENE-TOX, and the National Institute of Occupational Safety and Health's (NIOSH) Registry of Toxic Effects of Chemical Substances (RTECS). All of the above data bases except HEAST are available through TOXNET.[2] ATSDR's Toxicity Profiles also provide toxicity data summaries.

4.2.1.2. Contaminant Data

Information on the prevalence and measured concentrations of fish contamination has been generated through numerous sampling and analysis programs. EPA has provided a summary of preliminary screening results on the prevalence of selected bioaccumulative pollutants in fish in Volume 1 of the *National Study of Chemical Residues in Fish* (EPA 1992b). In addition, substantial guidance is provided on planning a sampling strategy and conducting fish contaminant analyses in Volume 1 of this series (EPA, 1993a).

Likely sources of contaminants are often known to state, regional, and tribal officials or can be identified through a review of data on manufacturing, toxic releases, or complaints regarding contamination of food, soil, air, or water. Recommended sources and lists for obtaining data regarding probable contaminants include:

- EPA recommended target analytes (see Table 1-1),
- Chemical releases reported in EPA's Toxics Release Inventory (TRI) data base,
- The Manufacturers' Index,
- EPA priority pollutants,
- State inventories of manufacturers and operations,
- Chemicals identified in industrial and POTW effluents as non-biodegradable,
- Known spills and contaminants (as reported under CERCLA to the Office of Emergency and Remedial Response),
- EPA source inventory for contaminated sediments,
- ATSDR's HAZDAT database,

[2] TOXNET is managed by the U.S. Department of Health and Human Services' National Library of Medicine (Bethesda, MD). For more information, call (800) 848-8990 (for Compuserve), (800) 336-0437 (for Telenet), (800) 336-0149 (for TYMNET), or (301) 496-6531 for technical assistance.

- Listing of Superfund (NPL) sites, and
- Common-use chemicals based on practices in the state or region (e.g., agriculture or fuels).

This information can be used to develop descriptions of local water bodies incorporating geographic and source-specific data. The geographic distribution of potential contaminants can be used to guide the selection of monitoring sites for sampling and analysis of potentially contaminated fish.

Volume 2 of the *National Study of Chemical Residues in Fish* (EPA, 1992b) provides an example of how information on the first three characteristics of chemical contaminants listed above (high persistence in the aquatic environment, high bioaccumulation potential, and high concentrations of contaminants in previous samples of fish or shellfish from areas of interest) can be summarized to form the basis for a hazard evaluation. The document provides a summary of the results of the National Bioaccumulation Study, correlates contaminant prevalence with sources of pollutants, and provides a brief description of the chemical and toxicological properties of 37 chemicals and chemical groups (EPA, 1992b).

4.2.1.3. Sources of Exposure

Hazard identification may also include a comprehensive evaluation of all sources of exposure, including those which augment the primary exposure of concern, to obtain an estimate of total exposure. For fish contaminants, a comprehensive exposure evaluation would involve an evaluation of exposures from other sources such as air, water, soil, the workplace, or other foods, including commercially-caught fish. In some cases, in fact, other routes of exposure may contribute more to overall contaminant body burden than does contaminated non-commercial fish. It is beyond the scope of this guidance document to provide direction on evaluating exposures occurring via other media; however, readers are encouraged to include an assessment of other sources of exposures in their hazard evaluations.

If exposure from non-commercial fish consumption were added to already elevated exposure levels arising from other sources, it could produce an overall exposure associated with adverse health effects. Under such circumstances, a more stringent fish consumption limit (or some other risk management option) may be needed. Readers may wish to determine whether such an evaluation is warranted through consideration of the likelihood that exposures are occurring via non-fish routes, and the availability of data and resources to carry out a comprehensive exposure evaluation.

EPA's Office of Water, in conjunction with the Interagency Relative Source Contribution Policy Workgroup, is currently developing guidance on the use of a "Relative Source Contribution" (RSC) approach. According to the preliminary information available on this approach:

> The RSC concept could be used in fish advisory activities. The amount of exposure from fish consumed is determined along with the estimated exposure from all other relevant sources (e.g., drinking water, food, air, and soil) for the chemical of concern. By comparing the overall exposure with the Reference Dose, it can then be determined whether the amount of total exposure to the chemical may result in an adverse effect and warnings can be issued regarding the safety of consuming such fish (Borum, 1994).

The CERCLA office at EPA, which offers assistance on multimedia assessments of hazardous waste sites, may also be consulted for information on methods to estimate background levels of various contaminants. They have developed guidance documents which may be useful to those readers who plan to conduct comprehensive exposure assessments. See Appendix B for a listing of sources of additional information.

4.2.2. Assumptions and Uncertainty Analysis

Hazard identification, as described in this guidance, is a screening process used to select the chemicals and exposure scenarios of greatest concern. As a screening process, it uses simplifications and assumptions in each step of the process. Because each aspect of hazard is not examined in its entirety, the process generates some uncertainty.

Uncertainty is introduced by the variability in persistence and bioaccumulation potential of chemicals which may occur in untested media. The behavior of chemicals in all types of media cannot be anticipated. For example, interactions of the target analytes in sediments containing multiple chemical contaminants may cause chemicals to change their forms as well as their bioaccumulation and persistence characteristics. For example, binding of the target analyte to organic matter may cause it to become more or less persistent or available for bioaccumulation, or decomposition may occur, producing metabolites which have significantly different properties than those of the original target analyte. These chemical and biological interactions are more likely to occur in a complex system (e.g., a hazardous waste site), with relatively unstable chemicals, and with metals having multiple valence states.

The persistence of a chemical in the aquatic environment and its bioaccumulative potential are based on its physical and biochemical properties. Although the critical information is available for many chemicals of concern, it is not available for all chemicals. For example, chemicals which have been recently introduced into the environment may not be well-characterized in terms of their persistence and bioaccumulation potential. Consequently, there is the potential for under- or overestimating the risk they pose to human health.

Estimation of chemical toxicity can be a source of significant uncertainty in the hazard identification process. A toxicity evaluation incorporates data on a variety of health endpoints and usually requires that human toxicity estimates be derived from studies in experimental animals. There are often insufficient data in the toxicological literature to fully characterize the toxicity of a chemical. Some types of toxicity are well-described in the toxicological and risk literature. Others, such as developmental toxicity, neurotoxicity, and immunotoxicity, have only recently become subjects of intensive research.[3] Consequently, there are limited data for most chemicals on these types of effects. Uncertainties associated with toxicity and health risk values (e.g., q_1^*s and RfDs) are discussed in Section 4.3.

The two remaining characteristics of hazard identification (known sources of contaminants in areas of interest and high concentrations of contaminants in previous samples of fish or shellfish) are excellent indicators of potential hazard. A major uncertainty associated with these characteristics arises from the potential for omitting areas not known to be contaminated from sampling programs. During an era of limited resources, it is a common, but not necessarily valid, assumption that known contaminated areas should be the focus of evaluation and action. Given an array of known contaminated sites, attempts to identify additional contamination may appear unnecessary. However, it is recommended that readers conduct a detailed review of potential contamination sources for all waterbodies before determining whether or not adequate hazard identifications have been conducted.

Because the goal of the risk assessment process is protection of human health, it is typically designed to provide the maximum protection against *under*estimating risk. Therefore, the hazard identification step in the risk assessment process may result in the inclusion of chemicals or exposure situations which, later in the process, are found not to pose significant health risks. This type of approach is taken because the consequences of

[3] Although studies of developmental toxicity date from the 19th century, there has been a dramatic increase in both epidemiological and toxicological studies in recent years.

underestimating risk, or excluding a chemical which poses a public health hazard, are potentially more serious than the risks of overestimating risk at this early stage of evaluation.

The hazard identification process forms the basis for decisions regarding those chemicals and exposure scenarios which warrant further analysis. It entails the collection and evaluation of information regarding toxicity, bioaccumulation potential, persistence, and prevalence. Although there is uncertainty associated with this aspect of the assessment, quantitative evaluation of the uncertainty can best be conducted in later steps in the risk assessment process. Because each aspect of hazard identification is carried out in more detail in the risk assessment steps which follow, the uncertainties and assumptions can be better refined and quantified during subsequent steps. The information generated on toxicity and exposure in this process also serves as the basis for the subsequent dose-response evaluation and exposure assessment steps in the risk assessment.

4.3. Dose-Response Assessment

This section briefly outlines the current EPA methodology for carrying out a dose-response assessment. Additional information on dose-response evaluations can be obtained from the references cited in Section 6, and in Appendix B.

A dose-response relationship expresses the correlation between exposure and health effects. To evaluate this relationship, the results of human and animal studies with controlled and quantified exposures are reviewed. This evaluation may focus on specific types of health effects, or be designed to encompass all adverse effects which could occur under any plausible exposure scenario. Dose-response evaluations result in the derivation of toxicity values such as cancer potencies and Reference Doses.

Actual fish consumption patterns may not correspond well to the typical periods of exposure which are studied in toxicity tests (i.e., acute or chronic exposure). Many fish consumers ingest intermittent doses of varying sizes and may consume fish over a short period of time (e.g., a vacation) or on a regular basis over a lifetime. The potentially large, intermittent dose (bolus dose) has not been evaluated in most toxicity studies. Chronic exposure studies commonly use daily dosing and acute studies may use one or a few very large doses over a very short time period (e.g., two to three days). Short-term dosing is frequently used in developmental toxicity studies (discussed in Section 5); two of the 23 target analytes have RfDs based on developmental toxicity (methylmercury and PCBs).

Fish consumption patterns are discussed in more detail in Volume 3; however, it is important to be aware that there is not information available on the impact of bolus dosing when developing fish advisories. The methods used to calculate fish consumption limits allow the daily RfD to be aggregated over a period of time (e.g., ten days or one month) into one or more meals. Thus the consumption *averaged* over the ten days or one month corresponds to an *average* daily dose indicated by the RfD. However, the actual dose which may be consumed in one day can be ten times (in the case of a ten-day advisory) or thirty to sixty times (in the case of a 30-day advisory) the daily RfD.

A bolus dose may not be a problem for many individuals; however, it is a concern for those who are particularly susceptible to toxics. For example, a relatively large single dose may be problematic for those with decreased ability to detoxify chemicals (e.g., children and the elderly) and those with special susceptibilities (e.g., persons taking certain medications, children, and pregnant or lactating women). Potential adverse effects in some subgroups are noted for many of the target analytes in Section 5. For example, organochlorines may interact with some commonly prescribed pharmaceuticals; consequently, individuals using specific drugs may find the efficacy altered by large doses of contaminants which interact with their drug-metabolizing systems. Infants have an immature immune system and may be less able to detoxify certain chemicals. Children have rapidly developing organ systems which may be more susceptible to disruption. A recent NAS report, *Pesticides in the Diets of Infants and Children* (NAS, 1993), concluded that children age zero to eighteen years are substantially different from adults in the relative immaturity of their biochemical and physiological functions and structural features. These differences can alter responses to pesticides, especially during windows of vulnerability, leading to permanent alteration of the function of organ systems. The authors, who included pediatricians, toxicologists, epidemiologists and other health specialists, concluded that:

> "[i]nfants and children may exhibit unique susceptibility to the toxic effects of pesticides because they are undergoing rapid tissue growth and development, but empirical evidence to support this is mixed"
>
> and
>
> "[t]raditional approaches to toxicological risk assessment may not always adequately protect infants and children" (NAS, 1993).

Although the focus of the NAS report was on pesticides (many of the target analytes are currently or were formerly used as pesticides) much of the analysis is relevant to other chemical exposures as well. Readers may wish to refer to

the NAS report for a more complete discussion of various related topics of interest including neurotoxicity in children, various dosimetry scaling methods, and consumption patterns.

A dose-response evaluation has already been carried out by EPA for the 23 target analytes addressed in this guidance series. These evaluations resulted in the calculation of risk values: either cancer potency factors (q_1^*s), Reference Doses (RfDs), or both. The risk values used in this work and cited in the toxicological discussions in Section 5 were obtained primarily from EPA's IRIS data base. All data searches were carried out in 1993 or early 1994. For chemicals lacking IRIS risk values, values were obtained from EPA's Office of Pesticide Programs (OPP) or EPA's Health Effects Assessment Summary Tables (HEAST, 1992).

A comprehensive dose-response evaluation requires an extensive review of both the primary literature, including journal articles and proceedings, and the secondary literature, such as books, government documents, and summary articles. It is typically very time-consuming and requires data evaluation by toxicologists, epidemiologists and other health professionals. Because risk values are available for the target analytes, it is not recommended that readers undertake further detailed dose-response evaluations for these chemicals. However, new data is continually being generated which may require evaluation. In addition, chemicals which are not included in the target analyte list may require analysis. It is strongly suggested that an evaluation begin with a review of current government documents on a chemical. In many cases, EPA, FDA, or the Agency for Toxic Substances and Disease Registry (ATSDR) conduct detailed dose-response evaluations when a chemical is identified as an environmental pollutant or when new data become available. This may save readers hundreds of hours of research by providing data and risk values.

4.3.1. Acute Exposure Toxicity

Acute exposures are those which occur over brief periods of time, e.g., a few hours or days. They do not necessarily result in an acute (immediate) response, and so the exposure and response periods must be considered separately. The pesticide paraquat is an example of a chemical which usually causes no immediate response to acute exposure but often results in fatal outcomes after several days or weeks.

Acute exposures have traditionally been considered primarily in the realm of occupational health or poisoning incidents, rather than environmental health, because the brief, low-level exposure associated with most environmental exposures do not usually result in overt symptoms. The exceptions to this have been individuals with allergies or chemical sensitivities. However, there

has been a very limited analysis of most environmental pollutants with regard to both the nature and the critical dose for acute non-lethal effects. Acute exposures are of concern for fish contaminants, due to the ability of fish to bioaccumulate chemical contaminants to fairly high levels, and the relatively large and frequent meals (i.e., bolus doses) which may be consumed by sport and subsistence fishers and their families.

The goal of an acute exposure dose-response evaluation is to identify a threshold exposure level below which it is safe to assume no adverse health effects will occur. There are no widely-used methods within EPA for setting such exposure levels. Prenatal acute exposures are discussed in Section 5 as a special case because there are substantial animal data on short-term prenatal exposure for many target analytes. Additional guidance on acute exposure risk assessment methods may be provided in future revisions to this document. EPA welcomes comments and recommendations on this and other methodologies.

Most toxicological information currently available on acute exposure is in the form of LD_{50}s from animal studies. These studies identify the (usually single) dose which was lethal to 50 percent of the study animals via a specific exposure route. The data are used primarily to give a qualitative sense of the acute toxicity of a chemical. The information is generally used for purposes of planning industrial and application processes, transportation, handling, disposal, and responses to accidental exposures. The data are also used for regulatory purposes and to select the less-toxic alternatives among a group of chemical options. LD_{50}s may also be used to evaluate ecological toxicity.

LD_{50}s are not easily adaptable to an evaluation of the human response to acute exposures. Because they are focused on the level at which 50 percent of animals die, they do not provide information on other types of toxic responses, including those which led to death. Fatal toxic responses may be substantially different from the responses observed at lower, but still acutely toxic, doses. The LD_{50} also does not provide information on the exposure threshold for lethality, which is always lower (and may be much lower) than the exposure level required to kill 50 percent of the study subjects. For these reasons, the LD_{50}s have very limited utility in identifying a threshold for effects of acute exposure. LD_{50}s may, however, provide comparative information regarding differences in sensitivity between various age groups or sexes which can be used to qualitatively evaluate toxicity.

Human and veterinary poisoning centers (e.g., Poison Control Centers) are primary sources of data on acute exposure effects and thresholds. The poisoning data are limited, however, in many of the same ways in which LD_{50} data are limited. The severe responses which often lead to the reporting of an

incident do not indicate the level at which more moderate responses may occur. In addition, the dose is often not known or is estimated imprecisely. The poisoned individual may have predisposing medical conditions, or have been exposed concurrently to other chemicals (including medicines) which affect the nature of their responses.

EPA's Health Advisories also provide some acute exposure information and guidance regarding one- and ten-day exposure limits for children with an assumed 10-kg body weight (available from the EPA's Office of Water). The Toxicological Profiles developed by ATSDR also contain some information on acute effects. Additional information may be obtained from HSDB. A qualitative summary of acute effects and estimated human lethal doses are provided for most target analytes in Section 5.

4.3.2. Chronic Exposure Toxicity

Chronic exposure toxicity refers to effects resulting from multiple exposures occurring over a significant period of time (IRIS, 1993). For humans, this usually means exposures over months or years. For animals in studies used to evaluate human chronic toxicity, the temporal definition of chronic exposure depends on the species, but is usually defined as a significant portion of the animal's life. Chronic studies are reviewed in order to determine critical effects for specific chemicals. The critical effect is the first adverse effect, or its known precursor, that occurs as the dose rate increases (IRIS, 1993). Subchronic exposures in toxicity studies (usually three months to one year) may also be used to evaluate chronic toxicity.

To protect against chronic toxicity resulting from exposure to contaminants, EPA has developed Reference Doses (RfDs). The RfD is defined as "an estimate (with uncertainty perhaps spanning an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." (EPA, 1987). The use of IRIS RfDs is recommended for evaluation of chronic exposure toxicity of the target analytes. These are listed in Table 2-2 in Section 2, and again in Section 5. Additional chronic exposure toxicity data for the target analytes are presented in Section 5, with a brief description of how estimated exposure limits could be calculated based on chronic toxicity. Note that the RfDs listed in IRIS are subject to change as new methodologies and toxicological data become available. Readers are advised to consult the IRIS data base to ensure that they are using the most up-to-date toxicity values.

RfDs calculated for chronic non-carcinogenic effects reflect the assumption that for non-carcinogens and non-mutagens, a threshold exists below which exposure does not cause adverse health effects. This approach is taken for

non-carcinogens because it is assumed that for these types of effects there are homeostatic, compensating, and adaptive mechanisms which must be overcome before a toxic endpoint is manifested (IRIS, 1993).[4] It is recommended that concern be directed to the most sensitive individuals in a population, with the goal of keeping exposures below calculated RfDs for them (IRIS, 1993). RfDs are generally expressed in terms of milligrams of contaminant per kilogram consumer body weight per day (mg/kg-d).

Methods used to calculate RfDs are described in the *IRIS Background Document 1A, Reference Dose (RfD): Description and Use in Health Risk Assessments* (IRIS, 1993) and in two recent publications on EPA risk assessment methods (Dourson et al., 1992; Abernathy and Roberts, 1994). The methods are also described briefly in Section 5.3.

4.3.3. Carcinogenicity

EPA has developed guidelines, published in the Federal Register, for conducting cancer risk assessments (EPA, 1986a).[5] EPA (and many other risk assessors) takes a probabilistic approach to estimating carcinogenic risks. Cancer risk is assumed to be proportional to cumulative exposure, and at low exposure levels may be very small or even zero. EPA assumes that carcinogens do not have "safe" thresholds for exposure; i.e., any exposure to a carcinogen may pose some cancer risk. Carcinogenic risk is usually expressed as a cancer potency (q_1^*) value with units of risk per mg/kg-day exposure. Risk may also be estimated for specific media. When risks in air and water are provided, these are referred to as unit risks because they are expressed as risk per one unit of concentration of the contaminant in air or water.

The cancer potency value is derived from dose-response data obtained in an epidemiological study or a chronic animal bioassay. Because relatively high doses are used in most human and animal toxicity studies, the data are usually extrapolated to the low doses expected to be encountered by the general population. The dose-response data from one or more studies are fit to standard cancer risk extrapolation models which usually incorporate an upper-

[4] Some chemicals such as lead, however, appear to show non-threshold non-carcinogenic effects.

[5] Subsequently, new information on a variety of issues related to cancer risk assessment has become available (e.g., mechanisms of carcinogenesis, weight-of-evidence classification, study design and interpretation, and dose-response assessment. EPA is currently reevaluating its cancer risk assessment methodology.

bound estimate of risk (often the 95 percent upper bound). This provides a margin of safety to account for uncertainty in extrapolating from high to low doses and variations in the animal bioassay data (IRIS, 1993). The model most often used to calculate the cancer potency is the linearized multistage model (LMS). Cancer potency is estimated as the 95 percent upper confidence limit of the slope of the dose-response curve in the low-dose region. This method provides an upper estimate of risk; the actual risk may be significantly lower, and may be as low as zero. It is important to recognize that the use of this model results in risk estimates that are protective, but not predictive of cancer incidence (Velazquez, 1994).

Cancer potencies may be calculated for both oral and inhalation exposure. There are four major steps in calculating cancer potencies:

- Identify the most appropriate dose-response data,
- Modify dose data for interspecies differences,
- Develop an equation describing the dose-response relationship, and
- Calculate an upper confidence bound on the data.

These are described in more detail in EPA (1986a), and in texts on risk assessment. Cancer potency values are provided for those target analytes which EPA has determined have sufficient data to warrant development of a value. The values are listed in Table 2-2 and discussed in Section 5; they were used to calculate the consumption limits in Section 3.

As discussed under chronic toxicity above, children may have special susceptibilities to some chemicals and some types of effects. Exposure to a carcinogen early in life may generate greater risk than exposure later in life. This is due to a variety of factors including the rapid growth and development ongoing in children and the proportionally-greater consumption by children of some foods. The experimental literature on this subject is not conclusive and readers may wish to review the NAS report to obtain additional information (NAS, 1993).

4.3.4. Mutagenicity/Genotoxicity

Mutagenicity and genotoxicity data are not generally used to develop risk estimates by themselves, although they are frequently used in conjunction with other information to evaluate other toxicity endpoints (e.g., cancer). There is a wide variety of assays designed to assess the mutagenicity of chemicals; however, there is a limited amount of mutagenicity dose-response data which can be used in quantitative risk assessment. The majority of data involve *in vitro* test systems, which can provide only qualitative evidence of mutagenicity.

The evaluation of weight-of-evidence (WOE) for carcinogenicity, carried out by EPA for all chemicals having a cancer classification, includes an evaluation of mutagenicity data. Information on genetic toxicity also needs to be considered when developing risk values for developmental and reproductive system effects. Mutagenicity data are summarized in the chemical discussions of target analytes in Section 5. Readers are urged to consider this information in reviewing the toxicity of target analytes. Because information is less readily available on genetic toxicity and mutagenicity than on other types of risk assessment, and because this type of toxicity is relevant to evaluating developmental toxicity, a brief summary of the current EPA guidelines on these types of toxicity have been included in Appendix A.

4.3.5. Developmental Toxicity

Developmental toxicity has been a recognized medical concern, research subject, and impetus for restricting exposures of pregnant women to developmental contaminants for several decades. However, it is not as well-studied as other health effects such as cancer, and significant gaps in our understanding of causality and appropriate protective measures remain. Developmental toxicity incorporates a wide range of effects involving all organ systems in the body. Prenatal and lactational exposure involve indirect exposure of the developing fetus; the effective dose may vary with the period of exposure and the specific chemical. In the last two decades, researchers have determined that the hypothetical maternal barrier, in the past thought to provide protection for the fetus during the prenatal period, does not effectively exist. In fact, prenatal exposure may be especially risky due to the rapid cell replication and differentiation which occurs in the fetus prior to birth. These same processes also occur at elevated rates in children and adolescents, causing them to be more susceptible to some chemical-induced toxicity than adults. Chemical exposures which cause alterations in the cell replication and developmental processes can lead to serious birth defects, miscarriage, stillbirth, developmental delays, and a variety of other adverse effects. A large number of toxic chemicals which have been tested in recent years have demonstrated developmental toxicity in animal test systems. Consequently, the exposure of pregnant women to toxic chemicals has become an area of considerable concern.

Many developmental effects may have environmental causes; however it is difficult to establish a causal link in epidemiological studies due to confounders which arise from the variability in human exposure. It has been estimated that 20 percent of the developmental defects observed in children are due to genetic causes, 10 percent to known factors, and 70 percent to unknown factors (EPA,

1991a); some portion of the 70 percent may be attributable to environmental exposures.

Section 5 provides a brief overview of definitions, some issues related to developmental toxicity risk assessment, an outline of methods currently recommended by EPA for conducting dose-response evaluation, and examples of calculations used to identify risk-based maximum exposure limits. This is followed by a summary of toxicological data for the 23 target analytes which readers are encouraged to consult to evaluate potential developmental risks and identify appropriate exposure limits for populations of concern.

4.3.6. Multiple Chemical Exposures: Interactive Effects

Most humans are simultaneously exposed to a number of environmental contaminants. Risk evaluations, however, typically proceed on a chemical-by-chemical basis. Similarly, the development of risk-based exposure guidelines typically focuses on the effects of exposure to chemicals individually rather than as a group. In many cases, the individual exposures and/or risks are then summed to estimate risks or safe exposure levels for a group of chemicals.

EPA provides guidance on mixtures in risk assessments in *Guidelines for the Health Risk Assessment of Chemical Mixtures* (EPA, 1986d). The guidelines advise the use of the additive approach when data are available only on individual mixture components. Section 2 provides a method for calculating exposure limits for multiple chemical occurrence in single or multiple species. The approach is recommended for use when chemicals have the same health endpoints and mechanisms of action. It does not address chemicals with dissimilar actions.

The 1986 Guidelines also address circumstances when data are available on antagonistic or synergistic interactions. They state that "information must be assessed in terms of both its relevance to subchronic or chronic hazard and its suitability for quantitatively altering the risk assessment". These two criteria are essential for selection of interactive data applicable to quantitative risk assessment. However, the criteria preclude the use of most interactive data in risk assessments of long-term exposures, because many interactive studies focus on short-term exposure. An additional complication is introduced to this type of analysis for mixtures containing more than two chemicals. For those groups, it is necessary to ascertain whether the presence of additional chemicals in the mixture will alter any known interactions between any two chemicals having interactive data (EPA, 1986d).

The type of information which is often available (acute effects interactions and mechanisms of action) is not readily applicable to the quantitative assessment

of chronic health risks of multiple chemical exposures (EPA, 1986d). The guidelines recommend that this type of information be discussed in relation to its relevance to long-term health risks and interactive effects, without making quantitative alterations in the risk assessment. Much of the interactive information included in the specific chemical discussions contained in Section 5 was obtained from the ATSDR Toxicological Profiles for various chemicals. Readers are encouraged to consult these ATSDR documents if they require interactive data.

The information obtained from ATSDR, and/or which may be implied from the toxicological nature of many of the target analytes, is related to the chemical's interaction with basic processes, such as metabolism. When these functions are altered (e.g., by the induction of microsomal enzymes), the metabolism of other endogenous or exogenous chemicals may be altered. This is particularly problematic for individuals using pharmaceutical drugs to address medical conditions. As the DDT discussion in Section 5 notes, alteration in metabolism of medications may require adjustment of dosages. This is not a hypothetical problem; exposure to various chemicals has reportedly resulted in altered response to medications. Information regarding these types of effects are discussed in Section 5 for the target analytes.

EPA has recently developed a data base to disseminate available information on interactive effects of chemical mixtures. This data base, called MIXTOX, contains summaries of information from primary studies in the open literature on binary mixtures of environmental chemicals and pharmaceutical chemicals. Data provided include the duration of the study, animal species, dose ranges, site, effects, and interactions. Available MIXTOX information on the target analytes is presented in Section 5. The majority of data obtained through MIXTOX consisted of the results of acute studies. Many studies indicated additive effects. Other types of interactions (e.g., inhibition, synergism) were usually not provided. The relevance of this information to specific water bodies will depend upon the chemical mixtures which are known to occur, based upon fish sampling results. In the absence of quantitative information on interactive effects, these guidelines suggest the use of an additive approach to evaluation of chemical mixtures *for carcinogens and for noncarcinogens which are associated with the same adverse health endpoints*. The equation used in this approach is presented and discussed in Section 2.

4.3.7. Assumptions and Uncertainties

Numerous assumptions are required to develop risk values from dose-response data. Uncertainties arise from the assumptions, from the nature of the dose-response data, and from our imperfect understanding of human and animal physiology and toxicology. Depending on the quality of the studies, there may

also be uncertainty regarding the nature and magnitude of the effects observed in toxicological and epidemiological studies. However, evaluation of study quality is a complex process and involves such diverse topics as animal housing conditions and pathological evaluations. Often there is not sufficient information provided in study summaries (either in a journal article or report) to fully evaluate the quality of the study and the assumption must be made that good laboratory practices and scientific methods were followed.

Major assumptions which are used in the evaluation of dose-response data are discussed at length in the EPA risk assessment guidance documents on specific toxicities (e.g., for carcinogenicity, numerous assumptions are discussed including: the selection of the dose-response model, use of benign tumors in estimating response, use of the upper bound estimate of the slope, and use of surface area instead of body weight to adjust dose; EPA, 1986 a,c,e). Many of these assumptions are in this document in sections dealing with specific types of toxicity.

A critical assumption underlying all animal-human extrapolations is that there is a relationship between toxicity in test animals and the toxicity anticipated in humans. There can be significant differences in metabolism and other physiological aspects of study animals and the human population (e.g., absorption, metabolism, and excretion). Although many of these aspects are well-characterized, the relationship between interspecies differences and the toxicity of specific chemicals is usually not known. There is also uncertainty regarding the appropriateness of the test species for evaluation of a chemical's effects on humans. Generally, the species of animal which most closely resembles humans in response to the toxicity of a particular chemical is used in the risk assessment. When such information is not available (as is often the case) the species of animal which is most sensitive to a particular effect is used in the evaluation of that effect for a chemical. Although the existence of a relationship between animal and human toxicity is acknowledged by most scientists, there is not universal consensus on the nature of the relationship for many chemicals and endpoints (e.g., male rat kidney toxicity associated with alpha-2u-globulin may not be applicable to humans).

A second critical assumption is the existence of a threshold for most non-carcinogens and no threshold for carcinogens. The threshold issue is under evaluation for many chemicals and endpoints (e.g., epigenetic (non-genetic) carcinogens, developmental effects). Issues of this type will be resolved as more information becomes available on the basic mechanisms of toxicity and actions of specific chemicals. Future revisions of this document will provide additional guidance as it becomes available.

Additional uncertainty regarding dose rate and the duration of exposure are generated by the use of test animals. Many animal studies are conducted for the lifetime of the animals; however, the human lifetime is significantly longer than the two-year study period of the usual experimental subjects (e.g., dogs or rodents), which may impact bioaccumulation and toxicity. When human studies are used as the basis for risk estimates, they are usually of occupationally-exposed individuals, who were exposed intermittently during adulthood over two to three decades, rather than continuously exposed over a lifetime. Often they are not followed into old age, when many effects become clinically detectable. In addition, human exposures are often confounded by concurrent exposure to other chemicals. Consequently, the use of human studies also introduces numerous uncertainties to the toxicity evaluation process.

Various assumptions are made in most risk assessments regarding the use of numeric adjustments for extrapolation of study results from animals or human studies to the general population. The extrapolation models which are used to estimate individual or population risks from animal or human studies introduce "margins of safety" to account for some aspects of uncertainty. These models are designed to provide an upper bound on cancer risk values and a conservative Reference Dose (RfD) for non-carcinogens. Uncertainties arise from the application of uncertainty and modifying factors in the calculation of RfDs. These factors are based upon the best available scientific information and are designed to provide a safe margin between observed toxicity and potential toxicity in a sensitive human. The RfD is considered to be an estimate with uncertainty spanning approximately perhaps one order of magnitude. EPA considers the RfD to be a reference point to be used in estimating whether adverse effects will occur (IRIS, 1993). The IRIS Background Documentation has provided additional insight into the uncertainty inherent in RfDs:

> "Usually doses less than the RfD are not likely to be associated with adverse health risks, and are, therefore, less likely to be of regulatory concern. As the frequency and/or magnitude of exposures exceeding the RfD increase, the probability of adverse effects in a human population increases. However, it should not be categorically concluded that all doses below the RfD are "acceptable" (or will be risk-free) and that all doses in excess of the RfD are "unacceptable" (or will result in adverse effects)" (IRIS, 1993).

For carcinogens, the upper 95 percent confidence bound on the linear component of the linearized multistage model is often used in estimating a cancer potency to introduce a safety margin. It is assumed that this provides a plausible upper bound estimate of potency in the human population.

Many numerical assumptions related to anatomy and physiology are used in calculating risk values (e.g., average adult body weight of 70 kg, animal dietary consumption estimates). The application of these assumptions depends on the type of data which is being used. These assumptions are typically based on a substantial amount of information on average or mean values. However, individual variations within the human population generate uncertainty related to the application of the assumptions.

Uncertainty is significantly related to the amount and quality of toxicological and epidemiological data which is available. There is a greater degree of certainty for chemicals having human epidemiological studies which encompass a variety of population subgroups over a dose range. However, this type of data is not usually available. Uncertainty related to the data base is often endpoint-specific. For example, there may be a substantial amount of data regarding carcinogenic effects but little information on developmental toxicity. This is the case for many of the target analytes discussed in Section 5.

Selection criteria for studies are listed for chronic toxicity, carcinogenicity, developmental toxicity, and mutagenicity in this section. Where the most appropriate types of data are not available (based on these selection criteria) there is usually greater uncertainty regarding the risk values and risk estimates which are calculated. Many of the criteria address the quality of the studies used to estimate dose-response parameters. Weight-of-evidence guidelines, also discussed in this section for specific toxicity types, provide useful insight into the adequacy of the data supporting a risk value.

Bioassays conducted on single cell lines generate greater uncertainty than animal studies due to their isolation from normal physiological processes. However, some types of effects can be most efficiently studied using these tests. Various types of mutagenicity and cellular level assays provide insight into the potential for genetic damage and damage to specific types of cell systems. This data is very difficult to interpret in the context of human risk because the relationship between study results and human effects has not been well-characterized. This type of study is most often used to support other study results (e.g., positive mutagenicity studies support animal studies indicating carcinogenicity).

Certain chemicals have such limited data for one or more toxic effects that toxicity reference values cannot be determined. Some of these chemicals are poorly characterized for all known/suspected toxicity endpoints. For other chemicals, data may be well-characterized for certain toxic effects, but inadequate for others. For instance, the carcinogenicity of organochlorines has been well-characterized in animals and humans, but other toxic endpoints, including systemic effects and reproductive effects, have not been extensively

investigated. Limitations for the 23 contaminants in this assessment are described in detail in Section 5.

EPA does not recommend specific factors for modifying toxicity data in cases where these data are so limited that a dose-response relationship cannot be determined. However, as the above examples show, lack of toxicity reference values for a given chemical does not necessarily mean that the chemical causes no effect. Therefore, readers will need to evaluate if the lack of specific kinds of toxicity data affect the adequacy of protection afforded by the consumption limit. For example, if the chemical is a suspected developmental toxin, but quantitative developmental toxicity data are lacking, readers may determine that a consumption limit based on other health endpoints is not sufficiently protective of women of reproductive age and children.

In summary, uncertainty may be generated by many components of a dose-response evaluation. Some of these are dealt with quantitatively through the application of uncertainty factors, modifying factors, or the use of an upper bound estimate. Others may be referred to qualitatively, through a discussion of data gaps or inferential information (e.g., studies that appear to show greater susceptibility at certain ages). The goal of providing the qualitative information on uncertainty is to give the risk assessor and decision makers sufficient information on the context and support for risk values and estimates so that they can make well-informed decisions.

4.4. Exposure Assessment

This section is meant to provide readers with a brief overview of EPA exposure assessment methodology. Readers wishing to do exposure assessments are advised to read the more detailed documents listed in Appendix B.

Exposure assessment of contaminants in fish involves six components:

- Chemical occurrence in fish,
- Geographic distribution of contaminated fish,
- Individual exposure assessment,
- Population exposure assessment,
- Multiple species exposure, and
- Multiple chemical exposure.

Each of these components is discussed below.

4.4.1. Chemical Occurrences in Fish

Contaminant concentrations vary among different fish tissues, fish species, fish sizes, and contaminants present in ecosystems. Chemical contaminants are not distributed uniformly in fish tissues; some toxics bind primarily to lipids and others to proteins. Fatty and/or larger fish often contain higher organic contaminant concentrations than leaner, smaller fish. Knowing how contaminants differentially concentrate in fish enables risk managers to advise fish consumers on alternative fishing and cooking practices to minimize exposure.

Many readers will have information on the geographic distribution of contaminants in fish from their sampling and analysis programs. Others may need to identify areas of likely contamination. This topic is discussed in *Guidance for Assessing Chemical Contamination Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis* (EPA, 1993a). This section only briefly reviews likely patterns of chemical distribution based on chemical properties and other factors. Such geographic information is important in population exposure assessment and for risk communication; readers are encouraged to develop maps showing areas of fish contamination which, combined with demographic information, help target exposed fisher populations for additional outreach efforts.

Volume 1 of this series provides comprehensive guidance on cost-effective, scientifically-sound methods for use in fish contaminant monitoring programs designed to protect public health. It is designed to promote consistency in the data states use to determine the need for fish consumption advisories. By standardizing protocols across regions, risk managers can avoid significant differences in advisories when actual concentrations of contaminants in fish are very similar.

Volume 1 suggests that screening values be compared to annual sampling and analysis data to determine where problems may exist. The document also discusses sampling design and field procedures for collecting and analyzing fish tissue samples for pollutant contamination. It discusses specific cost-effective analytical methods and QA/QC procedures and identifies certified reference materials and federal agencies that conduct interlaboratory comparison programs. Procedures for data reporting and analysis that are consistent with the development of the National Fish Tissue Data Repository are also included.

Information on contaminant distributions in different types of fish and fish tissues and across geographical areas is required for a number of reasons. Differential concentrations of contaminants in fish tissues and across fish species affect fish consumer exposures due to differences in individual

consumption practices. The geographic origins and modes of transport of chemical contaminants determine the extent and location of these chemicals in fish. Identifying areas of high contamination enables readers to choose initial screening sites and focus limited resources on fisher populations most at risk from consuming contaminated fish.

4.4.1.1. Distribution in Fish Tissues[6]

Chemical contaminants are not distributed uniformly in fish. Fatty tissues, for example, will concentrate organic chemicals more readily than muscle tissue. Muscle tissue and viscera will preferentially concentrate other contaminants. Some contaminants, such as methylmercury, are distributed throughout fish tissue. Contaminant distribution information has important implications for consumers. Depending on how fish are prepared and what parts are eaten, consumers may have greatly differing exposure levels to chemicals. In general, contaminant concentrations differ between:

- Fatty tissues, muscle tissue, and internal organs,
- Different species of fish,
- Larger and smaller fish within species, and
- The type of contaminant present in the fish.

Lipophilic chemicals accumulate mainly in fatty tissues, including the belly, lateral line, subcutaneous, and dorsal fat, and the dark muscle, gills, brain, and internal organs (Harrison and Klaverkamp, 1990, Kuehl et al., 1987, Kleeman et al., 1986a, Kleeman et al, 1986b, Branson et al., 1985). Some heavy metals, such as cadmium, concentrate more in the liver and kidneys. Muscle tissue often contains lower organic contaminant concentrations than fatty tissues (Anderson and Amrhein, 1993).

Most people remove the internal organs before cooking fish and trim off fat before eating, thus decreasing exposure to lipophilic and other contaminants. Removing the fat, however, will not decrease exposure to other contaminants, such as methylmercury, that are also concentrated in muscle and other protein-rich tissues (Minnesota Department of Health, 1992). Certain subpopulations eat more of the fish than just the fillet, and use whole fish for making soups. As a result, these subpopulations consume much more of the fish's body burden of contaminants and are at a higher risk of experiencing negative health effects. Readers are encouraged to, whenever possible, take preparation

[6] This section is an overview; states should consult primary research studies for more information.

methods of local fisher populations into account when assessing exposure levels (See Volume 3 of this series).

Different fish species in the same water body may contain very different levels of contaminants. Due to bioaccumulation, higher trophic level species are more likely to have higher contaminant concentrations. For some contaminants, the contaminant concentrations in the tissues of the top predators can exceed ambient water or sediment levels by many orders of magnitude. Where a fish feeds in the water body may also determine its relative bioaccumulation potential. Bottom feeders, for example, such as carp or flounder, are exposed to more sediments than are fish that feed in the water column, and have a tendency to accumulate more of the dense, hydrophobic contaminants, such as chlordane or PCBs, that are adsorbed to the sediment particles.

In addition, fish species vary widely in their fat content. Fish which are low in fat, such as bass, sunfish, crappies, yellow perch, and walleyes, are less likely to accumulate lipophilic toxics than fattier fish such as bluefish, some salmon, catfish, and carp. Aquatic organisms also differ in their abilities to metabolize and excrete contaminants. For example, one study found fish more able to metabolize benzo[a]pyrene than shrimp, amphipod crustaceans, and clams, respectively (EPA, 1993a). Since specific enzymes are required to metabolize different chemicals, it is likely that the ability to break down and excrete contaminants also differs among fish species. Because of this differential accumulation of contaminants, individuals eating different species of fish may have very different exposure levels.

Within species, larger fish generally contain higher concentrations of bioaccumulative contaminants, especially of more persistent chemicals (such as methylmercury, DDT, PCBs, and toxaphene; EPA, 1993a) because they are usually older than smaller fish of the same species, and have had more time to bioaccumulate chemicals from their food. In addition, larger predatory fish are more able to catch larger prey, which themselves have had a longer time to bioaccumulate chemicals (Minnesota Department of Health, 1992). Older fish also concentrate more contaminants in their muscle tissues, which are fattier than muscle tissue in younger fish, particularly along the dorsal area and lateral lines (Kleeman et al., 1986a). Taking these observations into account, readers may choose to issue size-specific consumption limits and/or explain this correlation in public education efforts.

4.4.1.2. Fish Contaminants

Due to contaminant-specific chemical and pharmacokinetic properties, the target analytes discussed in this volume preferentially concentrate in different

tissues in fish. Some data are described below; data on individual target analytes are discussed in more detail in Section 5.

Heavy Metals Methylmercury, unlike many other bioaccumulative fish contaminants, is found not only in fatty tissues, but also binds strongly to proteins, and thus concentrates in muscle tissues of fish (Minnesota Department of Health, 1992). Methylmercury also concentrates in the liver and kidneys, though at generally lower rates (Harrison and Klaverkamp, 1990, Marcovecchio et al., 1988). Thus, methylmercury concentrations in edible fish tissues are not effectively decreased through trimming. Cadmium largely concentrates in the liver, followed by the kidneys and gills, and not as much in the muscle tissue (Harrison and Klaverkamp, 1990, Marcovecchio et al., 1988, Jaffar et al., 1988, Norey et al., 1990) This indicates that cadmium concentrations could be decreased by trimming and gutting fish before consuming. Selenium was shown to concentrate in both the liver and muscle tissues at similar rates (Harrison and Klaverkamp, 1990).

Organochlorines Organochlorine pesticides and PCBs have a high affinity to concentrate in fatty tissues (Ryan et al., n.d., Kleeman et al., 1986a, Branson et al., 1985, EPA, 1993a). One study positively correlated PCB and mirex levels with fat levels across ten freshwater fish species (Ryan et al., n.d.). These compounds are neither readily metabolized nor excreted, and thus tend to bioaccumulate through the food web (EPA, 1993a). As fish species store fat differently, so will they concentrate organochlorines differently.

PCB levels have been studied in several species and tissues of fish. Higher chlorinated biphenyls have been found to bioaccumulate more readily than lower chlorinated biphenyls (Bruggeman et al., 1984, EPA, 1993a). Unfortunately, some of these higher chlorinated biphenyls tend to be the more potent toxics as well (Williams et al., 1992).

Other Contaminants The other chemicals examined in this exposure assessment (organophosphate pesticides and oxyfluorfen) have also been found to bioaccumulate in fish, but no information was found as to how they differentially accumulate in fish tissues. Organophosphates have some chemical characteristics which are similar to organochlorines, though they differ in lipophilicity, metabolism, mode of action, and persistence (EPA, 1993a; see Section 5).

Readers may wish to use this chemical-specific information on distribution in fish tissues to assess whether a local population may be unreasonably exposed to a given contaminant, due to particular eating habits such as eating only one species of fish, eating specific parts of the fish, or eating only fatty fish species.

4.4.2. Geographic Distribution of Contaminated Fish

The extent of contamination of fish is an important element in determining the need for further action. These data are also useful in performing population exposure assessments and risk characterization. Two types of information are particularly useful: the locations where contaminated fish have been found, and the sources of potential contamination. The first type of information is provided by fish sampling and analysis programs. When such data are absent, several available sources can help locate sites of possible contamination by the target analytes. Section 4.2.1.2 contains a list of sources of information on potential fish contaminants. Volume 3 discusses methods for mapping both population demographics and the distribution of pollutants.

4.4.3. Individual Exposure Assessment

Individual exposure assessments provide descriptions of the overall, media-specific, or site-specific exposure of an individual. These may be normative or high (e.g., highly exposed individual) estimates, or be based on actual measurement data.

Individual exposure assessments use essentially the same equation as is used with fish contaminants to calculate fish consumption limits, though they solve for different variables:[7]

$$E_m = \frac{C_m \cdot CR}{BW} \qquad \text{Equation 4.1}$$

where:

E_m = Individual exposure to contaminant *m* from ingesting fish (mg/kg-day),

C_m = Concentration of contaminant *m* in the edible portion of fish (mg/kg),

CR = Mean daily consumption rate of fish (kg/day), and,

BW = Body weight of an individual consumer (kg).

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[7] Exposure is defined in the U.S. EPA *Guidelines for Exposure Assessment* (1992a) as the "contact of [the] chemical with [the] outer boundary of a person, e.g., skin, nose, mouth."

Individual exposure assessments use data on known chemical residues in fish (C_m) and on human consumption patterns (CR/BW) to estimate exposure (E_m) for hypothetical individuals within given populations (See Equation 4.1). Conversely, the consumption limits described in Section 2 and provided in Section 3 use the data on known chemical residues in fish (C_m) combined with dose-response data (q_1^*s and RfDs, which correspond to maximum "safe" exposure) to estimate maximum safe human consumption rates (CR_{lim}/BW; see Equations 2.1 and 2.3). This document uses this equation only to calculate fish consumption limits. Volume 3 of this series provides additional information on estimating individual and population exposures for purposes of generating risk estimates used in risk management decision-making. Individual exposure assessment is discussed in this volume for informational purposes only; it is not used directly in calculating fish consumption limit tables. Increased detail is provided where information is shared between individual exposure assessments and consumption limit calculations.

Depending on the geographic region and/or contaminant involved, contaminant concentrations in fish (C_m) are determined by public health officials, natural resource agencies, environmental protection agencies, FDA, EPA, and/or agricultural departments through state, local and tribal sampling and analysis programs. The consumption rate (CR) represents the amount of fish an individual in a given population eats in a day, and may be estimated through fish consumption surveys. Finally, the daily dose is divided by consumer body weight (BW) to arrive at individual exposure.

By using information on the number of individuals in each exposure category, risk managers may aggregate exposures determined in individual assessments to derive population exposure assessments. Population exposure assessments can allow readers to focus limited resources on those contaminants or areas that may pose the highest risks to a large number of persons or to particular subpopulations of interest (e.g., subsistence fishers).[8]

[8] As mentioned before, the consumption limits described in this document assume that no other exposure to any of the 23 target analytes occurs. However, a potentially significant source of contaminant exposure is the consumption of commercially-caught freshwater and marine fish. Consumption limits for non-commercial fish may not be sufficiently protective of consumers of both commercial and non-commercial fish. It is recommended therefore, that, whenever possible, readers take other significant sources of exposure into account when doing exposure assessments and/or developing consumption limits.

4.4.3.1. Exposure Variables

Equation 4.1 (See Section 4.4.2.1) uses three parameters to calculate individual exposure (E_m) to non-commercial fish contaminants: consumption rate (CR), consumer body weight (BW), and contaminant concentration (C_m). Equations 2.1, 2.2, and 2.3 in Section 2 also use body weight and contaminant concentration, and also use meal size (MS) in developing consumption limits (See Section 2). With the exception of C_m, which is found in sampling and analysis programs, these parameters are discussed below.

Body Weight Both consumption limit and exposure assessment calculations require specific body weights (usually in kilograms) for individuals in order to derive the contaminant daily dose in milligrams contaminant per kilogram consumer body weight per day (mg/kg-d). The *Exposure Factors Handbook* (EPA, 1990a) recommends values for average weights for children and adults, based on the second National Health and Nutrition Examination Survey (NHANES II). Conducted from February 1976 to February 1980, NHANES II surveyed approximately 28,000 non-institutionalized U.S. civilians aged six months to 74 years. The survey oversampled population groups thought to be at risk from malnutrition (low-income individuals, preschool children, and the elderly). Adjusted sampling weights were then calculated for age, sex, and race categories to reflect body weight values for the estimated civilian, non-institutionalized U.S. population. Although EPA recommends these values for typical Americans, they may not adequately represent some subpopulations (e.g., Asian-Americans, who are generally smaller than the average U.S. citizen). Whenever more accurate data on average body weights of local fisher populations are available, readers are encouraged to use these data in place of the default values.

Table 4-1 lists recommended body weight values for general adults, women of childbearing age (women from 18 to 45 years of age), and children. These values are derived from data in the *Exposure Factors Handbook* (EPA, 1990a); the values listed for general adults are used directly, while the value for women of reproductive age represents an arithmetic average of three age groups (18-25, 26-35, and 36-45), and the value for children is an arithmetic average of two groups (children <3 and children from 3 to <6). A more protective body weight value for women of reproductive age would be to use the lower 95th percentile body weight of women age 18 to 25 years (Blindauer, 1994). In this document, however, a body weight of 70 kg was used for all adults, including women of reproductive age, to calculate the consumption limits shown in Section 3.

Table 4-1. Mean Body Weights of Children and Adults

Age Group	Mean Body Weight (kg)		
	Males	Females	Males and Females (Averaged)
Adults	78	65	70
Women of Reproductive Age	-	64	-
Children <6	14.8	14.2	14.5

Source: Adapted from EPA, 1990a.

Readers are encouraged to use values that average together male and nonpregnant female body weights when assessing exposure to the general adult population. Where consumption rates are known to differ significantly between men and women, however, readers may wish to make gender-specific exposure assessments and use unaveraged gender-specific body weight estimates. In cases where certain developmental toxins are of concern, readers are encouraged to make separate exposure assessments for children and women of childbearing age.

Meal Size Meal size is a critical parameter in expressing fish consumption limits, though is not used directly in calculating exposure (which is expressed in mg/kg-d). Limits expressed in terms of meal per given time period is a more understandable measure than consumption limits expressed in kilograms per day. Meal size estimates can also be used to calculate peak acute exposures to fish contaminants (although that information is not used in this document).

Several values for average meal size have been determined through both non-commercial and commercial fish consumption surveys, though these values may not be comparable across studies. For instance, some surveys report meal sizes on a basis of whole, raw fish, while others refer to cooked fillets. Still others do not specify whether the value is based on cooked or raw fish. The average meal size most often cited is 227 grams, or eight ounces (Minnesota Department of Health, 1992, Missouri Department of Health, 1992, Anderson and Amrhein, 1993, EPA, 1993a). This meal size corresponds to the value used in the Michigan Anglers Survey; in this survey, individuals were asked to estimate their average meal size compared to a picture showing a eight ounce (227 gram) fish meal (West et al., 1989). The same meal size also represents the high-end range used by Dourson and Clark (1990), which is based on the value used in the EPA *Region V Risk Assessment for Dioxin Contaminants*

(1988c). A discussion of fish consumption surveys is provided in Volume 3 of this series.

EPA has developed meal size estimates for both general adults and children under four. The general adult population includes all adult men and women. Children eat smaller portions than adults, although they may consume significantly more fish per unit body weight. Women of reproductive age were assumed to eat proportionally (per kg body weight) the same amount of fish per meal as other adults.

EPA suggests using a default value of 8 oz (227 grams) of cooked fish fillet per 70 kilogram consumer body weight as an average meal size for both the general adult population and for women of reproductive age for use in exposure assessments and fish advisories if population-specific data are not available. This meal size, however, is not likely to represent higher end exposures, where persons consume more than the average amount in a given meal. These larger meal sizes are important to consider in cases where acute and/or developmental effects from fish contamination are of concern.

Meal size can also differ for other subpopulations and must be scaled accordingly. Children and adolescents, for example, often consume more fish per kilogram body weight than adults. A national food consumption survey conducted by the United States Department of Agriculture (USDA) was used to scale the adult meal size value to child meal size values (USDA, 1983). The USDA survey evaluated consumption patterns of approximately thirty-eight thousand U.S. citizens over three-day periods from 1977 to 1978, and is the largest consumption survey of its kind that includes fish. The survey results included meal size data for ten age groups. Although respondents included both fishers and non-fishers, relative differences reported between the age groups were used to approximate differences in average meal size between different age categories within fisher populations in the current assessment. For children younger than four years old, EPA suggests using a default meal size of 3 oz (85 grams), if population-specific data are not available. For older children, modifications in consumption limits can be made to tailor limits to their body weights and consumption patterns. The methodology to do so is discussed in Section 2.

Consumption Rate Although it is necessary to estimate the overall average consumption rate in order to characterize risk, this information is not necessary to provide risk-based consumption limits as in Section 3. Consumption rate information is primarily used to make risk management decisions regarding the allocation of resources and implementation of various public health protection strategies related to consumption of contaminated fish. Consequently, fish consumption patterns and methods for evaluating the resulting risks are

presented in Volume 3 of this series (*Risk Management*). Volume 3 will contain a review of fish consumption rates for various population subgroups including the average national consumer, sport fishers, and subsistence fishers. However, due to the significant variability in fish consumption among individuals, readers are urged to conduct their own surveys to determine actual consumption levels when accurate risk estimates are required.

4.4.3.2. Averaging Periods Versus Exposure Durations

The exposure duration is the time period over which an individual is exposed to one or more contaminants. In the case of an individual fisher, the exposure duration is equivalent to the time interval over which he or she catches and consumes fish. However, fish consumption is frequently not constant over the time period of interest for examining certain health endpoints (e.g., lifetime for chronic effects), particularly for short-term or seasonal recreational fishers. For short-term or seasonal fishers, periods of consumption must be averaged with periods during which no consumption occurs, in order to correspond with the time periods over which chronic health effects are likely to develop. For example, the method usually employed to obtain a lifetime average daily dose is to divide the cumulative dose over an individual's lifetime by the number of days in an average lifetime. For developmental and subchronic effects, the time period over which dose is averaged is much shorter. Consequently, the time periods of concern chosen for use in exposure assessments are called averaging periods.

A ten-day averaging period was chosen for the short-term consumption limit tables for several reasons. Ten days is one of the averaging periods used by the EPA Office of Water in developing Health Advisories for drinking water. It is also relevant to the short time period often considered critical for exposure to developmental toxins (i.e., there may be a brief window of time during which adverse effects can be induced by toxins). This time period also corresponds to a typical vacation period. Although some fish consumption advisories use three weeks as an exposure period to describe recreational fish consumption (Missouri Department of Health, 1992, Minnesota Department of Health, 1992), no evidence was found to support it as a more accurate period than ten

days.[9] Ten-day meal consumption limit tables have been developed for chronic systemic toxins and for the developmental toxicity of methylmercury, as shown in Section 3.[10]

For pollutants with carcinogenic properties, EPA currently assumes that there is no threshold below which the risk is zero; i.e., for any non-zero exposure, there may be some increase in cancer risk. There is no current methodology for evaluating the difference in cancer risks between consuming a large amount of the carcinogenic contaminant over a short period of time and consuming the same amount over the course of one's lifetime. Therefore, EPA's current cancer risk assessment guidelines recommend prorating exposure over the lifetime of the exposed individual (U.S. EPA, 1986a). To provide usable and easily understood consumption guidance, the unit of one month was used as the basis for expressing meal consumption limits in Section 3. The limits for carcinogens are based on the assumption that consumption over a lifetime, at the monthly rate provided, would yield a lifetime cancer risk no greater than the acceptable risk listed in each column (i.e., one in ten thousand, one hundred thousand and one million).

The likelihood of occurrence of non-carcinogenic effects associated with chronic exposure is evaluated through the use of RfDs (as discussed in Section 4.3). Exposure below the RfD is assumed by EPA to be safe over a lifetime of exposure. Consequently, the relevant averaging period for both carcinogenic and non-carcinogenic chronic exposure is a lifetime.

As with the carcinogens, the unit of one month was used in Section 3 as the basis for expressing meal consumption limits based on chronic systemic health effects. The limits for non-carcinogens are based on the assumption that consumption over a lifetime, at the monthly rate provided, would not generate a health risk. Although consideration was given to inclusion of an acute exposure period (e.g., one day), insufficient information on one-day consumption and acute effects is available to evaluate acute exposure for many

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[9] Vacationers may identify better with two-week periods than with ten-day periods (Shubat, 1993a). For this reason, readers intending to develop advisories based on ten-day fish consumption should consider expressing consumption limits in terms of two-week vacations instead of ten-day periods.

[10] However, those fishers who catch and freeze large quantities of fish to eat later might be considered seasonal or subsistence fishers, depending on the extent of their catch and subsequent consumption.

of the fish contaminants at this time.[11] It is anticipated that subsequent revisions of this document will more fully characterize acute exposure (See Section 4.3 for a brief discussion).

Consumption of large, intermittent fish meals (bolus doses) do not correspond well to dosing patterns typically evaluated in toxicity studies. This is problematic for the application of an RfD based on chronic exposure studies to this fish consumption scenario. See Section 4.3 for further discussion.

4.4.3.3. Multiple Species Exposures

Local information on the consumption of multiple species and fish contamination levels can be used to assess exposure and establish consumption limits for consumers with multiple-species diets. Equation 4.1 can be modified, as follows, to consider consumption of multiple species:

$$E_{m,j} = \frac{\sum (C_{m,j} \cdot CR_j \cdot P_j)}{BW} \qquad \text{Equation 4.2}$$

where:

$E_{m,j}$ = Individual exposure to contaminant *m* from ingesting fish species *j* (mg/kg-day),

$C_{m,j}$ = Concentration of contaminant *m* in the edible portion of fish species *j* (mg/kg),

CR_j = Consumption rate of fish species *j* (kg/day),

P_j = Proportion of a given fish species in an individual's diet (unitless), and,

BW = Consumer body weight (kg).

Regional or local angler surveys that estimate catch data and measure fish consumption can provide data on the mix of species eaten by particular populations. One study, the Columbia River Survey (Honstead et al., 1971), is described in Rupp et al. (1979). This survey calculated the total number of each species of river fish eaten by residents in the area. Although the

[11] Chlorpyrifos and mercury are notable exceptions.

information is a composite of fishers and non-fishers, the data could be used to estimate the mix of species that an average individual in the area would eat. The Columbia River Survey also includes data on the mix of species consumed by each of ten individuals who ate the most fish during the year, which might be used to estimate exposure for high-risk individuals. Readers may wish to incorporate similar information from local surveys into multiple-species exposure assessments and/or consumption limits.

4.4.3.4. Multiple Chemical Exposures

Fish can be contaminated with more than one chemical, and individuals can consume multiple species of fish that contain different contaminants. In these cases, exposure across species needs to be calculated separately for each chemical; these exposures can then be combined in a variety of ways to estimate risks of different health endpoints. Section 2 provides methods for calculating consumption limits for individuals exposed to multiple contaminants. Readers also may adapt these calculations (s.f., Equation 4.2) to estimate individual exposure to multiple fish contaminants.

4.4.4. Population Exposure Assessments

Population exposure assessments are not directly used in developing risk-based consumption limits. Rather, they are primarily used in risk management (e.g., to prioritize resource allocation) and to identify particular subpopulations of interest (e.g., in areas where subsistence fishing is common). Consequently, methods for carrying out and utilizing population exposure assessments are discussed in Volume 3 of this guidance series.

4.4.5. Uncertainty and Assumptions

Readers must evaluate if the exposure assumptions made in deriving risk-based limits provide adequate protection to sensitive or highly exposed subpopulations. Some of the assumptions associated with the exposure parameters can lead to an underestimate of total risk (and therefore an overestimate of allowable consumption). For example, the calculation of exposure to a given chemical may ignore background sources of that chemical. For chemicals that exhibit health effects based on a threshold level, the combination of background contaminant and fish consumption exposure may exceed the threshold. The use of average fish contaminant concentrations to estimate exposure is another assumption that could underestimate risk if an individual regularly consumes fish from a contaminant hot spot.

Exposure assumptions may not always be sufficiently conservative. However, these assumptions may be balanced by overly conservative assumptions in

other aspects of the assessment. Readers need to judge if the overall margin of safety afforded by the use of uncertainty factors and conservative assumptions provides satisfactory protection to fish consumers.

4.4.5.1. Chemical Concentrations in Fish

Accurate determination of the chemical concentrations in fish is an important area of uncertainty which is discussed in detail in Volume 1 in this series.

4.4.5.2. Body Weight

The estimates used for body weight use several assumptions that affect the accuracy of the exposure assessment. First, the figures for body weight are taken from data in the late 1970s. Body weights can vary dramatically over time, and therefore the values may be an over or under-estimate of current body weights. In addition, average body weights were not distinguished for various ethnic populations. For example, Southeast Asian-American subsistence fishers may have slighter body frames and weight than the general adult population. Compared to other assumptions, however, body weight values are associated with relatively low variability and uncertainty. In addition, the consumption limit tables take differences in body weight into account by scaling meal size to body weight (e.g., 8-oz meal per 70-kg body weight).

4.4.5.3. Consumption Rate and Averaging Period

The two most sensitive variables involved in calculating individual exposure often are consumption rate and averaging period. Non-commercial fish consumers differ immensely in their consumption habits. Some may consume fish for one week during a year or for several weekends each year (e.g., as recreational fishers). Others may consume fish for much longer periods during a year or may rely on fish year-round as a major part of their diet. Within these groups, some individuals are more susceptible to contaminants, including women of reproductive age, children, and persons with pre-existing health problems:

Short-term recreational and seasonal fishers are assumed to be exposed to contaminated fish for only part of the year. Recreational vacation fishers are those who eat fish only a short time during the year. Seasonal fishers are often those who live near a lake or river, fish regularly throughout a season (e.g., summer fishing, winter ice fishing), eat their catch throughout the season, but do not rely on fish as a major dietary staple during the rest of the year. Sport fishers have been shown to have higher fish consumption rates than the general U.S. population (EPA, 1989a); the potential for large exposures over

short time periods make them especially susceptible to acute, developmental, and subchronic health risks as compared to non-fishers.

Subsistence fishers eat fish as a major staple in their diets for a greater percentage of the year than do recreational fishers. In addition, subsistence fishers may prepare fish differently than other groups; they may use the whole fish in soups, or consume more highly contaminated tissues, such as the liver, brains, and subcutaneous fat. Both their longer exposure durations and consumption habits make many subsistence fishers more likely to be affected by cancer and adverse chronic systemic, developmental, and reproductive health effects resulting from fish contaminant exposure than those who do not fish or fish for shorter periods of time. Some populations may subsist on non-commercial fish year-round, including Native Americans and certain recent immigrants accustomed to self-sufficiency and fishing (particularly Asian-Americans), and economically disadvantaged populations, who may be particularly at risk since much of their fishing might be expected to occur in more urbanized areas with higher levels of water pollution.

Any estimates of typical fish consumption patterns in a population include certain assumptions. West et al., (1989) described variations in fish consumption in communities in Michigan by ethnicity, income and length of residence. In general, African Americans and Native Americans ate more fish than Caucasians; older individuals ate more fish than younger individuals; individuals with lower incomes tended to consume greater quantities of fish than individuals with higher incomes; longer-term residents of the communities West studied tended to consume more fish than other individuals. To the extent that members of the target population have characteristics associated with higher-than-average consumption, the recommended consumption values may underestimate their consumption. Unless surveyed specifically, subsistence fishers may be under-represented by available surveys. Surveys associated with the issuance of fishing licenses are traditional mechanisms used in surveying fish consumption behavior; however, subsistence fishers may not apply for fishing permits or licenses.[12]

In addition, fish consumption limits that are based on single species for single chemicals do not account for exposures from multiple chemicals contaminating a single species, or for multiple species diets. Consumption limits that focus on a single water body do not account for the possibility that consumption can occur from a variety of water bodies. Single species consumption limits also

[12] Native Americans on reservations do not need fishing permits, and often times other individuals may not know that they need to have a license or find them too expensive to buy.

do not address related species that may be contaminated but were not sampled. Such consumption limits could seriously underprotect persons who eat a variety of fish species from a number of waterbodies. Readers need to decide if consumption limits have a wide enough margin of safety to protect such consumers.

Other methodological assumptions may also lead to increased uncertainty. The calculation of consumption limits that express allowable dose as a number of meals over a given time period may neglect potential acute effects if consumption occurs over a very short time period. For example, a meal limit of two meals per month conceivably could be interpreted by consumers to mean that two meals on one day in a given month is allowable; this behavior could lead to short-term acute effects. This could be avoided by always expressing the consumption in terms of the time interval in which one meal may be consumed, e.g., one meal per two weeks, rather than two meals per month.

The use of averaging periods treats large, short-term doses as toxicologically equivalent to smaller, long-term exposures when comparing exposure to the toxicity reference value. This assumption may underestimate the potential toxicity to humans if the toxicity depends on a mechanism sensitive to large, intermittent doses. (This may occur more often with acute and developmental effects than with other effects).

The averaging periods of 10 days and one month used in this document are based primarily on the types of health data currently available and the risk assessment methods recommended by EPA. Consequently, there is no acute exposure methodology recommended (which could correspond to bolus doses; see Section 4.3) in this document. In subsequent editions, this type of information may be included.

4.4.5.4. Multiple Species and Multiple Contaminants

As discussed above, individuals often eat more than one species of non-commercial fish in their diet. If consumption limits or exposure assessments consider only a single-species diet, exposure from contaminated fish could be underestimated if other species have higher concentrations than the species under consideration. On the other hand, an exposure assessment may be overprotective if an individual's diet is a mix between contaminated and uncontaminated species. Use of local information to the extent possible to characterize mixed diets can avoid some of this uncertainty.

An individual may consume a given species that is contaminated with multiple chemicals, or may consume several species, each with different contaminants,

or both. In these circumstances, exposure assessments that examine contaminants individually in individual species will underestimate exposure. This situation may be avoided by using the equation in Section 4.4.2.4 for multiple species exposures and characterizing exposure to all known contaminants for a given individual. These exposure values can be used in methods described in Section 2 to set consumption limits based on multiple species and multiple contaminants.

4.4.5.5. Other Sources of Exposure

The methods described in this guidance consider exposure only from non-commercial fish consumption. This approach may lead to an underestimate of exposure, and consequently an underestimate of risk for some contaminants. For individuals exposed to fish contaminants through other contaminant sources (e.g., other foods, inhalation, dermal contact, or drinking water), additional background exposure may cause them to experience negative health effects and/or increased cancer incidence, even if they abide by the consumption rates recommended in fish consumption advisories. Readers are encouraged to use available information on other sources of exposure whenever possible in setting consumption limits, or set the limits such that the allowable consumption accounts for only a fraction of the total allowable daily dose. These approaches would allow a margin of safety to guard against the potential for background exposure leading to an exceedence of contaminant thresholds and/or maximum acceptable risk levels.

4.5. Risk Characterization

In general, the risk characterization step of the risk assessment process combines the information for hazard identification, dose-response assessment and exposure assessment in a comprehensive way that allows the evaluation of the nature and extent of risk (Barnes and Dourson, 1988). Risk characterization can be used by risk managers to prioritize resource allocation and identify specific at-risk populations; it is also used to establish regulations or guidelines, and to estimate individual or population risk. In this document, risk characterization has been used to develop the risk-based consumption limits provided in Section 3. The methods involved in developing consumption limits are described in detail in Section 2 and will not be repeated here. When risk characterization is used to estimate individual or population risk, it serves to provide the risk manager with necessary information regarding the probable nature and distribution of health risks associated with various contaminants and contaminant levels. This latter aspect of risk characterization is discussed briefly here and is discussed in more detail in Volume 3 of this series. An overview of the methods which would be used when chemical concentrations exceed screening values is provided in Volume 1 (EPA, 1993a).

Risk characterization in general has two components: presentation of numerical risk estimates, and presentation of the framework in which risk managers can judge estimates of risk (EPA, 1986a). A characterization of risk, therefore, needs to include not only numerical characterizations of risk, but also a discussion of strengths and weaknesses of hazard identification, dose-response assessment and exposure and risk estimates; major assumptions and judgments should be made explicit, and uncertainties elucidated (EPA, 1986a).

Numerical presentations of risk can include either estimates of individual risk or risks across a population. For example, for cancer risks, numerical estimates can be expressed as the additional lifetime risk of cancer for an individual, or the additional number of cases that could occur over the exposed population during a given time period. Numerical risk estimates can also be expressed as the dose corresponding to a given level of concern (EPA, 1986a). These values can be used to estimate the environmental concentration or contact rate below which unacceptable health risks are not expected to occur. For the determination of fish advisories, the environmental concentration takes the form of screening levels (i.e., contaminant concentrations in fish, as discussed in Volume 1) and the contact rate takes the form of risk-based consumption limits for specified populations.

4.5.1. Carcinogenic Toxicity

In this guidance series, screening values are defined as the concentrations of target analytes in fish tissue that are of potential public health concern and that are used as standards against which levels of contamination can be compared. For carcinogens, EPA recommends basing screening values on chemical-specific cancer potency factors. Screening values are used to establish the concentration in fish that can trigger further investigation and/or consideration of fish advisories for the water bodies and species where such concentrations occur. The method for calculating screening values is given in Volume 1 of this series.

When presenting a risk characterization, it should be noted that use of most cancer potency values indicates that the cancer estimates are upper bound estimates or risk; the lower bound estimate of cancer risk may include zero. Other uncertainties and assumptions also need to be discussed. The influence of uncertainties of toxicity reference values and exposure assessment values on the risk assessment are described in detail in Sections 4.3 and 4.4.

4.5.2. Noncarcinogenic Toxicity

For chronic systemic toxicants, the RfD is used as a reference point in assessing risk. The RfD is calculated such that there is little probability of an

adverse health effect occurring due to chronic exposure to chemical concentrations below the RfD. Exceedence of the RfD implies there may be some risk of the adverse health effect occurring; however, the magnitude of risk and severity of the effect are not quantified by this approach.

Estimation of the incidence of noncarcinogenic health effects in the exposed population would require knowledge of the shape of the dose-response function above the RfD. Though methods have been developed for characterizing risk above the RfD (Farland and Dourson, 1992), these methods have not yet been widely applied. Until these methods are better developed and applied to a wider range of chemicals, alternative methods of characterizing noncancer population risks must be chosen. One way these risks often are expressed is to indicate the number of persons in the exposed population whose exposure exceeds the RfD. This numerical expression provides a quantitative way to gauge the extent of possible risk within the population, though it does not provide information on severity of the risk. Additional material, such as information on the health effect upon which the RfD is based and on the uncertainty factors applied to develop the RfD, can assist risk managers in putting the population risk estimates into perspective.

An alternative approach is to express the dose as the magnitude by which the NOAEL exceeds the estimated dose (terned the margin of exposure, or the MOE). Where the MOE is greater than the product of the uncertainty and modifying factors (used in calculating an RfD from a NOAEL), then concern is considered to be low (Barnes and Dourson, 1988).

4.5.3. Subpopulation Considerations

Certain subpopulations (women of childbearing age, children, and individuals with preexisting health conditions) may be of special concern when performing risk assessment and developing risk-based consumption limits. Not all risks to these populations are quantifiable; the toxicity literature may contain data that suggest an effect could occur from exposure to a chemical for particular sensitive subpopulations, but may not contain sufficient information to identify a NOAEL or develop dose-response functions (See chemical-specific information in Section 5).[13] For example, DDT is thought to cause effects in two sensitive populations for which no quantitative dose-response data exist. Based on nnimal studies, DDT may cause cardiac sensitization leading to ventricular fibrillation and death (Hayes, 1982). However, there are insufficient data to relate this quantitatively to human populations that have cardiac disorders or other stresses that could make them especially susceptible to these effects.

[13] RfDs are intended to protect sensitive populations.

DDT may also cause disturbances in the normal reproductive system of females (Hayes, 1982), although again, no quantitative dose-response data exist for these effects. Another example is that certain chemicals (such as organophosphate pesticides) are metabolized more slowly in certain individuals with specific enzyme deficiencies than in the general population (Hayes, 1982). The dose-response data for these effects are not available. In all these cases, the probability or the magnitude of the response that may result from a given dose cannot be adequately quantified.

Information on these subpopulation effects of DDT and other chemicals that may result in risk to certain sensitive populations are described in Section 5. Readers can use this information in several ways. Sections 5.3 and 5.4 briefly discuss methods for applying modifying factors to the toxicity reference values in cases where there is insufficient data to quantify risks. Readers may also choose to consider these effects qualitatively when developing consumption limits and/or making risk assessments. In addition, consumption advisories can contain a discussion of suspected effects of a given chemical for particular subpopulations, so that individuals with such conditions can make informed decisions regarding their consumption of fish. Finally, readers may wish to apply an additional safety factor to the meal advice aimed at such populations to provide some measure of additional protection.

4.5.4. Multiple Species and Multiple Contaminant Considerations

Readers are encouraged to take multiple species consumption and/or multiple contaminant exposures into account when developing consumption limits and/or assessing risk. Methods for doing so are described in Section 2, Section 4.4.2, and Section 5.

4.5.5. Incorporating Considerations of Uncertainty in Consumption Limits

Previous sections have discussed the many uncertainties associated with the estimates of exposure and toxicity data assessments that form the basis of the risk assessment and the derivation of risk-based consumption limits. Readers may wish to estimate the direction the uncertainties are likely to have on the risk estimates (i.e., do these uncertainties tend to exaggerate or diminish potential risk?). The assumptions made in the risk assessments to account for uncertainties need to be clearly outlined (e.g., Section 5 contains a description of the nature of the uncertainties associated with each uncertainty factor applied in deriving an RfD). The use of the 95 percent upper confidence limit for the slope of the dose-response function at low doses for carcinogens is an example of a conservative assumption imbedded in the most cancer potency values. Likewise, exposure assessments frequently include conservative assumptions where data on actual exposure are absent, such as the assumption

that no dose modification occurs when the cooking and preparation methods of target populations are unknown. Where possible, readers are encouraged to attempt to quantify the magnitude of the effect of such assumptions on the numerical risk estimates.

SECTION 5.

TOXICITY DATA FOR TARGET ANALYTES AND METHODOLOGY FOR RISK VALUE CALCULATION

5.1. Introduction

This section contains toxicological and human health risk data for the target analytes listed in Table 1-1. This section also contains a discussion of methods which can be used to calculate exposure limits[1] based upon study data presented in this document or other sources. These can be used to calculate fish consumption limits analogous to those provided in Section 3. Section 5.2 contains a description of the categories of information provided for each target analyte, 5.3 contains the methods for calculating exposure limits for developmental toxics, 5.4 contains the methods for calculating exposure limits for chronic exposure toxicity, 5.5 contains chemical class information for organochlorine and organophosphate pesticides, and 5.6 contains toxicological information on the individual target analytes.

Toxicity data were collected for the target analytes from a variety of sources. Information on acute, chronic, carcinogenic, mutagenic, and developmental toxicity, as well as interactive effects are included. The major sources used were IRIS, HSDB, ATSDR Toxicological Profiles, the Office of Pesticide Programs (OPP) tox one-liners, and recent toxicological reviews. The EPA risk values discussed in this section were used along with exposure data (e.g., meal size and fish contaminant concentration) to calculate the fish consumption limits provided in Section 3. Primary literature searches and reviews were **not** conducted for the development of this section, due to time and resource constraints. Data on developmental and other types of systemic non-carcinogenic effects (e.g., neurotoxicity, immunotoxicity, nephrotoxicity) were reviewed and summarized.

EPA evaluates dose-response data for chemicals of environmental concern on an ongoing basis. However, new toxicological data is continually being generated. Consequently, there may be recent information which is not yet

[1] An exposure limit is a daily limit on exposure (in mg/kg-day) based upon health and toxicity data, which the reader may calculate, using the study data provided in this or other sources.

incorporated into EPA risk values. This may be particularly relevant for developmental toxicity, which is the subject of much current research. The toxicological summaries found in Section 5.6 provide the reader with information which they may elect to use to calculate alternative health-based risk values and fish consumption limits. The methods for carrying this out are included in Sections 5.3 and 5.4.

Risk values are provided in Section 5.6, accompanied by a discussion of a number of toxicity studies for each target analyte, which yield various dose-response results.[2] These give some indication of the variability in the types of effects and doses at which various effects were observed. Although EPA has developed guidelines for study selection (discussed in Section 5.3.3), it is clear that for many chemicals a number of study results could, potentially, be used to estimate exposure limits. The reader is urged to review the information presented, particularly the studies of chemicals of interest in their areas, so that they may choose the optimal health endpoints from among those discussed in this document (e.g., carcinogenic toxicity, chronic exposure toxicity) or develop their own risk values, based upon their review of the information.

5.2. Categories of Information Provided in Section 5.6 for Target Analytes

Specific types of information were sought for all target analytes to address health and risk concerns for carcinogenic, developmental, and chronic exposure noncarcinogenic effects. These include pharmacokinetics, acute and chronic toxicity, developmental toxicity, mutagenicity, carcinogenicity, special susceptibilities, interactive effects, and critical data gaps. The categories of information provided for each target analyte in Section 5.6 are listed in Table 5-1. Although the same types of information were sought for all analytes, the information presented for the contaminants varies, depending on the types of data available. Many of the analytes listed have been recognized as environmental contaminants for a number of years and have a fairly comprehensive toxicological data base. Others have been introduced to the environment relatively recently; consequently, only limited information is available on these chemicals.

When a substantial amount of information was available on a contaminant, the information included in the discussions focused on areas relevant to the toxicities under evaluation. For example, a significant amount of pharmacokinetic data is available for some chemicals in the ATSDR

[2] Only a brief discussion is provided for dioxin because it is currently undergoing extensive review within EPA.

Table 5-1. Health and Toxicological Data Reviewed for Target Analytes

Category	Specific Information
Background	Chemical structure/group Use and occurrence
Pharmacokinetics	Target tissues Absorption Deposition-bioaccumulation potential/half-life/body burden Metabolism Excretion Susceptible subgroups
Acute toxicity	Quantitation Susceptible subgroups
Chronic toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Data base quality Susceptible subgroups Current risk values
Developmental toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Data base quality Susceptible subgroups Current risk values
Mutagenicity	Type Quantitation Source Data base quality
Carcinogenicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Data base quality Outstanding issues
Special susceptibilities	Subgroups of concern
Interactive effects	Qualitative Quantitative MIXTOX results
Critical data gaps	Description
Summary of EPA risk values	

Toxicological Profiles. In this document, most information was briefly synopsized; however, detailed information on human milk bioconcentration was included for developmental toxics where lactational exposure is of concern. In addition, when the toxicological data indicated that a particular type of information, not reported, was required for full exploration of relevant toxic effects, additional information was provided (e.g., the interaction of DDT with pharmaceutical efficacy arising from DDT-induced increases in levels of microsomal enzymes).

The information collected is categorized by the temporal nature of the exposure (e.g., acute, chronic). These groupings are most applicable to the standard risk assessment methods that were employed to calculate risk values. The temporal groupings and methods of evaluating dose-response data are briefly discussed in Section 4, with a description of uncertainties and assumptions associated with dose-response evaluation.

5.2.1. Pharmacokinetics

A brief summary of the pharmacokinetic data is presented for many chemicals. The information, obtained primarily from ATSDR toxicological profiles, was included if it had a bearing on the development of fish consumption limits or would be useful to the reader in evaluating the toxicological characteristics of a chemical. For more detailed information on pharmacokinetics the reader is referred to the ATSDR profiles and the primary literature.

For most chemicals there was not sufficient quantitative information, such as absorption, uptake, distribution, metabolism, excretion, and metabolite toxicity, in the data reviewed to recommend modifications in exposure to yield an altered internal dose. Some chemicals contained in the IRIS data base have risk values which have incorporated pharmacokinetic considerations. If additional information relevant to quantitative risk assessment becomes available, it may be included in future versions of the guidance document.

5.2.2. Acute Toxicity

Very little acute exposure toxicity data were located which could have a quantitative bearing on the development of fish consumption limits. A qualitative description of acute effects is included. The minimum estimated lethal dose to humans and a brief discussion of the acute effects are included if the data were available. In addition, the Minimum Risk Levels (MRLs) developed by ATSDR are included when available. They provide estimates of the levels of exposure for a chemical (e.g., toxaphene) at which minimum risk is expected to occur (ATSDR, 1990b). In addition, Section 5.5 contains a discussion of general class information for two major categories of chemicals,

the organochlorines and organophosphates, which comprise 15 of the 23 target analytes.

5.2.3. Chronic Toxicity

Under the chronic exposure heading, significant effects associated with long term exposure are listed. Data relevant to calculating an RfD are discussed, as well as relationships between chronic effects and pharmacokinetic data or other effects. The chronic exposure data for each analyte includes a description of an RfD listed in IRIS or obtained from other sources and the critical study serving as the basis for that RfD, including the species tested, duration of the study, and critical effect noted. Information is provided on any unusual aspects of the study or RfD (e.g., if the study is old or has very few subjects, or if the confidence in the RfD is listed as "low").

Data are also provided on effects observed in recent dose-response studies or which were not the subject of the IRIS RfD critical study. This was done to provide a more comprehensive picture of the overall toxicological nature of the chemicals than could be obtained from reviewing the RfD critical study alone. For most analytes, the information is primarily a qualitative description of effects. For some chemicals having significant new toxicological data, details are provided on NOAELs, LOAELs, some study characteristics, and the usual categories of uncertainty and modifying factors which should be considered for significant studies. These are provided to give readers the option of developing exposure limits as they deem necessary. Methods for doing so are discussed in Section 5.4.

5.2.4. Developmental Toxicity

Developmental toxicity data were obtained for each target analyte (dioxin information will be provided when EPA analysis is complete). Section 5.3 contains general information on developmental toxicity, including definitions, methods for calculating exposure limits, and special issues related to developmental toxicity. Chemical-specific toxicological information is presented in Section 5.6 and relevant class information is provided in Section 5.5. The data and methods information are provided to give readers the option of developing exposure limits based on developmental effects, as they deem necessary.

For many chemicals, information is provided on the tendency of the chemical to accumulate in body tissue. Many of the target analytes bioaccumulate and/or preferentially seek fat tissues. When such accumulation occurs, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. Any body

burden may result in exposure, but lipid-seeking chemicals, such as organochlorines, are often rapidly mobilized at the onset of pregnancy and may result in elevated contaminant exposure to the developing fetus. As a result of this, it may be necessary to reduce the exposure of females with childbearing potential in order to reduce their overall body burden. Even if exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure. This is noted for bioaccumulative analytes in the individual toxicity discussions in Section 5.6.

5.2.5. Mutagenicity.

Although there were many reported mutagenicity bioassays for target analytes, little *in vivo* mutagenicity dose-response data were located. As discussed in Appendix A, *in vivo* studies are recommended by EPA for risk assessments of suspected mutagens. A brief summary of the results of the mutagenicity assays for the analytes is provided. There are numerous studies available for some of the contaminants; consequently, all results could not be feasibly listed. To provide a more concise overview of the results of greatest concern, the nature of the positive studies is given. The direction of the majority of results is also given (e.g., primarily positive, negative, or mixed).

5.2.6. Carcinogenicity

Cancer slope factors and descriptive data were obtained primarily from IRIS, HEAST, and OPP. Preference was given to IRIS values; however, when IRIS values were not available values developed by Agency program offices (e.g., OPP) are provided. The program office values have not necessarily undergone the extensive interagency review which is required for inclusion in the IRIS data base, although many have been reviewed by scientists within and outside of EPA.

There are often insufficient studies to evaluate the carcinogenicity of a chemical. EPA has recognized this and formalized the lack of data as classification D: "not classifiable as to human carcinogenicity" in their cancer weight of evidence scheme (EPA, 1986a). Many target analytes fall into this category; for others, no data were found in the sources consulted regarding their carcinogenicity. For chemicals with insufficient or no data on carcinogenicity in the data bases consulted, the text under the "Carcinogenicity" heading states that: "insufficient information is available to determine the carcinogenic status of the chemical". This statement is used for chemicals lacking a cancer slope factor unless an Agency-wide review has determined that there is evidence that the chemical is **not** carcinogenic (i.e., an E classification is provided in IRIS, 1993). For a complete description of the

weight of evidence classification scheme see EPA's Guidelines for Carcinogenic Risk Assessment (1986a).

5.2.7. Special Susceptibilities

Toxicity data often indicate that some groups of individuals may be at greater risk from exposure to chemicals or chemical groups. For example, a chemical which causes a specific type of organ toxicity will usually pose a greater risk to individuals who have diseases of that organ system (e.g., immunotoxicity poses a greater risk to those with immunosuppression or with immature immune systems). Persons with some genetic diseases (e.g., enzyme disorders) nutritional deficiencies, and metabolic disorders may also be at greater risk due to exposure to some chemicals. Qualitative data on special susceptibilities is provided for many of the target analytes. In addition, information is provided on susceptibilities of special concern for groups of chemicals (e.g., organophosphates) in Section 5.5. However, there is not quantitative data on subgroup susceptibilities for most chemicals which would enable the risk assessor to modify risk values.

The RfDs are designed to take into account the most susceptible individuals and RfDs often incorporate an uncertainty factor to account for variability within the human species (See Table 5-2). The U.S. Public Health Service has provided specific non-quantitative guidance regarding susceptible subgroups in the ATSDR Toxicity Profiles; it is included in the target analyte discussions in Section 5.6. In addition, there are some general caveats regarding special susceptibilities that should be considered. Exposure to many types of toxics pose higher risks to children due to their immaturity:

> "embryos, fetuses, and neonates up to age 2 - 3 months may be at increased risk of adverse effects...because their enzyme detoxification systems are immature"

and

> "Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10 - 12 years of age" (ATSDR, 1990b).

ATSDR has also cautioned that:

> "the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults" (ATSDR, 1993a).

5.2.8. Interactive Effects

Data on interactive effects were located for many, but not all, of the target analytes. Most data on interactive effects were obtained from ATSDR Toxicological Profiles. Often the data indicate that certain classes of chemicals may be of concern. For example, most organochlorines induce the mixed function oxidase system. These chemicals may lead to unanticipated and exaggerated or diminished effects arising from simultaneous exposure to other chemicals which rely on the same metabolic system. In some cases this leads to potentiation (increased toxicity) and in others it hastens the process of detoxification.

The MIXTOX data base, developed by EPA, was also used to obtain information on interactive effects (MIXTOX, 1992). The data base provides a very brief summary of results of studies on combinations of chemicals. Most interactions are reported as "potentiation", "inhibition" or "antagonism" (decreased toxicity), "no apparent influence", or "additive." The interactions which differ from additive or no apparent influence are reported because it is assumed in the absence of contrary information, that the toxicity of mixtures of chemicals will be additive for the same target tissue (See Section 4.3). The interactive terminology used in MIXTOX is used in this document.

5.2.9. Data Gaps

Data gaps noted in IRIS files, OPP tox one-liners, RfD summaries, and the ATSDR Toxicological Profiles are listed. In addition, data gaps that have been identified from a review of the studies are listed, along with the reasons that additional data are considered necessary. For example, if very limited study data is available on developmental toxicity but developmental toxicity is indicated in the data base, developmental studies are listed as a data gap.

5.2.10. Summary of EPA Risk Values

The EPA risk values (RfDs and cancer potencies) which were discussed in each section and were used in the development of fish consumption limits are listed. They are summarized in Table 2-2.

5.2.11. Major Sources

At the end of each target analyte file is a list of the major sources of information consulted. Major sources are those which have been frequently cited (i.e., more than once). Within the text of each target analyte file, all information is provided with citations.

The IRIS files were consulted in late 1993 for cancer potency values, chronic exposure RfDs and additional study data. ATSDR Toxicological Profiles were also consulted when available. The profiles have extensive toxicity, pharmacokinetic, and epidemiological data reviews and provide estimated Minimum Risk Levels (MRLs), which are analogous to RfDs in that they are "estimates of levels posing minimal risk to humans" (ATSDR, 1992a). They are based upon risk assessment methods similar to those used by EPA. The ATSDR documents were particularly useful because they provide detailed information and because many provide extensive discussions of developmental effects as well as some MRLs for these effects. Some ATSDR profiles cited are draft documents; however, the profiles have undergone extensive review within and outside of the U.S. Public Health Service before they are released as the draft bound copies which were cited in this work.

5.2.11. Statement Regarding Uncertainty

There are always significant uncertainties associated with estimating health risks and safe exposure levels for human populations. While these are discussed in Section 4, their importance warrants their mention in this section also. The risk values provided for each chemical in this section are based upon human or animal studies which evaluated either a small subset of the human population, or an entirely different species. In either case, we can only **estimate** the relevance of the study results to humans. Although a quantitative methodology is used to extrapolate from various types of studies to the general human population, there is considerable uncertainty in the estimated relationship between study populations and the human population.

The use of uncertainty factors and upper bound cancer risk estimates provides a margin of safety to account for some aspects of uncertainty in the extrapolation. However, our knowledge of response variability in the human population is very limited. The variations in response, which are engendered by age, sex, genetic heterogeneity, and preexisting disease states, may be considerable. Consequently, although current approaches to assessing risk involve estimating the upper bound values for deriving exposure or risk and are intended to be protective rather than predictive, the reader is urged to carefully review the information provided in this section on data gaps and uncertainties.

It is important to describe the uncertainties and assumptions when recommending fish consumption limits. With respect to toxicity, these include both uncertainties associated with specific chemicals and uncertainties and assumptions associated with the dose-response evaluation process (described in Section 4). In some cases, a variety of dose-response data will enable the reader to provide a quantitative estimation of the range of potential risk values which could be used to calculate exposure and fish consumption limits. A

description of data gaps is may also be useful to the risk manager in determining the best course of action. For chemicals having little data, only a qualitative description may be possible.

5.3. Methods for Estimating Developmental Toxicity Exposure Limits

EPA has studied issues in developmental toxicity and risk assessment for developmental toxics over the last two decades and has developed guidance for evaluating developmental toxics and establishing health-based exposure limits. The initial guidance for risk assessment of developmental toxics was provided in 1986 (EPA, 1986e) and has been refined in the current *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991a). The recommended approach utilizes a NOAEL to calculate an RfD in a manner similar to that used for the calculation of an RfD based upon chronic exposure toxicity. EPA is also considering use of a benchmark dose approach for developmental toxics under some circumstances; consequently, the guidelines may be amended in the future (EPA, 1991a). The methodology described in this guidance document follows the current EPA recommendations. The reader is referred to this and other sources cited throughout this section for further information on developmental toxicity risk and risk assessment.

EPA is working to incorporate new data on developmental and other types of toxicity into the RfDs. The reader can use the information provided on individual target analytes (in Section 5.6) and the methodology discussed in this section to calculate exposure limits based upon their evaluation of the toxicological literature. Section 5.6 contains text which identifies specific developmental outcomes and the associated dose-response data (i.e., LOAELs or NOAELs), which can be used to carry out the calculations. The reader may also wish to conduct a data search to identify any recent data on the chemicals of major interest in their areas.

Several chemicals are known to cause developmental toxicity in humans. These include lead, PCBs, methylmercury and some pharmaceuticals. These are primarily known due to large-scale poisoning incidents which results in serious effects in a large number of offspring. Human dose-response studies cannot be carried out with planned dosing for developmental toxics. However, developmental toxicity studies have been carried out on many environmental contaminants in animals. Many of these have yielded positive results (EPA, 1991a). It is difficult to specifically interpret the dose-response relationship between effects in animal studies and anticipated observable effects in the human population. Research has been conducted to evaluate the relationship between known human developmental toxics and animal testing results; many similarities in response were found. Alternatively, chemicals which caused developmental effects in animals were studied for effects in humans. These

evaluations have yielded mixed results. It has been theorized that the lack of concurrence in results may be due in part to the limited nature of the human data and differences in route, timing and duration of exposure (EPA, 1992e). Further analysis has indicated that:

> "the minimally effective dose for the most sensitive animal species was generally higher than that for humans usually within 10-fold of the human effective dose, but sometimes was 100 times or more higher" (EPA, 1991a).

The Guidelines go on to state that:

> "Thus, the experimental animal data were generally predictive of adverse developmental effects in humans, but in some cases, the administered dose or exposure level required to achieve these adverse effects was much higher than the effective dose in humans." (EPA, 1991a)

A number of assumptions are made in approaching developmental toxicity risk assessment in the absence of specific information. These assumptions include:

- adverse effects in experimental animals may pose a hazard to humans,
- the four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are all of concern, rather than only malformations and death, which were the primary effects considered in the past,
- the type of developmental effects seen in animals is **NOT** necessarily the same as those produced in humans,
- the most appropriate species is used to estimate human risk when data are available (e.g., pharmacokinetic). In the absence of such data, the most sensitive species is used, and
- a threshold is assumed based on the capacity of the developing organism to repair or compensate for some amount of damage (EPA, 1991a).

Although it is assumed there is a threshold for developmental toxicity, EPA has stated that:

> "a threshold for a population of individuals may or may not exist because of other endogenous or exogenous factors that may increase the sensitivity of some individuals in the population."(EPA, 1991a)

The Agency is currently sponsoring research to better characterize the dose-response relationship for developmental toxicants. This includes an evaluation

of the threshold concept (EPA, 1991a). The process of risk assessment, as recommended in the 1991 EPA guidelines, generally follows the four step process described in this document. However, hazard identification and dose-response evaluation are combined in the developmental toxicity guidelines because "the determination of hazard is often dependent on whether a dose-response relationship is present" (EPA, 1991a).

5.3.1. Definitions

There is no one consistent definition of developmental toxicity (EPA, 1986e). Developmental toxicity may include the range of effects from early pregnancy loss to cognitive disorders only detectable long after birth. The severity of developmental effects ranges from minor alterations in enzyme levels with no known associated pathology, to death. Developmental toxicity also encompasses health endpoints having genetic and non-genetic bases. EPA's 1986 guidelines (EPA, 1986b) provide useful definitions which are used in this document the purpose of classifying different types of developmental effects, and for defining the scope of effects which are included under the overall heading of developmental effects.

Developmental Toxicology: the study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: 1. death of the developing organism, 2. structural abnormality, 3. altered growth (defined below), and 4. functional deficiency.

Functional Developmental Toxicology: the study of alterations or delays in the physiological and/or biochemical functioning of the individual during critical pre or postnatal development periods.

Embryotoxicity and Fetotoxicity: include any toxic effect on the conceptus as a result of prenatal exposure. The distinguishing feature between the two terms is the stage of development during which the injury occurred (the embryonic stage lasts until approximately eight weeks post-conception followed by the fetal stage). The terms include malformations and variations, altered growth, and *in utero* death.

Altered Growth: includes an alteration in offspring organ or body weight or size. These alterations may or may not be accompanied by a change in crown-rump length and/or in skeletal ossification. Altered growth can be induced at any stage of development, and may be reversible, or may result in a permanent change.

Malformations: includes permanent structural changes that may adversely affect survival, development, or function. The term teratogenicity is used to describe only structural abnormalities.

Variations: includes divergences beyond the usual range of structural constitution that may not adversely affect survival or health. Distinguishing between variations and malformations is difficult because responses form a continuum from normal to extremely deviant. (from EPA, 1986b and 1991a).

Other terminology is often used (e.g., anomalies, deformations, and aberrations) but definitions may vary.

For purposes of this guidance document, the definition of developmental toxicology given above will be used to describe the range of effects considered in this section. This provides a broad scope for evaluation of developmental effects, including those resulting from both prenatal and preconception exposures and effects which are observable pre- and postnatally. This section does **not** include a discussion of reproductive system effects (i.e., damage to the reproductive system), such as sterility, that result from exposure **during** adulthood, and which may prevent conception from occurring, but which do not effect the development of another individual. This type of toxicity is included under the Chronic Toxicity heading.

Carcinogenic effects occurring prior to adulthood may be considered developmental effects under some circumstances. These can be evaluated using the methods described in the previous section on carcinogenicity (in keeping with EPA recommendations in 1986e) and similarly, mutagenic effects can be evaluated using criteria discussed in *Guidelines for Mutagenicity Risk Assessment* (EPA, 1986c), as described in Appendix A.

5.3.2. Special Issues in the Evaluation of Developmental Toxics

Studies of developmental toxics which are most useful in quantitative risk assessment include human epidemiological studies and animal toxicology studies. Epidemiological studies have been conducted on very few chemicals. Animal studies, which are more readily available, pose problems related to interspecies extrapolation (See statements in Sections 4 and 5 regarding uncertainty). The *Guidelines for the Health Assessment of Suspect Developmental Toxicants* (EPA, 1991a) provide guidance on evaluating various types of developmental toxicity studies.

Some aspects of the evaluation of developmental toxicity studies differ from the approaches and data that would be sought from most other types of toxicity studies. One area of concern is the need to ascertain overall

reproductive performance, not only adverse effects on developing individuals. Toxic exposure often results in developmental damage at a very early stage of growth. This may prevent implantation or lead to very early fetal loss. Such losses are usually only detectable in animal studies by comparing the number of individuals per litter or the number of litters produced to the same outcomes in control populations. Very early losses are often absorbed and are not identifiable via other means. In human studies such losses are not usually identified, although prospective studies have used the monitoring of pregnancy markers, such as human chorionic gonadotropic (HCG) hormone, to identify very early post-implantation pregnancy losses (See EPA's guidelines for further discussion in 1991a).

Another area of concern in developmental toxicity studies which is not usually of significant interest in other types of toxicity studies is the importance of weight changes. According to the federal guidelines "A change in offspring body weight is a sensitive indicator of developmental toxicity..." (1986e). A relatively small weight change is not generally considered important in toxicological studies of adult subjects; however, this is considered an important effect during development. For example, the human corollary to decreased weight in animals may be low birth weight, although this cannot be directly implied from animal studies. Low birth weight in infants is a significant and often serious public health problem. Weight gain or loss may also be organ-specific and may be indicative of organ toxicity. For example, decreased brain weight may be indicative of retarded neuronal development.

An issue which is often raised in developmental toxicity studies is maternal toxicity. Although some researchers have suggested that the presence of maternal toxicity undermines the validity of results observed in offspring, some level of maternal toxicity should be observed in this type of study at the high end of the dose regimen (EPA, 1986e). The EPA health assessment guidelines provide a description of appropriate endpoints of maternal toxicity. One reason that identification of maternal toxicity is an important component of a developmental toxicity study is that it can provide information on the likelihood of developing individuals being more or less susceptible than adults to an agent. Agents which produce developmental toxicity in offspring at doses which do not cause maternal toxicity are of greatest concern because these dynamics suggest that developing individuals are more sensitive or selectively affected (EPA, 1986e). Those which produce effects in parent and offspring at the same dose are also of concern; it should not be assumed that offspring toxicity results from maternal toxicity because both may be sensitive to the given dose level (EPA, 1986e).

5.3.3. Methods for Estimating Exposure Limits

This section was not designed to provide detailed guidance on conducting dose-response evaluations. Rather, it provides an overview of an EPA method used to calculate RfDs which can be used by the reader to estimate exposure limits for developmental effects as they deem necessary. (The following section discusses methods for calculating exposure limits for chronic exposure effects, which are similar to methods used for non-developmental RfDs.) The major steps are identification of the most appropriate NOAEL or LOAEL, and application of relevant uncertainty factors and modifying factors.[3] This discussion assumes a familiarity with basic concepts in epidemiology, toxicology, and human biology. Guidance is also provided in the discussions of individual target analytes (See Section 5.6) on selection of a sensitive health endpoint or study, and use of uncertainty and modifying factors.

5.3.3.1. Identify the Most Appropriate NOAEL or LOAEL.

The approach discussed in this section utilizes "No Observable Adverse Effects Levels" (NOAELs) and "Lowest Observable Adverse Effects Levels" (LOAELs) in a manner analogous to that used for the development of chronic toxicity RfDs.[4] It is recommended that the reader review the 1991 guidance on developmental toxicity risk assessment, which provides extensive specific guidance on the evaluation and selection of various types of developmental toxicity studies (EPA, 1991a). The 1991 guidelines provide a scheme for categorization of health-related data, which includes descriptions of sufficient evidence and insufficient evidence for dose-response evaluations. The guidelines recommend that a dose-response evaluation not be conducted unless

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[3] Characterization of the data base is also an important step. However, it is assumed in this document that an abbreviated approach will be taken to estimating exposure limits. If the summary data provided in this work or taken from other sources are used, it will not be possible to fully characterize and categorize the data base. For a full discussion of this refer to EPA, 1991a, pages 63816-63817.

[4] The EPA guidance on developmental toxicity (1991a) also contains a discussion of the use of a benchmark dose to evaluate toxicity. This approach employs a different method of evaluation than that described under chronic exposure later in Section 5. The benchmark approach utilizes the response rate as a critical factor (e.g., the dose which is effective in 10 percent of the study subjects). Such an approach requires more extensive information than was available for most target analytes.

there is sufficient evidence. To evaluate developmental toxicity, data from human studies may be used. However, for most chemicals human study data are not available and toxicity studies in animals are used (EPA, 1987 and 1991a). EPA's Office of Health Effects Assessment may also be consulted for guidance on obtaining additional information and identifying existing data bases on developmental toxics.

Exposure limits may be estimated using the NOAEL or LOAEL obtained from toxicological studies of animals and humans or epidemiological studies of humans. The NOAEL, usually expressed in mg dose per kg body weight of the subject per day, is the highest dosage given to the animals over their lifetime that results in no observable adverse effects (NOAEL). When a NOAEL is not available, the lowest dose at which an adverse effect (LOAEL) was observed is used. Often there are several NOAELS and LOAELs for a chemical; selection of the most appropriate value is a judgement based upon the quality of the studies, sensitivity of the health endpoint and test species and numerous other factors. The following hierarchy may be useful in selecting a study from which to use a NOAEL or LOAEL:

- a human study is preferable to an animal study. When a human study is unavailable, an animal study is selected which uses a species most relevant to humans, based on the most defensible biological rationale (e.g., pharmacokinetic data),
- in the absence of a clearly most relevant species, using the most sensitive species for the toxic effect of concern is preferable (e.g., exhibiting a toxic effect at the lowest dose),
- a study with the appropriate exposure route(s) is preferable, oral or gavage is appropriate for oral exposure,
- a study with sufficient subjects to obtain statistical significance at relatively low exposure levels is required,
- a recent study identifying adequately sensitive endpoints is preferred (e.g., not mortality),
- an adequate control population is required, and
- in general, a NOAEL is preferable to a LOAEL. When a NOAEL is unavailable, the LOAEL which generates the lowest exposure threshold (after the application of Uncertainty and Modifying Factors) is usually selected.

It is necessary to consider overall study quality and study design in selecting the most appropriate study or studies. The reader should refer to the 1991 *Guidelines for Developmental Toxicity Risk Assessment* for further details (EPA, 1991a).

5.3.3.2. Apply Relevant Uncertainty and Modifying Factors.

Once a LOAEL or NOAEL is selected, the value obtained (in mg/kg-day) is divided by factors to account for the various types of uncertainty inherent in estimating a threshold for developmental effects. These factors, referred to be EPA as uncertainty factors and modifying factors are summarized in Table 5-2. It was adapted from a discussion of RfD development from Abernathy and Roberts (1994). Many developmental toxicity studies utilize a brief dosing period during gestation (although use of a study with a single dose is not recommended). An uncertainty factor is usually not added for the short duration of the study under these circumstances. This differs from the calculation of exposure limits based on chronic exposure toxicity (discussed in Section 5.3.3), when an uncertainty factor is typically applied for the use of a less-than-lifetime study.

The total product of all of the uncertainty and modifying factors may range widely depending on the types of studies available. If a chronic human epidemiologic study is available, the uncertainty factor may be as small as 1. However, uncertainty factors of 10,000 have been used (IRIS, 1993). While the uncertainty factors address specific concerns, the modifying factors cover a wider range of circumstances. A common modifying factor adjustment results from differences in absorption rates between the study species and humans, differences in tolerance to a chemical, or lack of a sensitive endpoint. The default value for a modifying factor is 1. The uncertainty factor which deals with data gaps is relatively new (Abernathy and Roberts, 1994). It has been developed because the dose-response data often address a limited number of effects and do not adequately address effects of major concern. In some cases there are a number of studies, but the focus of analysis is narrow and insufficiently sensitive. In other cases, there is not a sufficient number or breadth of studies (See Dourson et al, (1992) for experimental support of this data base factor). Other reasons for applying a modifying factor are discussed in the specific developmental toxicity guidance (EPA, 1991a); these include data on pharmacokinetics or other considerations that may alter the level of confidence in the data.

Table 5-2. Uncertainty Factors and Modifying Factors For Estimating Exposure Limits For Developmental Effects

Uncertainty or Modifying Factor	General Comments	Standard Value
Uncertainty Factor: Human (Intraspecies)	Used to account for the variability of response in human populations.	10
Uncertainty Factor: Animal to Human (Interspecies)	Used to account for differences in responses between animal study species and humans.	10
Uncertainty Factor: Data Gaps	Used to account for the inability of any study to consider all toxic endpoints. The intermediate factor of 3 (1/2 log unit) is often used when there is a single data gap exclusive of chronic data (See IRIS Documentation).	3 to 10
Uncertainty Factor: LOAEL to NOAEL	Employed when a LOAEL instead of a NOAEL is used as the basis for calculating an exposure limit. For "minimal" LOAELs, an intermediate factor of three may be used.	3 to 10
Modifying Factor	Has been used for differences in absorption rates, tolerance to a chemical, or lack of sensitive endpoint. The default value is 1.	1 to 10

Source: Adapted from Abernathy and Roberts (1994). Their work also cites: Barnes and Dourson, 1988; Abernathy et al, 1993; IRIS, Background Documentation, 1993; and Jarabek et al, 1990.

The uncertainty and modifying factors are divided into the NOAEL or LOAEL to obtain a Reference Dose (RfD) using the following equation:

$$RfD = \frac{NOAEL \text{ or } LOAEL}{UF \cdot MF} \qquad \text{Equation 5.1}$$

where:

RfD	=	the RfD or exposure limit for the target analyte,
NOAEL or LOAEL	=	the NOAEL from the selected study,
UF	=	the multiplicative product of uncertainty factors and,
MF	=	the modifying factor

If an exposure limit is calculated for developmental toxicity, the results, in mg/kg-day, can be used in Equations 2.3 and 2.2 discussed in Section 2, to calculate fish consumption limits. Examples of how this is carried out are provided in Section 2.

As discussed above, it is necessary to have a full characterization of the uncertainties and assumptions incorporated in fish consumption limits. Assumptions and uncertainties associated with dose-response assessment are discussed in Section 4.3.7 and 5.2.11. As a point of reference, EPA has estimated that the RfDs which they develop have an uncertainty spanning approximately one order of magnitude (EPA, 1987). A description of the variability in dose-response results and their impact on fish consumption limits, descriptions of the data gaps, study limitations, and assumptions are also important in providing a context for fish consumption limits based upon developmental toxicity, or other types of toxic effects. It may be useful to review the description of uncertainties and assumptions associated with dose-response evaluations provided in Section 4.3 to identify major sources of uncertainty. In addition, the list of study characteristics provided in Section 5.3.3.1 may be useful for identifying data gaps and sources of uncertainty. If this document is the only source consulted for dose-response data, it should be noted that the literature review conducted for the development of values was limited to secondary sources such as ATSDR Toxicological Profiles, IRIS, HDSB, and standard toxicological texts (all are cited in the individual chemical discussions). The inclusion of this type of information in the risk management process following risk assessment will provide a better overall understanding of the limitations and uncertainties inherent in the fish consumption limits.

The 1991 developmental toxicity risk assessment guidelines provide a scheme for categorization of health-related data, including descriptions of sufficient and insufficient evidence for dose-response evaluations. The guidelines recommend that a dose-response evaluation not be conducted unless there is sufficient evidence (EPA, 1987 and 1991a). The reader is referred to this source for additional information on all aspects of risk assessment for developmental toxicity.

EXAMPLE

The chemical group DDT, DDD, and DDE was chosen as an example of how an estimated exposure limit for developmental effects can be developed for target analytes. It was chosen because there is sufficient information from a recent study with sensitive health endpoints to conduct such an analysis. In addition, the current RfD is based upon a study which is over 40 years old.

It is advisable to conduct a thorough literature search to identify all relevant studies. The summaries of dose-response and other toxicity data provided in Section 5 provide an overview; however, it is advisable to seek additional data, including any newly released information, whenever practical. A discussion of an abbreviated approach to estimating an exposure limit, using the information provided in this guide, is given below.

The developmental toxicity from the DDT[5] section (5.6.2) is duplicated below for the reader's convenience.

DDT causes embryotoxicity and fetotoxicity but not teratogenicity in experimental animals (ATSDR, 1992c). Studies indicate that estrogen-like effects on the developing reproductive system occur (ATSDR, 1992c)(this also occurs with chronic exposure as discussed under chronic effects). Rabbits exposed to 1 mg/kg-day early in gestation had decreased fetal brain, kidney and body weights (ATSDR, 1992c). Prenatal exposure in mice at 1 mg/kg on three intermittent days resulted in abnormal gonad development and decreased fertility in offspring, which was especially evident in females (Hayes, 1982). A three-generation rat reproduction study found increased offspring mortality at all dose levels with a LOEL of 0.2 mg/kg-day. Three other reproduction studies found no effects at much higher dose levels (IRIS, 1993). Effects on the urogenital system were found with eight days prenatal exposure in mice.

[5] The chemical group DDT, DDD, and DDE will be referred to as DDT throughout this section.

Behavioral effects in mice exposed prenatally for seven days were noted at 17.5 mg/kg-day (HSDB, 1993).

Prenatal one day exposure of rabbits to DDT resulted in an abnormal persistence of pre-implantation proteins in the yolk sac fluid. The results suggest that DDT caused a cessation of growth and development before implantation or during later uterine development. The authors suggest that damage can be repaired but may result in offspring with prenatal growth retardation in the absence of gross abnormalities (HSDB, 1993). Most dosages tested for these effects have been relatively high. Postnatal exposure of rats for 21 days at 21 mg/kg (only dose tested) resulted in adverse effects on lactation and growth.

Biomagnification of DDT in human milk has been observed. In lactating women with an intake of 5 x 10^{-4} mg/kg-day of DDT, the milk contained 0.08 ppm. This was calculated to result in infant doses of 0.0112 mg/kg-day, which are approximately 20 times the doses taken in by the mothers (HSDB, 1993). In dogs placental passage of DDT to the fetus has been demonstrated. This was confirmed in mice. Primary targets include the liver, adipose tissue and intestine. Rabbit blastocysts (a very early stage of development) contained a significant amount of DDT shortly after administration to the mother (HSDB, 1993).

DDT is suspected of causing spontaneous abortion in humans and cattle (Hayes, 1982). It is not known whether this is related to the reproductive system toxicity of DDT (See Chronic Toxicity section) or developmental toxicity. The average concentration of DDE in the blood of premature babies (weighing less than 2500 grams) was significantly greater than those of higher birth weight infants (HSDB, 1993). The relationship between spontaneous abortion, premature delivery and maternal exposure and body burden requires clarification.

ATSDR reports a recent developmental study in mice found behavioral abnormalities in offspring exposed prenatally at 0.5 mg/kg-day. Latent effects were observed following cessation of exposure, and subsequent tissue evaluation found structural/function alterations in the brain. Effects reported include an abnormal increase in activity and probable altered learning ability. The effects occurred at levels approximately 50-fold lower than those which were noted in adults and did not cease when dosing was discontinued, or when tissue levels had decreased. This information was used to support the hypothesis of permanent structural changes in the brain. The results of this study were used by ATSDR to calculate an acute exposure MRL of 5 x 10^{-4} mg/kg-day using standard uncertainty factors of 10 each for inter- and intraspecies variability and the use of a LOEL rather than a NOEL (ATSDR,

1992c). This MRL is based upon a sensitive endpoint with structural and functional toxicity correlations and should be considered for use as an exposure limit for developmental effects of DDT, DDE, and DDD.

DDT accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

In addition to the data specifically discussing developmental toxicity, it is also useful to review other relevant data. This includes chronic toxicity and carcinogenicity, including especially reproductive system toxicity, and other organ toxicities which are similar to, or affect the same system as that observed in developmental toxicity studies. All other sections of the target analyte file may also have a bearing on understanding and interpretation of the results of developmental toxicity studies. They may support or refute the results observed or point out potential data gaps (e.g., organ toxicities which were observed in numerous studies of adult animals but which were not evaluated in developmental toxicity studies).

It is especially necessary to review any discussions of reproductive system toxicity in the "Chronic Toxicity" section of a target analyte discussion. This may have a bearing on the interpretation of developmental toxicity study results. For example, alteration in hormonal balances, structural changes in the reproductive system, and other adverse effects may modify the ability to maintain pregnancy. This could lead to a reduction in the number or size of litters, or other impact on pregnancy outcome. These factors would need to be considered when reviewing developmental toxicity studies which identify effects such as increased fetal resorptions, fetal death, reduced litter size, and related effects, because these effects could arise from damage to the mother, rather than offspring.

There are numerous other effects on reproductive toxicity which may affect interpretation of developmental toxicity study results. The reader may wish to consult texts on this subject for further information. Some of these are listed at the end of Section 5.3. A copy of the relevant reproductive system toxicity discussion taken from the chronic toxicity section of the DDT profile (Section 5.6.2) is provided below.

DDT may cause reproductive system toxicity. It appears to bind to uterine tissue and have estrogenic activity (Hayes, 1982). Metabolites of DDT bind to

the cytoplasmic receptor for estrogen which may result in inadvertent hormonal response (agonist) or depression of normal hormonal balance (antagonist). Either may result in reproductive abnormalities (HSDB, 1993). The animal studies of the reproductive system have yielded mixed results. Chronic animal studies have identified LOELs which range over orders of magnitude. Serious adverse effects (decreased fertility and decreased litter size) have been observed at 0.35 and 0.91 mg/kg-day respectively in subchronic animal studies. Edema of the testes occurred at 2 mg/kg-day in a rat study. NOELs are not available for these studies. Other studies have identified NOELs ranging from 2.4 to 10 mg/kg-day with severe effects at 12 mg/kg-day (increased maternal and offspring death) (ATSDR, 1992c). Significant reproductive (function and lactation) abnormalities have also been observed at higher doses (83 mg/kg-day in rats and at 33.2 mg/kg-day in mice). Function abnormalities have also been observed in dogs (Hayes, 1982).

It may also be helpful to survey the available information on related chemicals (e.g., structural relatives of DDT would include other organochlorine pesticides). This may provide general information on effects which are common to all or many members of a chemical group. Such findings lend support to conclusions regarding toxicity. In addition, studies on related chemicals may have explored effects which are anticipated (based on adult studies in the chemical of concern) in developing individuals, but which have not been evaluated in developmental studies on the chemical of concern. This provides useful information for qualitatively evaluating potential toxicity and may point out critical data gaps.

It is not feasible to duplicate the information on all organochlorines here for purposes of discussing DDT; however, the reader may wish to review those sections for their own information. The nervous system appears to be a sensitive organ for developmental effects of organochlorines, based on a review of the chronic and acute exposure toxicity of DDT's structural relatives. The reader may wish to summarize the toxicity of structurally similar chemicals with respect to the most relevant type of toxicity (e.g. a critical effect) for establishing exposure limits. Only data regarding the nervous system is summarized below for DDT since it appears to be the most sensitive indicator of developmental toxicity in many of the organochlorines evaluated.

In summary, organochlorines are known to cause nervous system disorders in acutely exposed humans, and central nervous system depression is a common serious effect of organochlorine poisoning. Organochlorine exposure has caused adverse nervous system effects in multiple species in numerous chronic and developmental toxicity studies in animals. The association between DDT exposure and nervous system effects in developing individuals is a plausible and anticipated effect based upon the behavior of structurally similar chemicals.

Based on the information reviewed, prenatal exposure to DDT is associated with adverse effects on multiple organ systems in multiple species. There are limited human data, and they are not sufficiently quantified to use in calculating an exposure limit. The study which identified behavioral abnormalities in offspring exposed prenatally at 0.5 mg/kg-day appears to be the most sensitive study available (See above). The results are supported by tissue evaluations which found structural/functional alterations in the brain. The effects include an abnormal increase in activity and probable altered learning ability. The effects appeared permanent in nature. This information was used by ATSDR to calculate an MRL of 5×10^{-4} mg/kg-day. Using the same approach as was taken by ATSDR, with standard uncertainty factors of 10 each for inter- and intraspecies variability and the use of a LOEL rather than a NOEL yields an overall uncertainty divisor of 1000. This is divided into the LOAEL of 0.5 mg/kg-day to obtain an estimated exposure limit of 5×10^{-4} mg/kg-day.

$$\textit{Estimated Exposure Limit} = \frac{0.5\ mg/kg\text{-}d}{1000} = 5\ x\ 10^{-4}\ mg/kg\text{-}d$$

where:

0.5 = the LOAEL from the selected study

1000 = the multiplicative product of the uncertainty factors for inter- and intraspecies variability and the use of a LOAEL rather than a NOAEL

A modifying factor equal to 1 was used in this example. The estimated exposure limits developed by readers can be used in Equations 2.3 and 2.2 (discussed in Section 2), to calculate meal fish consumption limits. Examples are provided in Section 2.

Although MRLs are not available to support an estimated exposure limit for most chemicals, information is provided for each target analyte on studies with sensitive developmental health endpoints[6]. The categories of uncertainty factors and the need for a modifying factor are discussed. Readers are encouraged to evaluate the data and utilize the factors they consider most appropriate. Information on uncertainty and modifying factors is qualitative and should be used in the context of the overall toxicity data for each target analyte. The information provided on health endpoints with NOAELS and/or

[6] In the absence of sensitive health endpoints, the lack of data is clearly noted in the text.

LOAELS and regarding uncertainty and modifying factors should enable readers to calculate and exposure limit as they deem necessary.

A discussion of uncertainty, assumptions, and data gaps should be a part of information supporting an estimated exposure limit. This information can include a summary of the various sources of uncertainty described in Sections 4 and 5 of this document, information included in the target analyte discussion, and any other information the reader feels would be useful in characterizing uncertainty. A copy of the "data gaps" section from the DDT discussion follows.

IRIS notes the lack of a NOEL for reproductive effects and a relatively short duration for the critical study on which the RfD is based. No intermediate or chronic oral MRLs were calculated by ATSDR because of the lack of a NOEL and the seriousness of the LOEL in significant studies (ATSDR, 1992c).

Information is not available for this document on the specific relationships between various pharmaceuticals and DDT/E/D body burdens or intakes. Information on the relationship between pre- and postnatal exposure and behavioral effects and maternal exposure and milk concentrations are also needed.

An interagency group of researchers from NTP, ATSDR, and EPA have identified the following data gaps, pharmacokinetic data, animal studies on respiratory, cardiovascular, GI, hematological, musculoskeletal and dermal/ocular effects, the significance of subtle biochemical changes such as the induction of microsomal enzymes in the liver and the decreases in biogenic amines in the nervous system in humans, an epidemiological study in humans of estrogen-sensitive cancers including endometrial, ovarian, uterine, and breast cancer, reproductive system toxicity, developmental toxicity, a multiple assay battery for immunotoxicity, subtle neurological effects in humans, and mechanisms of neurotoxicity in the neonate (ATSDR, 1992c).

This discussion includes a list of the types of studies which are needed based on an interagency review of the available data. Most major categories of uncertainty are covered by this list of studies. The reader may wish to elaborate on why certain studies are needed (e.g., pharmacokinetic studies to generate better information on bioaccumulation, body burden, accumulation in milk, etc).

5.3.3.3. Sources of Additional Information on Developmental Toxicity

The primary source the reader is referred to for additional information on conducting risk assessment for developmental toxicity is: *Guidelines for*

Developmental Toxicity Risk Assessment (EPA, 1991a). In addition, there are 165 citations listed in the Guidelines, which cover a broad spectrum of literature on developmental toxicity and risk assessment. The reader may wish to consult these sources for additional guidance on this topic.

5.4. Methods for Calculating Alternative Values for Systemic Chronic Effects.

EPA RfDs are provided for use in establishing exposure limits for chronic (non-carcinogenic) effects. They have been used to calculate the fish consumption limits provided in Section 3. If the reader wishes to calculate alternative exposure limits based on the data which is provided in the toxicity discussions which follow (e.g., if new data are indicated), or based upon data from other sources, the EPA methodology shown below may be used. It is taken primarily from the *IRIS Background Document 1A, Reference Dose (RfD): Description and Use in Health Risk Assessments (IRIS, 1993)*, Abernathy and Roberts (1994), and Dourson et al. (1992). The method is very similar to the approach used for developmental toxics, discussed in Section 5.3. The major difference is that an uncertainty factor for the use of a less-than-lifetime study is not generally applied for a developmental toxicity analysis; however, it is applied for developing a chronic toxicity exposure limit when the selected LOAEL or NOAEL is obtained from subchronic (e.g., three-month) studies are used. A very brief overview of methods is provided below. The reader is urged to consult additional sources cited in this section for more detailed information. There are two major steps to calculating chronic exposure limits: identification of the most appropriate NOAEL or LOAEL and the application of relevant uncertainty and modifying factors (as with exposure limit estimating for developmental toxicity).

5.4.1. Identify the Most Appropriate NOAEL or LOAEL.

The hierarchy for selection of a study described in section 5.3 is also appropriate for use in identifying appropriate chronic toxicity studies. In addition to the criteria listed, a chronic (lifetime) study is preferable to a subchronic study (an acute study cannot be used to quantify risks associated with chronic exposure). It is important that exposure occurs over a significant portion of the experimental subject's life in order to parallel a lifetime exposure of the human population. Issues related to the quality of the study should also be considered in selecting the most appropriate studies. Additional information on selection criteria can be reviewed in the IRIS documentation file (IRIS, 1993).

5.4.2. Apply Relevant Uncertainty and Modifying Factors.

The calculations for chronic systemic toxicity utilize the modifying and uncertainty factors listed for developmental toxicity (See Table 5-2). In addition, an uncertainty factor may be used when a chronic study is not available and a subchronic (e.g., 90-day) study is used. This is generally a 10-fold factor (Abernathy and Roberts, 1994, IRIS, 1993). The product of all uncertainty/modifying factors may range widely depending on the toxicity data base. If a chronic human epidemiologic study is available, the uncertainty factor may be as small as 1. However, uncertainty factors of 10,000 may be appropriate (U.S. EPA, 1990b; Bolger et al., 1990).

While uncertainty factors address specific concerns, the modifying factor covers a wider range of circumstances. A common modifying factor adjustment results from differences in absorption rates between the study species and humans, differences in tolerance to a chemical, or lack of sensitive endpoint. The default value for a modifying factor is 1, but may range up to 10 (See Table 5-2).

The uncertainty factor which deals with data gaps is relatively new (Abernathy and Roberts, 1994). It has been developed because the dose-response data often address a limited number of effects and may not adequately address effects of major concern. In some cases there are a number of studies, but the focus of analysis is narrow and not sufficiently sensitive. In other cases, there is not a sufficient number or breadth of studies. Other reasons for applying a modifying factor are discussed in the specific developmental toxicity guidance (EPA, 1991a); these include data on pharmacokinetics or other considerations that may alter the level of confidence in the data. EPA has used the criteria that the following studies be available for a high level of confidence in an RfD:

> "two adequate mammalian chronic toxicity studies in different species, one adequate mammalian 2-generation reproductive toxicity study, and two adequate mammalian developmental toxicity studies in different species" (Dourson et al, 1992 and EPA, 1989c).

The same type of concern regarding the completeness of a data base is reflected throughout the ATSDR Toxicological Profiles. For example, the profiles do not provide an MRL for chemicals which have no NOAELs and only LOAELs resulting in severe effects.

The uncertainty and modifying factors are divided into the NOAEL or LOAEL to obtain an estimated exposure limit in mg/kg-day. This value is analogous to EPA's Reference Dose (RfD). The equation is the same as that listed for

developmental toxicity (See Equation 5.1). If an alternative exposure limit is calculated, the results, in mg/kg-day, can be used in Equation 2.3 and 2.2 which are discussed in Section 2, to calculate meal fish consumption limits.

As a point of reference, EPA has estimated that the RfDs they develop have an uncertainty spanning approximately one order of magnitude (EPA, 1987). As discussed previously, it is necessary to have a full characterization of the uncertainties and assumptions which are incorporated in fish consumption limits. A description of the variability in dose-response results and their impact on fish consumption limits, descriptions of the data gaps, study limitations, and assumptions are also important in providing a context for fish consumption limits based upon developmental toxicity, or other types of toxic effects. It may be useful to review the description of uncertainties and assumptions associated with dose-response evaluations provided in Section 4.3.7 and 5.2.11.. If this document is the only source consulted for dose-response data, it should be noted that the literature review conducted for the development of these values was limited to secondary sources such as ATSDR Toxicological Profiles, IRIS, HDSB, and standard toxicological texts (all are cited in the individual chemical discussions). The list of study characteristics provided in Section 5.3.3.1 may be useful for identifying data gaps and sources of uncertainty. The inclusion of this type of information in the risk management process which follows risk assessment, will provide a better overall understanding of the limitations and uncertainties inherent in the fish consumption limits.

EXAMPLE

The reader is referred to the example provided in Section 5.3.3 for guidance. The difference between calculating chronic exposure limits and developmental exposure limits is in the use of the uncertainty factor for a less-than-lifetime study when evaluating chronic exposure toxicity. As with the example in 5.3.3, it is important to review all available information on a chemical and its close structural analogs prior to making decisions regarding study selection and the application of uncertainty and modifying factors.

5.5. Toxicity Characteristics of Groups of Analytes

Many chemicals on the list of target analytes (See Table 1-1) fall into two groups: organochlorine pesticides and organophosphate pesticides. Chemicals in these groups, while having many individual characteristics, have multiple toxicity attributes in common with other members of the same group, due to their structural similarity. Rather than listing all aspects of the toxicity of each member under the individual chemical discussions, those characteristics shared by members of the group are listed in this section.

The following information is of a qualitative nature and includes the spectrum from acute high dose-responses to chronic exposure low dose-responses. This range was included for a number of reasons. Individual responses to chemical exposures will vary considerably. It is not anticipated that all people exposed at the same dose will respond in the same manner. Those individuals who are chemically sensitive may respond to chronic low doses as severely as less sensitive individuals who are exposed to high doses. Secondly, the effects elicited by organophosphate and organochlorine pesticides can be characterized on a continuum for many organ systems (e.g., nervous system effects, liver damage). Therefore, many effects are associated with both acute and chronic exposure. Finally, there are very limited dose-response data establishing specific human thresholds for effects to occur. The risk values (RfDs), derived primarily from animal studies, do not predict the exposure level at which response will occur, but rather incorporate uncertainty factors with the study data to determine a level at which no one is anticipated to experience adverse effects. Consequently, it is not possible, in most cases, to provide quantitative data regarding the dose associated with a specific level of effect in a specific organ system. Under most circumstances it is assumed that the very severe effects such as convulsions, coma, and death are associated with acute high level exposures to chemicals. The information provided below was obtained from the following sources (See Literature Cited in Section 6 for full citation):

Recognition and Management of Pesticide Poisonings, USEPA (1982)
Casarett and Doull's Toxicology, Klaassen et al. (1986)
Pesticides and Human Health, Cunningham-Burns & Hallenbeck (1984)
Pesticides Studied in Man, Hayes (1982)
Handbook of Pesticide Toxicology, Hayes & Laws (1991)

In addition, the Hazardous Substances Data Bank (HSDB,1993) which was consulted for specific information on target analytes, contains general clinical effects information for organophosphate exposures and organochlorine exposures which was used in the development of this section.

5.5.1. Organochlorine Pesticides

Organochlorine pesticides are readily absorbed via the digestive system. They often accumulate in fatty tissue, including brain and adipose tissue, and may also be found in human milk due to its high lipid content. The neurological effects of organochlorine exposure are based upon interference with axonic transmission of nerve impulses. This causes altered functioning of the nervous system, primarily the brain.

The following symptoms are commonly associated with exposure to organochlorines: behavioral changes, sensory and equilibrium disturbances,

involuntary muscle activity, depression of vital centers (particularly those controlling respiration), myocardial irritability, tremor, twitching, nausea, confusion, apprehension, excitability, dizziness, headache, disorientation, weakness, paresthesias, convulsions, and unconsciousness (EPA, 1982, HSDB,1993).

Organochlorines stimulate synthesis of hepatic drug-metabolizing microsomal enzymes, primarily in the liver; however, they do so in different ways (Hayes and Laws, 1991, p.739). Many organochlorines are associated with liver and kidney toxicity. Organochlorine pesticides' induction of the hepatic microsomal enzyme system causes alterations in the rate of metabolism of all other endogenous or exogenous chemicals metabolized by this system. Metabolism may detoxify or increase the toxicity of chemicals, depending on whether the parent or metabolite is more toxic. For example, DDT is reported to promote some tumorigenic agents and antagonize others as a result of the induction of microsomal enzymes (ATSDR, 1992c). In addition, exposure to other chemicals that induce the same enzymes may increase the toxicity of the chemical under evaluation by enhancing its metabolism to its toxic intermediate.

The induction of microsomal enzymes by organochlorines has serious implications for the metabolism of some pharmaceutical drugs. Alterations in response to drugs have been observed in both humans and in experimental animals. For example, increased phenobarbital metabolism resulting from an increased body burden of DDT (10 micrograms) led to a 25 percent decrease in effectiveness of the drug in experimental animals (HSDB,1993). Concern regarding interaction with drugs is indicated in discussions of especially susceptible populations in the ATSDR Toxicological Profiles. For example, due to the interactive effects of chlordane with other chemicals via microsomal enzymes, ATSDR has cautioned that: "doses of therapeutic drugs and hormones may require adjustment in patients exposed to chlordane" (ATSDR, 1990d). A similar caution is provided for DDT and its analogs: individuals who use medications which involve the mixed function oxidase system (MFO inhibitors) directly or for metabolic processes may be at risk for alteration of the drugs efficacy and/or timing if they are exposed to DDT (ATSDR, 1992c).

For most chemicals, information was not available on the quantitative relationships between various pharmaceuticals and organochlorine body burdens or intakes. When information was located on these types of interactions, it was included in the chemical discussions. For more information on this, the reader is referred to the ATSDR Toxicological Profiles and to the open literature.

5.5.2. Organophosphate Pesticides

Organophosphates are efficiently absorbed via ingestion. Their toxicity depends in part on the rate at which the chemicals are metabolized in the body. This occurs principally by hydrolysis to nontoxic or minimally toxic byproducts. The most studied and obvious effect of organophosphate poisoning is cholinesterase inhibition. This results from phosphorylation of the acetylcholinesterase enzyme at nerve endings. Loss of enzyme function allows accumulation of acetylcholine (the neurotransmitter) at cholinergic neuroeffector junctions causing muscarinic effects, and at skeletal myoneural junctions, and in autonomic ganglia (nicotinic effects). Organophosphates cause CNS disturbances through impairments of nerve impulse transmission in the brain (EPA, 1982).

It is not clear what, if any, adverse effects are associated with exposure at levels which produce only cholinesterase inhibition in the absence of any other effects. This is currently under evaluation at EPA. In 1993 EPA's Scientific Advisory Board (SAB) issued a report on cholinesterase inhibition and risk assessment (EPA, 1993q). A key finding was:

> "To date, analyses of studies of cholinesterase inhibition in plasma and in red blood cells do not provide information useful for evaluating potential hazards and risks in the nervous system. This finding justifies a new science policy against the use of blood cholinesterase inhibition data for risk assessment purposes."(EPA, 1993q)

Multiple adverse effects resulting from cholinesterase inhibition and other toxic mechanisms have been associated with organophosphate exposure. The SAB report states that:

> "Clinical effects associated with exposure to cholinesterase inhibitors can be used in risk assessment to define hazard and to calculate benchmark doses and RfDs."(EPA, 1993q)

While the issue may be more clear for clinical effects, there has not, as yet, been resolution of the questions as to whether cholinesterase inhibition alone should be used as a critical endpoint. The 1993 report "does not provide a simple yes or no answer to the issue of using RBC cholinesterase inhibition data by itself (i.e., in the absence of clinical symptoms) for risk assessment." Concern arises, in part, from the fact that blood enzyme inhibition may precede and predict brain enzyme inhibition, which is of significant concern (EPA, 1993q). Additional information is required to clarify this issue.

The SAB report suggests that EPA continue research designed to evaluate the correlation of clinical signs with blood cholinesterase inhibition, especially correlations with respect to dose, time, and linearity (EPA, 1993q). Cholinesterase inhibition has been used as the critical endpoint, on which RfD calculations are based, for many organophosphates included in the IRIS data base. The uncertainty surrounding the use of cholinesterase inhibition as an effect is an example of a circumstance when the reader may wish to calculate their own exposure limits. When the RfD for the target analytes is based on cholinesterase inhibition, other chronic toxicity data are provided for analytes having sufficient data. This enables the reader to calculate estimated exposure limits (using Equation 5.1) and derive fish consumption limits (using Equations 2.2 and 2.3) based on other health endpoints if appropriate.

Effects commonly associated with organophosphate exposure include the following: headache, dizziness, weakness, incoordination, muscle twitching, tremor, nausea, abdominal cramps, diarrhea, sweating, blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, pulmonary edema, slow heartbeat, salivation, tearing, toxic psychosis with manic or bizarre behavior, influenza-like illness with weakness, anorexia, malaise, incontinence, unconsciousness, and convulsions (EPA, 1982, HSDB,1993). In addition, some, but not all, organophosphates cause peripheral neuropathy resulting from demyelination of the nerves. Specific effects include numbness, tingling, pain, weakness, and paralysis in the arms and legs. These effects may be delayed and may be reversible or irreversible (EPA, 1982).

Muscarinic effects in children exposed to organophosphates may differ from those in adults. Those most commonly encountered with acute exposure include: CNS depression, stupor, flaccidity, dyspnea, and coma. Seizures may be more common in children than in adults (HSDB,1993).

Psychiatric symptoms which have been reported include defects in expressive language and cognitive function, impaired memory, depression, anxiety or irritability and psychosis. These are more common in individuals with other clinical signs of organophosphate poisoning or with pre-existing psychological conditions (HSDB,1993). Behavioral effects are a prominent concern based upon the results of toxicity data reviewed for the target analytes. It appears to be one of the most sensitive indicators of toxicity related to chronic exposure. Behavioral effects, such as aggressiveness, irritability and hyperactivity, occurred at low levels of exposure in animal studies. These effects are particularly problematic because they are difficult to specifically associate with organophosphate exposure in the human population, but could have serious consequences.

There is a recognized high-risk human population with respect to organophosphate exposure. Approximately three percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include: persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis, because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions are at greater risk than the general population from exposure to organophosphates (EPA, 1982).

Compounds which are known to reduce plasma pseudocholinesterase activity and thereby aggravate the effects of cholinesterase inhibitors are carbon disulfide, benzalkonium salts, organic mercury compounds, ciguatoxins, and solanines (EPA, 1982).

The Hazardous Substances Data Bank (HSDB,1993) contains a summary of diseases and disorders which are of special concern for individuals exposed to organophosphates. The following are listed as contraindications for work with (and exposure to) these chemicals: "organic diseases of the CNS, mental disorders and epilepsy, pronounced endocrine and vegetative disorders, pulmonary tuberculosis, bronchial asthma, chronic respiratory diseases, cardiovascular diseases and circulatory disorders, gastrointestinal diseases (peptic ulcer), gastroenterocolitis, diseases of the liver and kidneys, and eye diseases (chronic conjunctivitis and keratitis)" (HSDB,1993).

5.6. Toxicity Data for Target Analytes

This section contains a contaminant specific discussion of toxicity data and risk values. The target analytes are listed with their section number in chemical groupings in Table 5-3. This is the order in which they are presented in this section. A summary of the cancer potency values and RfDs is provided in Table 2-2.

Abbreviations Used

The abbreviations NOEL, NOAEL, LEL, LOEL, and LOAEL are used in this document as they appear in the original sources. While they have specific meanings (See the Glossary for abbreviations), NOEL-NOAEL and LEL-LOEL-LOAEL are sometime used interchangeably. Since it was not possible to determine the intent of the authors of the source documents, the terms were used as they appeared in those documents.

The glossary contains a description of additional terms and abbreviations which are found in this section

SCIENTIFIC NOTATION

Scientific notation is used where the values are less than 0.001 unless it would introduce confusion to the text (e.g., when presenting a range, the same format is used for both values in the range). In the summaries of risk values all non-cancer risk values are presented in scientific notation to facilitate comparison across health endpoints.

Table 5-3. Target Analytes and Chemical Categories

Chemical Category	Target Analyte	Section Number
Organochlorine pesticides	Chlordane	5.3.1
	DDT, DDD, DDE	5.3.2
	Dicofol	5.3.3
	Dieldrin	5.3.4
	Endosulfan (I and II)	5.3.5
	Endrin	5.3.6
	Heptachlor epoxide	5.3.7
	Hexachlorobenzene	5.3.8
	Lindane	5.3.9
	Mirex	5.3.10
	Toxaphene	5.3.11
Organophosphate pesticides	Carbophenothion	5.3.12
	Chlorpyrifos	5.3.13
	Diazinon	5.3.14
	Disulfoton	5.3.15
	Ethion	5.3.16
	Terbufos	5.3.17
Chlorophenoxy herbicides	Oxyfluorfen	5.3.18
Polychlorinated biphenyls (PCBs)	Total Aroclors	5.3.19
Dioxins	2,3,7,8-Tetrachloro-dibenzo-p-dioxin	5.3.20
Metals	Cadmium	5.3.21
	Mercury	5.3.22
	Selenium	5.3.23

ORGANOCHLORINE PESTICIDES

In addition to the discussions of individual target analytes, please refer to the discussion of toxicity characteristics of the organochlorine chemical group in Section 5.5.

5.6.1. Chlordane

Background

Chlordane is an organochlorine pesticide which is comprised of the sum of cis- and trans-chlordane and trans-nonachlor and oxychlordane for purposes of health advisory development (EPA, 1993a). It was used extensively until most uses were banned in 1988. Due to its long half-life and ability to concentrate in biological materials, it is still widely distributed in fish in the United States.

Pharmacokinetics

Chlordane bioaccumulates in biological materials (IRIS, 1993). It is highly lipophilic and readily absorbed via all routes. Chlordane is metabolized via oxidation which results in a number of metabolites, including oxychlordane, which is very persistent in body fat. Reductive dehalogenation of chlordane forms free radicals which are hypothesized to be significant in chlordane toxicity (ATSDR, 1992d).

Human studies have found chlordane in pesticide applicators, residents of homes treated for termites and those with no known exposures other than background (e.g., food or airborne). Human milk fat contained a mean chlordane residue of approximately 188 ppm. Oxychlordane residues were detected in 68 percent of human milk samples in a low pesticide usage area and in 100 percent of the 50 samples tested in Hawaii. It is anticipated that all routes of exposure were involved in maternal exposure to chlordane. Fat accumulation of chlordane appears to depend on the exposure duration (ATSDR, 1992d).

Mechanisms of toxicity include: the binding of chlordane and its metabolites irreversibly to cellular macromolecules, causing cell death or disrupting normal cellular function; increasing tissue production of superoxide radicals which accelerates lipid peroxidation and disrupt function of membranes; possible suppression of hepatic mitochondrial energy metabolism, and alteration of neurotransmitter levels in various regions of the brain, a reduction in bone

marrow stem cells prenatally, and suppression of gap junction intercellular communication (ATSDR, 1992d).

Acute Toxicity

Chlordane is moderately to highly toxic with an estimated lethal dose to humans of 6 to 60 grams (IRIS, 1993). See the listing of usual effects associated with organochlorine exposure in Section 5.5.

Chronic Toxicity

Chlordane has classic organochlorine toxicity as described in Section 5.5. The principal systems affected by exposure are liver, nervous system, and immune system. Other effects include neurological abnormalities including gran-mal seizures and altered EEG results (ATSDR, 1992d).

Reduced fertility and survivability in mice and rats has occurred at 25 and 16 mg/kg respectively and may be associated with reduced binding of progesterone in the endometrium or with altered metabolism and circulating levels of steroid hormones. The studies were not designed to identify thresholds or mechanisms for action (ATSDR, 1992d) and cannot be used to derive dose-response data for estimation of an RfD.

Jaundice has been reported in humans living in homes treated with chlordane for termite control. Chemistry changes indicative of altered liver function were observed in pesticide applicators in Japan exposed to chlordane (ATSDR, 1992d).

Multiple neurological effects have been reported in humans exposed both acutely and chronically. According to ATSDR, neither animal or human studies have evaluated subtle neurological or behavioral effects which may occur at low levels. Consequently, it is not possible to assess the likelihood of human effects at environmental exposure levels (ATSDR, 1992d).

IRIS provides an RfD of 6.0×10^{-5} based on a NOAEL of 0.055 mg/kg-day in a study which found liver atrophy in female rats. The standard uncertainty factors of 10 each for inter- and intraspecies variability were applied. An additional safety factor of 10 was applied "to account for the lack of an adequate reproduction study and adequate chronic study in a second mammalian species, and the generally inadequate sensitive endpoints studies in the existing studies, particularly since chlordane is known to bioaccumulate over a chronic duration" (IRIS, 1993). Confidence in this RfD is low for the above stated reasons (IRIS, 1993).

Developmental Toxicity

According to the IRIS file "there have been 11 case reports of CNS effects, blood dyscrasias and neuroblastomas in children with pre/postnatal exposure to chlordane and heptachlor" (IRIS, 1993). There was insufficient data to calculate an exposure limit for developmental effects from this study.

ATSDR reports a number of developmental effects. Pre- and early postnatal exposure in mice may have permanent effects on the immune system, including a reduction in the number of stem cells which are required to form the mature immune system. Effects were observed at 4 mg/kg-day. Neurological effects include abnormal behavior and increased seizure thresholds in mice at 1 mg/kg-day prenatal and postnatal (via lactation) exposure (no NOEL was identified). Alterations in plasma corticosterone levels were observed which may result from a change in the neuroendocrinological feedback mechanisms (ATSDR, 1992d).

There is insufficient information to develop a well-based estimated exposure limit for developmental effects. According to ATSDR, neither animal or human studies have evaluated subtle neurological or behavioral effects which may occur at low levels. Consequently, it is not possible to assess the likelihood of human effects at environmental exposure levels (ATSDR, 1992d). Neurological and behavioral effects may be the most sensitive measures of chlordane developmental toxicity. This appears to be the case for some other organochlorine pesticides (See DDT and toxaphene). However, it is not possible to estimate the threshold level because the LOEL caused multiple and serious effects. If readers elect to calculate an exposure limit for developmental effects, it should be considered a limited estimate due to the lack of information on the threshold for effects. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, the use of a LOEL rather than a NOAEL, and the poor quality of the data base.

Chlordane accumulates in body tissues; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Regarding cancer in children, see the discussion in the "carcinogenicity" section below.

Mutagenicity

Mutagenicity assays of chlordane have yielded mixed results with positive results generally obtained in higher organism cell assays and negative results in bacterial assays (IRIS, 1993).

Carcinogenicity

Chlordane is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer potency factor of 1.3 per mg/kg-day is the geometric mean of the cancer potencies calculated from four data sets (IRIS, 1992). This value was used to develop fish consumption limits for carcinogenic toxicity listed in Section 3.

Positive results have been obtained in four strains of mice of both sexes and in male rats. In addition, numerous structurally related organochlorine pesticides have been found to be carcinogenic.

Neuroblastoma and acute leukemia have also been associated with prenatal and early childhood exposure to chlordane (ATSDR, 1993c - heptachlor epoxide document).

Special Susceptibilities

Based on the results of animal studies showing prenatal exposure causes damage to the developing nervous and immune systems, fetuses and children may be at greater risk than adults from chlordane exposure. According to ATSDR:

> "Given the generally greater sensitivity to toxics of incompletely developed tissues, it seems possible that prenatal exposure of humans to chlordane could result in compromised immunocompetence and subtle neurological effects." (ATSDR, 1992d).

Due to the interactive effects of chlordane with other chemicals via microsomal enzymes (See interactive effects below), ATSDR has cautioned that: "doses of therapeutic drugs and hormones may require adjustment in patients exposed to chlordane." The results of an acute aminal study suggest that protein-deficient diets may also increase the toxic effects of chlordane (ATSDR, 1992d).

ATSDR has listed the following populations as unusually susceptible: those with liver disease or impaired liver function, infants, especially those with a hereditary predisposition to seizures, and the fetus regarding immunosuppression. In addition, it has been hypothesized that a subpopulation

may exist with a predisposition to blood dyscrasias resulting from chlordane exposure. Identification of such a population is not now possible (ATSDR. 1990d).

Interactive Effects

Chlordane is a potent inducer of hepatic microsomal enzymes. (See a discussion of organochlorine effects related to this induction in Section 5.5.) Chlordane exposure has been associated with an increased rate of metabolism of therapeutic drugs, hormones and many other endogenous and xenobiotic compounds. Exposure to other chemicals which induce the same enzymes may increase the toxicity of chlordane by enhancing its metabolism to its toxic intermediate. The acute toxic effects of aldrin, endrin and methoxychlor with chlordane were greater than the additive sum of the individual toxicities (ATSDR, 1992d).

It has been suggested that increased dietary vitamins C or E or selenium may be protective against free radical-induced toxicity (ATSDR, 1992d).

MIXTOX reported synergistic effects between chlordane and endrin in mice exposed via gavage and both potentiation and inhibition with gamma-hexachlorocyclohexane in rodents exposed via gavage. Synergism is reported with toxaphene and malathion together with chlordane in mice exposed via gavage (MIXTOX, 1992).

Critical Data Gaps

IRIS lists the following data gaps for chlordane: chronic dog feeding study, rat reproduction study, rat teratology study, rabbit teratology study (IRIS, 1993). It is clear from this list that the developmental effects of chlordane have not been adequately evaluated.

According to ATSDR, neither animal or human studies have evaluated subtle neurological or behavioral effects which may occur at low levels. These types of studies are needed to assess the likelihood of human effects at environmental exposure levels (ATSDR, 1992d).

ATSDR has declined to develop oral MRLs for acute, intermediate or chronic duration oral exposure due to the lack of data on sensitive endpoints for these durations. They note the need for a behavioral study because it appears to be a sensitive endpoint. Other studies which are needed include a multigeneration study which includes a measurement of reproductive system toxicity, immunological effects, particularly with developmental exposures,

pharmacokinetic studies, and studies to determine methods for reducing body burden (ATSDR, 1992d).

Summary of EPA Risk Values

Chronic Toxicity	6×10^{-5} mg/kg-day
Carcinogenicity	1.3 per mg/kg-day

Major Sources: IRIS (1993), HSDB,1993, ATSDR (1992d)

5.6.2. DDT, DDE, DDD

Background

DDT is an organochlorine pesticide which has not been marketed in the United States since 1972, but which is ubiquitous due to its widespread use in previous decades and its relatively long half-life. DDT's close structural analogs, DDE and DDD, are metabolites of DDT and have also been formulated as pesticides in the past (Hayes, 1982). DDT is very widely distributed; it has been found in seals in Finland and reptiles in the Everglades (HSDB,1993). The NHANES II study (National Human Monitoring Program of the EPA) detected DDE, a metabolite of DDT, is found in 99 percent of the 12 to 74 year old study subjects (living in the Northeast, Midwest, and South). The median level was 11.8 ppb in blood serum (HSDB,1993).

Although some use of DDT continues throughout the tropics, it remains of human health concern in the United States primarily due to its presence in water, soil, and food (Hayes, 1982). Since individuals are typically exposed to a mixture of DDE, DDT, and DDD and their degradation and metabolic products (ATSDR, 1992c), the sum of the 4,4'- and 2,4'- isomers of DDT, DDE, and DDD should be considered in the development of fish consumption limits for this group of chemicals (EPA, 1993a).

Pharmacokinetics

DDT and its analogs are stored in fat, liver, kidney and brain tissue; trace amounts can be found in all tissues (Hayes, 1982). DDE is stored more readily than DDT (Hayes, 1982). DDT is eliminated through first-order reduction to DDD, and to a lesser extent to DDE. The DDD is converted to more water-soluble bis (p-chlorophenyl)-acetic acid, with a biological half-life of one year. DDE is eliminated much more slowly, with a biological half-life of eight years. Because elimination occurs slowly, ongoing exposure may lead to an increase in the body burden over time.

Acute Toxicity

See the listing of usual effects associated with organochlorine exposure in Section 5.5. The low effect dose for severe effects (acute pulmonary edema) in infants has been reported to be 150 mg/kg. In adults, behavioral effects were noted at 5 to 6 mg/kg and seizures at 16 mg/kg (HSDB,1993).

Evidence from acute exposure studies of dogs indicate that DDT may sensitize the myocardium to epinephrine. This was observed for both injected epinephrine and epinephrine released by the adrenal glands during a seizure,

and resulted in ventricular fibrillation (Hayes, 1982). DDT may concurrently act on the CNS, in a manner similar to that of other halogenated hydrocarbons, to increase the likelihood of fibrillation (Hayes, 1982). Chronic exposure to 10 mg/kg-day did not produce increased incidence of arrhythmias in rats or rabbits (Hayes, 1982).

DDD is considered less toxic than DDT in animals. Symptoms develop more slowly and have a longer duration with DDD than with DDT exposure. Lethargy is more significant and convulsions are less common than with DDT exposure (HSDB,1993).

Chronic Toxicity

Extensive research has been conducted on chronic and subchronic exposure effects of DDT in animals and in humans working with DDT. These studies have primarily focused on carcinogenic effects, which are discussed below. Studies have also identified liver damage, and there is limited evidence that DDT may cause leukocytosis and decreased hemoglobin level (Hayes, 1982).

Immunological effects have been associated with exposure to DDT. Exposure to DDT at 2.63 mg/kg-day for 10 days resulted in immunological effects in rabbits. With 31 days of exposure at 1 mg/kg-day in rats a decrease in the number of mast cells were observed. A relatively recent eight week study in rabbits found decreases in germinal centers of the spleen and atrophy of the thymus (categorized as a serious effects by ATSDR) at 0.18 mg/kg-day. Other effects were observed at higher doses. No studies were provided on immunological effects following chronic exposure (ATSDR, 1992c).

DDT may have reproductive system toxicity. It appears to bind to uterine tissue and have estrogenic activity (Hayes, 1982). Metabolites of DDT bind to the cytoplasmic receptor for estrogen which may result in inadvertent hormonal response (agonist) or depress normal hormonal balance (antagonist). Either may result in reproductive abnormalities (HSDB,1993). The animal studies of the reproductive system have yielded mixed results. Chronic animal studies have identified LOELs which range over orders of magnitude. Serious adverse effects (decreased fertility and decreased litter size) have been observed at 0.35 and 0.91 mg/kg-day respectively in subchronic animal studies. Edema of the testes occurred at 2 mg/kg-day in a rat study. NOELs are not available for these studies. Other studies have identified NOELs ranging from 2.4 to 10 mg/kg-day with severe effects at 12 mg/kg-day (increased maternal and offspring death) (ATSDR, 1992c). Significant reproductive (function and lactation) abnormalities have also been observed at higher doses (83 mg/kg-day in rats and at 33.2 mg/kg-day in mice). Function abnormalities have also been observed in dogs (Hayes, 1982).

IRIS lists an oral RfD of 5 x 10^{-4} mg/kg-day, based on liver effects with a NOEL of 0.05 mg/kg-day from a 27 week rat feeding study conducted in 1950. Uncertainty factors of 10 each for inter- and intraspecies variability were used; however, the usual factor of 10 for a less-than-lifetime study was not applied "because of the corroborating chronic study in the data base" (IRIS, 1993). The corroborating study was conducted in 1948.

More recent studies of the immunological and reproductive systems (noted above) suggest a LOEL from subchronic studies in the range of 0.18 to 0.35. There are numerous studies supporting the occurrence of both types of effects, and both are serious in nature. An alternative estimated exposure limit could be calculated using this more recent data. The most sensitive endpoint appears to immunological effects observed in the rabbit study (noted above). This study had a LOEL of 0.18 mg/kg-day. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, the use of a LOEL rather than a NOAEL, and the use of a less-than-lifetime study.

Developmental Toxicity

DDT causes embryotoxicity and fetotoxicity but not teratogenicity in experimental animals (ATSDR, 1992c). Studies indicate that estrogen-like effects on the developing reproductive system occur (ATSDR, 1992c). This also occurs with chronic exposure as discussed above under chronic effects. Rabbits exposed to 1 mg/kg-day early in gestation had decreased fetal brain, kidney and body weights (ATSDR, 1992c). Prenatal exposure in mice at 1 mg/kg on three intermittent days resulted in abnormal gonad development and decreased fertility in offspring, which was especially evident in females (Hayes, 1982).

A three-generation rat reproduction study found increased offspring mortality at all dose levels with a LOEL of 0.2 mg/kg-day. Three other reproduction studies found no effects at much higher dose levels (IRIS, 1993). Effects on the urogenital system were found with eight days prenatal exposure in mice. Behavioral effects in mice exposed prenatally for seven days were noted at 17.5 mg/kg-day (HSDB,1993).

Prenatal, one day exposure of rabbits to DDT resulted in an abnormal persistence of preimplantation proteins in the yolk sac fluid. The results suggest that DDT caused a cessation of growth and development before implantation or during later uterine development. The authors suggest that damage can be repaired but may result in offspring with prenatal growth retardation in the absence of gross abnormalities (HSDB,1993). Most dosages tested for these effects have been relatively high. Postnatal exposure of rats

for 21 days to 21 mg/kg (the only dose tested) resulted in adverse effects on lactation and growth.

In dogs, placental passage of DDT to the fetus has been demonstrated. This was confirmed in mice. Primary targets include the liver, adipose tissue and intestine. Rabbit blastocysts (a very early stage of development) contained a significant amount of DDT shortly after administration to the mother (HSDB,1993).

Biomagnification in human milk has been observed. In lactating women with an intake of 5×10^{-4} mg/kg-day of DDT, the milk contained 0.08 ppm. This was calculated to result in infant doses of 0.0112 mg/kg-day, which is approximately 20 times the dosage to the mothers (HSDB,1993).

DDT is suspected of causing spontaneous abortion in humans and cattle (Hayes, 1982). It is not known whether this is related to the reproductive system toxicity of DDT (See Chronic Toxicity section above) or developmental toxicity. The average concentration of DDE in the blood of premature babies (weighing less than 2500 grams) was significantly greater than those of higher birth weight infants (HSDB,1993). The relationship between spontaneous abortion, premature delivery and maternal exposure and body burden requires clarification.

ATSDR reports that a recent developmental study in mice found behavioral abnormalities in offspring exposed prenatally at 0.5 mg/kg-day. Latent effects were observed following cessation of exposure, and subsequent tissue evaluation found structural/function alterations in the brain. Effects reported include an abnormal increase in activity and probable altered learning ability. The effects occurred at levels approximately 50-fold lower than those which were noted in adults and did not cease when dosing was discontinued, or when tissue levels had decreased. This information was used to support the hypothesis of permanent structural changes in the brain. The results of this study were used by ATSDR to calculate an acute exposure MRL of 5×10^{-4} mg/kg-day using standard uncertainty factors of 10 each for inter- and intraspecies variability and the use of a LOEL rather than a NOEL (ATSDR, 1992c). This MRL is based upon a sensitive endpoint with structural and functional toxicity correlations and should be considered for use as an exposure limit for developmental effects of DDT, DDE, and DDD. Readers may elect to consider the ATSDR MRL for developmental toxicity. The MRL is the same value as the current IRIS RfD (as listed in Chronic toxicity above).

DDT accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to

reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

"Genotoxicity studies in human systems strongly suggest that DDT may cause chromosomal damage" (ATSDR, 1992c). This is supported by *in vitro* and *in vivo* studies in animals (ATSDR, 1992c) and in some bacterial assays (HSDB,1993). There are multiple positive assays including human lymphocytes, human leukocytes, human fibroblasts, an oncogenic transformation and unscheduled DNA synthesis in rats in multiple studies (ATSDR 1992c; HSDB,1993).

Carcinogenicity

DDE, DDT, and DDD are all considered probable human carcinogens (B2) based upon animal studies, with cancer potencies of 0.24, 0.34, and 0.34 per mg/kg-day respectively (IRIS, 1993). Liver tumors were associated with each chemical. It is noted in the IRIS file that 24 of the 25 carcinogenicity assays of DDT have yielded positive results. The occupational studies of workers exposed to DDT are of insufficient duration to assess carcinogenicity (IRIS, 1993). Elevated leukemia incidence, particularly chronic lymphocytic leukemia, was noted in two studies of workers. Lung cancer has also been implicated in one study. Bone marrow cells in experimental animals have also been affected by exposure, including an increase in chromosomal fragments in the cells (HSDB,1993).

It is recommended that the total concentration of the 2,4'- and 4,4'-isomer of DDT and its metabolites, DDE and DDD be evaluated as a group using the cancer potency of 0.34 per mg/kg-day (EPA, 1993a). In addition, the EPA Carcinogenicity Assessment Group has recommended that this value be used for combinations of dicofol with the above three compounds (EPA, 1993a).

Special Susceptibilities

Based on the information obtained from a recent developmental study which found neurotoxicity and structural brain alterations at relatively low exposures (approximately 50-fold less than in adults), children may be at greater risk from DDT exposure than adults.

The results of the cardiac toxicity studies are not consistent; however, it is safest to assume that exposure to DDT or its analogs **may** pose a risk for

individuals with cardiac disease, at exposure levels which are estimated to be safe for the general population (Hayes, 1982).

Individuals exposed to DDT may metabolize some drugs more rapidly than the general population (HSDB,1993) (See also Section 5.5 on this topic). For example, increased phenobarbital metabolism resulting from an increased body burden of DDT (10 micrograms) led to a 25 percent decrease in effectiveness of the drug in experimental animals. The toxicity of chloroform was enhanced by the addition of DDT to the diet due to its capacity as a microsomal stimulator (HSDB,1993). Alterations in the metabolism of drugs, xenobiotics and steroid hormones may result from DDT exposure due to DDT's induction of the hepatic mixed-function oxidase system at relatively low doses (HSDB,1993). Individuals who use medications which involve the mixed function oxidase system directly (MFO inhibitors) or through metabolic processes may be at risk for alteration of the drugs efficacy and/or timing if they are exposed to DDT. Information is not available for this document on the specific relationships between various pharmaceuticals and DDT/E/D body burdens or intakes. This type of information merits further investigation.

ATSDR notes that persons with diseases of the nervous system of liver may be particularly susceptible to the effects of DDT (ATSDR, 1992c). Based on information discussed above regarding biomagnification in milk, nursing infants may also be at greater risk due to their increased exposure.

Interactive Effects

As discussed under special susceptibilities above, DDT exposure may alter the response to drugs, xenobiotics and endogenous steroid hormones. (See the discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5.) DDT is reported to promote some tumorigenic agents and antagonize others. The actions may be related to the induction of microsomal enzymes (ATSDR, 1992c).

Critical Data Gaps

IRIS notes the lack of a NOEL for reproductive effects and a relatively short duration for the critical study on which the RfD is based. No intermediate or chronic oral MRLs were calculated by ATSDR because of the lack of a NOEL and the seriousness of the LOEL in significant studies (ATSDR, 1992c).

Information was not located for this document on the specific relationships between various pharmaceuticals and DDT/E/D body burdens or intakes. Information on the relationship between pre- and postnatal exposure and

behavioral effects and maternal exposure and milk concentrations are also needed.

An interagency group of researchers from NTP, ATSDR, and EPA have identified the following data gaps: pharmacokinetic data, animal studies on respiratory, cardiovascular, G.I., hematological, musculoskeletal and dermal/ocular effects, the significance of subtle biochemical changes such as the induction of microsomal enzymes in the liver and the decreases in biogenic amines in the nervous system in humans, an epidemiological study in humans of estrogen-sensitive cancers including endometrial, ovarian, uterine, and breast cancer, reproductive system toxicity, developmental toxicity, a multiple assay battery for immunotoxicity, subtle neurological effects in humans, and mechanisms of neurotoxicity in the neonate (ATSDR, 1993c).

Summary of EPA Risk Values

These values should be used for the sum of the 4,4'- and 2,4'- isomers of DDT, DDE, and DDD.

Chronic Toxicity	5×10^{-4}
Carcinogenicity	0.34 per mg/kg-day

Major Sources: IRIS (1993), ATSDR (1992c), HSDB,1993, Hayes (1982)

5.6.3. Dicofol (Kelthane)

Background

Dicofol is an organochlorine pesticide which is structurally similar to DDT and which is frequently contaminated with isomers of DDT, DDE, and DDD (EPA, 1993a). Dicofol is considered a DDT analog based upon its structure and activity (Hayes and Laws, 1991). In the past, dicofol often contained nine to 15 percent DDT and its analogs. EPA has recently (1989) required that these contaminants comprise less than 0.1 percent of dicofol (HSDB,1993).

Pharmacokinetics

Very little data were located regarding the pharmacokinetics of dicofol. Due to its structural similarity to DDT, it may be assumed to have some of the same properties. Data regarding metabolites are not consistent. The mechanism of action is hypothesized to be inhibition of the ATPase associated with oxidative phosphorylation and cation transport in the plasma membranes (HSDB,1993).

Acute Toxicity

See the listing of usual effects associated with organochlorine exposure in Section 5.5. The acute oral LD50s for dicofol from animal studies ranged from 640 to 1810 mg/kg (EPA, 1993g).

Chronic Toxicity

No IRIS file was located for this chemical (search 10/93). OPP lists an RfD of 0.001 mg/kg-day based upon a NOEL of 1 mg/kg-day in a two year rat feeding study (no information was located on the critical effect). Uncertainty factors totaling 1000 were applied (EPA, 1992d).

The liver is a target organ for dicofol both for systemic and carcinogenic effects. Studies have also reported thyroid hypertrophy in rats at 25 mg/kg-day. A NOEL of 0.9 mg/kg-day was identified in a recent study of liver toxicity, based on gross and microscopic pathology and enzyme alterations, in a one year dog study (EPA, 1993g). This study would yield an estimated exposure limit within approximately one order of magnitude of the RfD listed above.

Due to the limited information which was available for this review on the dose-response dynamics for dicofol, it is recommended that the OPP value of 0.001 mg/kg-day be used for chronic systemic toxicity.

Developmental Toxicity

Two 3-generation reproductive studies in mice and rats both identified a NOEL of 1.5 mg/kg-day with effects at 3.375 mg/kg-day noted as reduced litter size, reduced body weight, and reduced offspring survival (EPA, 1993g). The reviewed data did not contain information regarding underlying mechanisms of fetal or neonatal toxicity. Additional uncertainty arises because of the limited information available in the data base regarding the study outcomes. They are gross measures of toxicity and do not provide any indication of the level of exposure at which organ toxicity which led to death was occurring. Consequently, an estimated exposure limit for developmental effects cannot be estimated with precision. If these studies were used, the standard uncertainty factors employed in the calculation would typically take into account consideration of inter- and intraspecies variability. An additional modifying factor for the limited information available in the data base could also be used.

As with the other organochlorines, it is anticipated that dicofol can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

Studies of dicofol in human lymphoid cells *in vitro* were positive with an incidence of events 13 times that of controls. It induced sister chromatic exchange with activation. Other mutagenicity studies in bacteria have yielded negative results (HSDB,1993).

Carcinogenicity

Dicofol has been classified as a B2 and C carcinogen by offices within EPA. OPP lists the potency value as 0.44 per mg/kg-day (EPA, 1992c). The EPA Carcinogenicity Assessment Group (CAG) has recommended that 0.34 per mg/kg-day be used for combinations of dicofol with DDT, DDE, and DDD (EPA, 1993a). The value of 0.44 per mg/kg-day was used to develop fish consumption limits listed in Section 3 for carcinogenic effects.

Special Susceptibilities

Individuals taking medications which involve the mixed function oxidase system may need to alter their dosages when exposure to dicofol is occurring at significant levels. No specific information was available on the critical dosage for interaction. See Section 5.5 for more information on this topic.

Individuals with liver disease and children exposed prenatally may also be at risk based on the toxicity information which was reviewed.

Interactive Effects

As with other organochlorine pesticides, microsomal enzyme induction occurs and may cause interactions with other chemicals. See a discussion of this in Section 5.5. No additional data were located.

Critical Data Gaps

Information is lacking on neurotoxicity endpoints for chronic and developmental toxicity. Based upon data available on other organochlorines, this type of toxicity commonly occurs and may be a sensitive endpoint which could serve as a useful basis for chronic or developmental toxicity exposure limits. The reviewed data did not contain information regarding underlying mechanisms of fetal lethality. A sensitive measure of developmental toxicity is necessary to generate a protective exposure limit. Clarification is also needed regarding the carcinogenic nature of dicofol.

Summary of EPA Risk Values

Chronic Toxicity	1.0×10^{-3} mg/kg-day
Carcinogenicity	0.44 per mg/kg-day for dicofol alone 0.34 per mg/kg-day in combination with DDT, DDE, DDD (See text)

Major Sources: tox one-liners (EPA, 1993g), HSDB,1993

5.6.4. Dieldrin

Background

Dieldrin is an organochlorine pesticide which was phased out between 1974 and 1987. It continues to be detected nationwide due to its relatively long half-life. Dieldrin is also a product of aldrin metabolism (ATSDR, 1991a).

Pharmacokinetics

Dieldrin is absorbed from the GI tract and transported via the hepatic portal vein and the lymphatic system. It is found shortly after exposure in the liver, blood, stomach and duodenum. Dieldrin is lipophilic and is ultimately stored primarily in fat and tissues with lipid components (e.g., brain) (ATSDR, 1991a).

In human dosing studies at 0.0001 to 0.003 mg/kg-day over two years, the time to achieve equilibrium was approximately 15 months. A dynamic equilibrium was theorized with the average ratio of the concentration in adipose tissue to blood of 156. Cessation of dosing led to decreases in blood levels following first order kinetics with a half-life ranging from 141 to 592 days and an average of 369 days (ATSDR, 1991a).

The metabolism of dieldrin is described in detail in ATSDR, 1991a. Sex and species differences have been reported in the metabolism and tissue distribution of dieldrin based upon chronic exposure studies and toxicokinetic studies in animals. Males appear to metabolize and excrete dieldrin more rapidly than females (ATSDR, 1991a).

A correlation between exposure and dieldrin levels in human breast milk has been established. Placental transfer of dieldrin has been observed in women, with higher concentrations measured in fetal blood than in maternal blood (ATSDR, 1991a).

Acute Toxicity

See the listing of usual effects associated with organochlorine exposure in Section 5.5. Effects noted in addition to those discussed in Section II include: possible hematological effects in humans (pancytopenia and thrombocytopenia, immunohemolytic anemia) (ATSDR, 1991a). An estimated human lethal dose is 65 mg/kg (HSDB,1993).

Chronic Toxicity

IRIS provides an RfD of 5 x 10^{-5} mg/kg-day based upon a NOAEL of 0.005 mg/kg-day from a 1969 two year rat feeding study which found liver lesions. Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1993). Liver toxicity has been observed in multiple animal studies and in human acute exposure episodes. Adaptive changes (e.g., liver enlargement) have been observed at 0.00035 mg/kg-day in a subchronic rat study. ATSDR has calculated an MRL which is equal to the RfD listed in IRIS (ATSDR, 1991a).

Although the critical effect in the IRIS study was liver lesions, it was noted that at the next highest dose (0.05 mg/kg-day) "all animals became irritable and exhibited tremors and occasional convulsions" (IRIS, 1993). There was no listing of additional neurobehavioral studies in the IRIS file. As an organochlorine pesticide it is expected that dieldrin is a CNS toxicant. This is supported by acute toxicity effects of dieldrin and the neurotoxicity studies listed below.

Other effects associated with dieldrin exposure include: arterial degeneration in rats with a chronic exposure to 0.016 mg/kg-day, hematological disorders in experimental animals at 0.25 and 1 mg/kg-day, musculoskeletal pathology at 0.015 mg/kg-day in a chronic rat study, kidney degeneration and other changes at 0.125 mg/kg-day in chronic animal studies in multiple species, hypertension in humans (exposure level unknown), and multiple deficits in immune system function in multiple studies (ATSDR, 1991a). Increased susceptibility to tumor cells was observed in a subchronic mouse study (dose not specified in material reviewed) (HSDB,1993).

Neurological effects of dieldrin have been observed in experimental animals and in humans exposed acutely and chronically. Wheat mixed with aldrin and lindane was consumed for six to 12 months by a small human population. Effects were attributed to aldrin (converted to dieldrin via metabolism) because the wheat had been mixed with lindane in previous years without adverse effect. A variety of CNS disorders were observed and abnormal EEGs were noted. Some symptoms (myoclonic jerks, memory loss, irritability) continued for at least one year after cessation of exposure. A child is believed to have developed mild mental retardation as a result of exposure. Quantitative exposure information was not available in the data reviewed (ATSDR, 1991a).

Neurotoxicity has been observed in humans with chronic inhalation and dermal exposures (ATSDR, 1991a). Chronic exposure by dieldrin of spraymen led to idiopathic epilepsy which ceased when exposure was terminated (HSDB,1993).

Dermal and inhalation exposure were the likely routes of exposure. No exposure quantitation was available.

A 1967 study of human exposure effects over 18 months at levels up to 0.003 mg/kg-day identified no effects on the CNS (as measured by EEG), peripheral nerve activity, or muscle activity (ATSDR, 1991a).

Animal studies have identified neurological effects including behavioral disorders and learning deficits at doses of 0.1 to 0.25 mg/kg-day in subchronic and chronic studies. Higher doses produced more dramatic effects (e.g., convulsions, tremors). Cerebral edema and degeneration were found with chronic exposure of rats to 0.016 mg/kg-day (ATSDR, 1991a). Neural lesions (cerebral, cerebellar, brainstem and vascular) were observed in chronically exposed rats at 0.004 mg/kg-day (HSDB,1993).

With the exception of the neurological study discussed directly above, the information reviewed regarding neurotoxicity indicates that the IRIS RfD would be protective against adverse effects, using standard assumptions for the development of an exposure limit. Although the neurological rat study cited above noted effects at 0.004 mg/kg-day, the human study of exposure over an 18 month period at 0.003 mg/kg-day found no effects on the CNS based upon various sensitive measures. Taking the results of the human study under consideration, it appears, based upon the information reviewed, that the IRIS RfD provides adequate protection against neurological effects in the human population.

Dieldrin causes reproductive system disorders in animals and one study suggests that it may cause adverse effects in humans. In a study evaluating the blood and placental levels of organochlorines associated with premature labor or spontaneous abortions in women, positive results were obtained for aldrin. Most exposed subjects had multiple chemical exposures; consequently, interpretation of study results is difficult (ATSDR, 1991a). See also notes regarding estrogenic activity in the carcinogenicity section below.

Studies of reproductive effects in animals indicate that exposure to dieldrin may cause a number of adverse effects. Dieldrin exposure causes changes in the levels of serum luteinizing hormone (LH) in females and gonadotropin in males. Dieldrin interferes with the binding of dihydrotestosterone to male sex hormone receptors (HSDB, 1993). These three hormones are critical to normal reproductive function. A mouse study found decreased fertility with exposure to 1.3 mg/kg-day in females and 0.5 mg/kg-day in males. Another study found no effects at much higher exposure levels. Adverse reproductive effects in dogs exposed at a LEL of 0.15 mg/kg-day for 14 months prior to mating included increased stillbirth rates, delayed estrus, reduced libido, and a lack of

mammary function and development. Maternal behavior was studied in mice exposed for four weeks prior to delivery until weaning at 1.95 mg/kg-day. Exposed maternal animals violently shook the pups, ultimately killing them; others neglected their litters (ATSDR, 1991a).

Based on the information reviewed regarding reproductive toxicity, it appears that the IRIS RfD would be protective against adverse effects, using standard assumptions and uncertainty factors for calculating an estimated exposure limit.

Developmental Toxicity

IRIS provides limited information regarding the developmental toxicity of dieldrin. A NOEL of 6 mg/kg-day was obtained from a mouse teratology study with exposure occurring from the 7th to 16th day of gestation. Fetotoxicity (decreased numbers of caudal ossification centers and an increased incidence of extra ribs) was observed with an LEL of 6 mg/kg-day. This study was not considered in development of the IRIS file because 41 percent of the maternal fatalities occurred at the LEL dose (IRIS, 1993). An RfD based on developmental effects is not provided in IRIS.

A variety of effects in multiple organ systems have been observed in experimental animals exposed prenatally to dieldrin. Skeletal anomalies and malformations (e.g., cleft palate, webbed foot, open eyes, extra ribs) were identified at relatively large doses (LEL of 3 mg/kg-day) (ATSDR, 1991a).

Abnormalities of the CNS, eye and ear were noted with a TD Lo (similar to a LOEL) of 30.6 mg/kg prenatal exposure, and craniofacial abnormalities were observed at single prenatal dose of 15 mg/kg-day (HSDB,1993). Liver damage has been observed in experimental animals at dosages as low as 0.016 mg/kg-day (ATSDR, 1991a).[7] A multigeneration study in mice found histological changes in liver, kidney, lungs and brain tissues in the 1st and 2nd generation offspring at an LEL of 3 ppm (0.075 mg/kg-day) (HSDB,1993).

Multiple studies have reported increased postnatal mortality following prenatal exposure to dieldrin. Studies in dogs, rats and mice have found LELs of 0.125 to 0.65 mg/kg-day associated with high mortality in offspring in the absence of increased maternal mortality. Studies designed to evaluate the underlying causes of mortality suggest that cardiac glycogen depletion, leading to cardiac failure, may be causal (ATSDR, 1991a).

[7] Note that liver lesions are the basis for the chronic toxicity RfD derived from a study of adult animals, as reported in IRIS (IRIS, 1993).

Neural lesions in prenatally exposed rats were found at an LEL of 0.004 mg/kg-day. Effects included cerebral edema, internal and external hydrocephalus and focal neuronal degeneration. Postnatal exposure of rats from day five of gestation to 70 days of age resulted in increased learning ability at 3.5×10^{-4} mg/kg-day (the only dose tested). ATSDR has cautioned that "interpretation of the results is difficult because the significance of improved performance in behavioral paradigms is unknown, and the study is limited because only one dose of dieldrin was tested" (ATSDR, 1991a). In a rat multigeneration study a TD Lo of 0.014 mg/kg-day with behavioral effects was observed (HSDB,1993).

Dieldrin is known to accumulate in human milk. In one study of 102 samples in the U.S., 91.2 percent of the samples contained measurable levels of dieldrin, with a mean concentration of 0.062 ppm lipid basis. Another U.S. study found 80 percent of the 1436 samples were positive with a range of 0.16 to 0.44 ppm milk fat (HSDB,1993). This indicates that lactation may provide a significant dietary source in infants with mothers who have been exposed to dieldrin. As discussed above, studies in humans also determined that dieldrin can pass through the placenta and is found in fetal blood.

Neurotoxicity appears to be a relatively sensitive endpoint for developmental toxicity. The association of neurotoxic effects with dieldrin exposure is supported by the observation of neurological effects in human populations exposed to dieldrin. The study noted in the paragraph above which identified neural lesions associated with prenatal exposure provided an LEL of 0.004 mg/kg-day provides the most sensitive developmental toxicity measure of those reviewed. If the LEL from this study were used to calculate an estimated exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration inter- and intraspecies variability, and the use of a LEL rather than a NOAEL.

As with the other organochlorines, it is anticipated that dieldrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

There is limited information on the mutagenicity of dieldrin. Positive *in vivo* studies have found an increased incidence in the number of abnormal

metaphases in dividing spermatocytes and in univalents. Dominant lethal assays (*in vivo*) have yielded mixed results. *in vitro* assays have also yielded mixed results. Positive results have been obtained in cultured human lung cells and mouse bone marrow cells (both found increases in chromosome aberrations), and sister chromatid exchange (SCE) assays.

Dieldrin may not act directly on DNA; however, it may act by depressing transfer RNA activity, increasing unscheduled DNA synthesis, and inhibiting metabolic cooperation and gap junctional intercellular communication, according to mechanistic studies. The inhibition of gap junctional communication may be responsible for carcinogenic activity through depressing the cells' ability to control excess proliferation. This inhibition has been correlated with strains and species in which dieldrin has been shown to be carcinogenic. This type of activity is considered promotion, rather than initiation of tumors (ATSDR, 1991a).

Carcinogenicity

Dieldrin is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer potency value is 16 per mg/kg-day. Liver carcinoma was identified in the animal studies. The geometric mean of 13 data sets (with a range of a factor of 8) were used to develop the cancer potency (IRIS, 1992). This value was used to calculate fish consumption limits listed in Section 3 for carcinogenic effects.

A variety of tumor types have been observed in animal studies including pulmonary, lymphoid, thyroid, and adrenal (ATSDR, 1991a). ATSDR has concluded that dieldrin is probably a tumor promotor, based upon genotoxicity and mechanistic studies which have been reviewed (ATSDR, 1991a). Dieldrin has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto, et al, 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis, et al, 1993). In addition to potential carcinogenic effects, dieldrin may also cause disruption of the endocrine system due to its estrogenic activity (Soto, et al, 1994).

Special Susceptibilities

ATSDR has identified the following populations as unusually susceptible: very young children with immature hepatic detoxification systems, persons with impaired liver function, and persons with impaired immune function (ATSDR, 1991a). Based upon the toxicity data reviewed above, individuals with the following diseases or disorders may also be at increased risk: hypertension, hematological disorders, musculoskeletal diseases, neurological diseases and kidney disease.

The data also indicate that prenatal exposure may generate risks to children at relatively low levels of exposure. Postnatal exposure, especially via lactation, may also be a significant concern.

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

See the discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5. In cows, dieldrin exposure increased the toxicity of diazinon; greater depression in blood cholinesterase activity occurred, leading to severe clinical signs (HSDB,1993).

MIXTOX has reported inhibition between dieldrin and hexachlorobenzene in rats exposed orally via food. Studies have also reported additive effects (MIXTOX, 1992).

Critical Data Gaps

A joint team of scientists from EPA, NTP, and ATSDR have identified the following study data gaps: animal carcinogenicity, genotoxicity *in vivo* and *in vitro*, reproductive system toxicity, developmental toxicity, especially mechanisms of postnatal mortality and teratogenesis, immunotoxicity, neurotoxicity focusing on sensitive endpoints, and pharmacokinetics (ATSDR, 1991a).

Summary of EPA Risk Values

Chronic Toxicity	5×10^{-5} mg/kg-day
Carcinogenicity	16 per mg/kg-day

Major Sources: IRIS (1993), ATSDR (1991a), HSDB (1993)

5.6.5. Endosulfan I,II

Background

Endosulfan is an organochlorine pesticide comprised of stereoisomers designated I and II which have similar toxicities (EPA, 1993a).[8] Endosulfan has been found widely in food samples, including one of 10 fruit and fruit juice samples for infants at a mean concentration of 0.01 ppb (HSDB,1993).

Pharmacokinetics

Endosulfan is absorbed through the GI tract and is distributed throughout the body. Endosulfan is metabolized to lipophilic compounds and both the parent and metabolites are found initially primarily in the kidney and liver and fatty tissue, with distribution to other organs occurring over time. Endosulfan can induce microsomal enzyme activity and is a non-specific inducer of drug metabolism. In sheep approximately one percent of a single dose was recovered in milk. Females may accumulate endosulfan more readily than males according to animal studies. This may be causal in the higher toxicity seen in females (See acute toxicity below) (ATSDR, 1993b).

Acute Toxicity

Endosulfan has a high acute toxicity to humans, with an estimated lethal dose of 50 to 500 mg/kg. Multiple animal studies found females much more sensitive to exposure than males (e.g., acute oral LD50 of 9.5 in females and 40.4 in males) (EPA, 1992c). See the listing of usual effects associated with organochlorine exposure in Section 5.5. In addition to those listed in Section 5.5, bluing of the skin (IRIS, 1993), hematopoietic system damage and anemia, possibly damage to red blood cell membranes, cardiac toxicity, and immunotoxicity have been noted (ATSDR, 1993b).

Chronic Toxicity

IRIS previously provided an RfD of 5^{-5} mg/kg-day for endosulfan based upon a LOAEL of 0.15 mg/kg-day from a two-generation rat reproduction study which identified kidney toxicity. Uncertainty factors totaling 3000 were applied (IRIS, 1992). The RfD was withdrawn in December, 1992 and a new RfD summary is under development (IRIS, 1993). The Office of Pesticide Programs has recently re-evaluated this chemical. The new value was not available on

[8] Endosulfan I and II will be referred to collectively as endosulfan and discussions will refer to both isomers unless specific note is made.

IRIS when this document was prepared; however, it is anticipated that the new value will be listed in future versions of the document. Although the IRIS file has been temporarily removed, the previous IRIS RfD can be used until a new file entry is completed.

ATSDR developed intermediate exposure duration (14 - 365 days) and chronic duration MRLs of 0.002 mg/kg-day for both intermediate and chronic exposures. These MRLs are based upon immunotoxicity and hepatotoxicity respectively (ATSDR, 1993b).

Other chronic effects of endosulfan noted in studies include: blood vessel aneurysms at 0.65 mg/kg-day, neurological effects at 1.71 mg/kg-day, damage to the hematopoietic system at 3.75 mg/kg-day, and elevated hemoglobin levels at 0.1 mg/kg-day (EPA, 1993i). It appears that the old IRIS RfD would be protective against the effects noted, based upon current risk assessment methods.

Two National Cancer Institute studies have identified the following effects: interstitial fibrosis or acute tubular necrosis of the kidney, atrophy of the testes, polyarteritis, parathyroid hyperplasia, osteitis fibrosis of the bone, and abscesses of the lung. The kidney effects led to most deaths (dosages were not listed in the data base) (HSDB,1993). A number of additional studies have also found damage to the male reproductive system associated with exposure to endosulfan (e.g., testicular necrosis, aspermatogenesis, degeneration of seminiferous tubule epithelium) (ATSDR, 1993b).[9]

A neurological study in rats exposed at 3 mg/kg-day for 30 days found increased aggressive behavior at both doses along with a significant increase in serotonin binding in the frontal cortical membranes that may have been due to an increase in the affinity of the serotonin receptors (HSDB,1993). This effect has negative implications for human behavior. Abnormal increases in behavior in prenatally exposed animals has also been noted for other organochlorine pesticides (See Section 5.5.1 on organochlorines); however, this level of mechanistic detail has not been located for other organochlorines in the reviews conducted for this document.

Developmental Toxicity

Multiple teratogenic effects were associated with endosulfan exposure in a rat developmental toxicity study including webbed forelimb, clubbed hind limbs, hypoplastic aortic arch, edema and lordosis, increased incidence of small 4th

[9] See also estrogenic activity discussed under carcinogenicity below.

and unossified 5th sternebrae, and decreased pup size and weight. An increased incidence of misaligned vertebrae was observed at all dose levels with a LEL of 0.66 mg/kg-day (EPA, 1993i).

Other developmental studies have yielded a variety of results which are often inconsistent (e.g., two separate studies found unspecified effects at the lowest dose tested of 5 mg/kg-day in one study and no effects at the highest dose tested of 1.8 mg/kg-day in another study). A range-finding single-generation reproductive study found increased liver weights at the lowest dose tested of 2.5 mg/kg-day. A two-generation reproductive study found increased pituitary and uterine weights at 3.75 mg/kg-day and a NOEL of 0.75 mg/kg-day. Kidney discoloration, which was originally attributed to hematopoietic damage at all doses, has been reevaluated and is now considered by OPP to be part of the elimination process rather than an adverse effect (EPA, 1993i). It is not clear why significant differences in effects were noted in multiple recent rat studies (i.e., the first and last studies discussed in this paragraph).

Postnatal exposure of rats for five weeks at 1 mg/kg-day resulted in aggressive behavior and increased serotonin binding. This persisted after the dosing stopped. The study authors concluded that the developing study subjects had a greater sensitivity to endosulfan than adults (ATSDR, 1993b).

In the absence of more complete information, a conservative approach is recommended for calculation of an estimated limit for developmental effects, due to the severity of effects observed in the teratogenicity study with a LOEL of .66 mg/kg-day (listed first above). If this study, which appears to be the most sensitive, were used to calculate an estimated exposure limit, the uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, and the use of a LEL rather than a NOEL.

As with the other organochlorines, it is anticipated that endrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

Results of mutagenicity assays of endosulfan are mixed, with multiple positive and negative studies (IRIS, 1993, HSDB,1993, ATSDR, 1993b). Endosulfan

has resulted in an increase in the percentage of aberrant colonies and the frequency of gene convertants and revertants in yeast and was genetically effective without activation. Longer duration of exposure increased effects (HSDB,1993). *in vivo* assays have found chromosomal aberrations and gene mutations in mice (ATSDR, 1993b).

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of endosulfan I and II. The carcinogenic assays have yielded mixed results, with carcinomas, sarcomas and lymphosarcomas identified at increased incidences in some studies. ATSDR has concluded that the available animal study data were negative or inconclusive (ATSDR, 1993b). Endosulfan has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto, et al, 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis, et al, 1993). In addition to potential carcinogenic effects, endosulfan may also cause disruption of the endocrine system due to its estrogenic activity (Soto, et al, 1994).

Special Susceptibilities

As noted above, multiple animal studies found females much more sensitive to endosulfan exposure than males, some by nearly one order of magnitude (EPA, 1992c). However, toxicity studies indicate that the male reproductive system is a target organ for endosulfan toxicity (ATSDR, 1993b).

Animal neurobehavioral study results indicate that the developing test animals had a greater sensitivity to endosulfan than adults based upon neurotransmitter patterns and behavioral effects observed (ATSDR, 1993b). This may indicate that children are at greater risk for neurotoxicity than adults. ATSDR has noted that:

> "There is evidence from animal studies indicating that unborn and neonates may be more susceptible to the toxic effects of endosulfan because hepatic detoxification systems are immature and therefore unable to metabolize xenobiotic substances efficiently." (ATSDR, 1993b)

Additional groups who may be at greater risk from endosulfan exposure include those with: liver, kidney, immunological, or blood diseases, compromised immune systems such as AIDS patients, infants, and elderly people, hematologic disorders, seizure disorders, and those with low protein diets (See below) (ATSDR, 1993b). See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

Human anecdotal information suggests that endosulfan may act synergistically with alcohol (ATSDR, 1993b). In laboratory animals moderate protein deprivation doubled the toxicity of endosulfan (Hayes and Laws, 1991).

Pentobarbital and endosulfan have demonstrated an interactive effect which is probably related to microsomal enzyme activity. Endosulfan induces the mixed function oxidase system (ATSDR, 1993b). Vitamin A inhibited the endosulfan-induced activity of the mixed function oxidase system (ATSDR, 1993b). See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5.

Critical Data Gaps

The increased susceptibility of females to endosulfan should be studied to determine the underlying cause, evaluate whether the effect occurs with chronic exposure, and identify a numerical modifier to adjust toxicity estimates and exposure recommendations so that they provide adequate protection for females.

Additional data is needed on the teratogenic and neurobehavioral effects during development resulting from endosulfan exposure. Current data do not provide a consistent picture nor do they explain underlying mechanisms of toxicity, and thus somewhat compromise the determination of a exposure limit for developmental effects.

A joint team of scientists from ATSDR, NTP, and EPA have identified the following data gaps: acute oral exposure studies, mechanisms of anemia-inducing effects, reproductive system toxicity and related performance, developmental toxicity studies, mechanisms of immunotoxicity, sensitive neurological function and histological studies for long-term exposures, epidemiological studies, pharmacokinetics of intermediate and chronic duration exposures, and studies evaluating mechanisms underlying the differences in male and female toxicity. No ongoing studies were identified for endosulfan (ATSDR, 1993b).

Summary of EPA Risk Values

Chronic Toxicity	5×10^{-5} mg/kg-day
Carcinogenicity	Insufficient data to determine carcinogenic status

Major Sources: IRIS (1993), tox one-liners (EPA, 1993i), HSDB (1993), ATSDR, (1993b)

5.6.6. Endrin

Background

Endrin is an organochlorine pesticide whose registration was canceled in 1984 (EPA, 1993a).

Pharmacokinetics

Endrin, like the other organochlorine pesticides, is lipophilic. It bioaccumulates in fat and probably brain tissue and can cross the placenta. Endrin is metabolized via oxidation of the methylene bridge. Metabolic products are probably more toxic than endrin and the toxic entity has been hypothesized to be 12-ketoendrin. In humans, this compound is excreted directly in urine and feces (ATSDR, 1990c).

Acute Toxicity

Endrin has a high acute toxicity (IRIS, 1993). See the listing of usual effects associated with organochlorine exposure in Section 5.5. Blood pressure elevation has also been noted (IRIS, 1993). The primary target of endrin is the central nervous system (ATSDR, 1990c).

Chronic Toxicity

IRIS provides an RfD of 2×10^{-4} mg/kg-day based on a NOAEL of 0.025 mg/kg-day from a 1969 chronic exposure dog study which identified histological lesions in the liver and convulsions in study subjects exposed at the LEL of 0.05 mg/kg-day. Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1993). ATSDR utilized the same study and safety factors to calculate an MRL equal to the IRIS RfD (ATSDR, 1990c).

OPP tox one-liners list a 1959 two year dog feeding study with a LOAEL of 0.015 mg/kg-day based upon hypersensitivity in the neck and shoulder area. Increased erythropoiesis was noted at 0.125 mg/kg-day (EPA, 1993m). The LOAEL of 0.015 is within one order of magnitude of the LEL identified in the critical IRIS study. The IRIS value was used to calculate fish consumption limits for chronic exposure effects listed in Section 3.

Developmental Toxicity

No developmental effects were listed in the IRIS file for endrin (IRIS, 1993). ATSDR listed a number of prenatal exposure studies which identified structural

abnormalities and neurotoxicity associated with endrin exposure. Structural abnormalities have been observed in mice and hamsters exposed to endrin. These include fused ribs and cleft palate at 5 mg/kg-day for three prenatal days and webbed foot and open eye effects in hamster fetuses prenatally exposed for one day. Meningeocephaloceles in hamsters were caused by a single prenatal exposure "above" 1.5 mg/kg and fused ribs "above" 5 mg/kg in hamsters. In mice, a single prenatal exposure to 2.5 mg/kg caused an increase in open eyes. Exencephaly and fused ribs were seen with one exposure at 9 mg/kg endrin. A rat study reported no developmental effects with exposure to 0.45 mg/kg-day (it was not clear if behavioral effects were evaluated) (ATSDR, 1990c). The variation in effects is probably due in part to the different prenatal periods during which exposure occurred (See ATSDR, 1990c). Reproductive outcome was adversely affected in hamsters exposed to 1.5 mg/kg-day with decreased survival of pups (16 percent mortality). The underlying cause was not discussed (ATSDR, 1990c).

Nervous system effects are a significant concern with organochlorine exposure. In hamsters, abnormally increased pup activity in hamsters was observed with 1.5 mg/kg prenatal exposures for nine days. The NOEL for these behavioral effects was 0.075 mg/kg-day (ATSDR, 1990c). In rats increased activity was seen with prenatal exposure to 0.3 mg/kg-day (ATSDR, 1990c). Abnormally increased activity has been observed for other organochlorine pesticides (See DDT) and has been associated with probable altered learning ability and permanent structural changes to the brain.

Both structural skeletal changes and neurological abnormalities are significant developmental effects associated with endrin. Decreased survival, while a significant effect, is not usually a sensitive measure of toxicity. The behavioral effects observed with a NOEL of 0.075 mg/kg-day (discussed above) are recommended for estimation of an exposure limit for developmental toxicity due to their greater sensitivity. The uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability.

As noted in the pharmacokinetics section above, endrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

in vitro assays of endrin suggest that it is not genotoxic. There were no *in vivo* assay results located (ATSDR, 1990c).

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of endrin. EPA has classified this as a Group D carcinogen (insufficient information available). Some studies have yielded positive results and some studies which reported negative results were considered to be inadequate (IRIS, 1993). Tumors have been noted in the adrenal glands, pituitary glands, liver, mammary gland, uterus and thyroid in various studies and multiple species (IRIS, 1993). Endrin is structurally related to a number of chemicals which are carcinogenic in test animals including chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1993). Because endrin has been classified as a Group D carcinogen, no cancer potency has been listed by EPA.

Special Susceptibilities

ATSDR has reported that children may be more sensitive to acute endrin exposure than adults, based upon effects observed in children during a poisoning incident. Children appeared more susceptible to neurotoxic effects and have exhibited convulsions. This is supported by results observed in experimental animals where young rats were more susceptible than adults (ATSDR, 1990c).

In addition, the skeletal and behavioral abnormalities associated with endrin exposure in experimental animals indicate that prenatal exposure may generate special risks.

Based upon animal studies, females may be more susceptible than males to endrin-induced toxicity (ATSDR, 1990c).

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5. Dietary pretreatment with endrin potentiates the hepatotoxicity of carbon tetrachloride. MIXTOX has reported

synergism between endrin and chlordane in mice with gavage exposure (MIXTOX, 1992).

Critical Data Gaps

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposures, subchronic reproductive tests in various species, immunotoxicity studies of animals and humans, human dosimetry studies, pharmacokinetic studies, and studies of interspecies differences in metabolism and toxicity (ATSDR, 1990c).

Summary of EPA Risk Values

Chronic Toxicity	3×10^{-4} mg/kg-day
Carcinogenicity	Insufficient data to determine carcinogenic status.

Major Sources: IRIS (1993), ATSDR (1990c), tox one-liners (EPA, 1993m)

5.6.7. Heptachlor Epoxide

Background

Heptachlor epoxide is a breakdown product of the organochlorine pesticide heptachlor and chlordane and is a contaminant of both products. It is more toxic than either parent compound (ATSDR, 1993c). Although most uses of heptachlor were suspended in 1978 and chlordane was removed from the market in 1988 (EPA, 1993j), heptachlor epoxide continues to be a widespread contaminant due to its relatively long half-life.

Pharmacokinetics

Based upon animal and limited human data, heptachlor epoxide is absorbed through the GI tract and is found primarily in the liver, bone marrow, brain, and fat, although it is distributed widely to other tissues as well. It is stored primarily in fat. Fetal blood levels were approximately four times those measured in women. Levels in human milk range from zero to 0.46 ppm (ATSDR, 1993c).

Heptachlor epoxide has a very long half-life, particularly in adipose tissue. Human tissue levels have correlated well to age, with 97 percent of North Texas residents tested (ages 41 to 60) having measurable levels. Based on the Texas study, heptachlor epoxide tissue levels have not decreased appreciably since the 1960s (ATSDR, 1993c).

Acute Toxicity

See the listing of usual effects associated with organochlorine exposure in Section 5.5. The LD50s for heptachlor range from 40 to 162 mg/kg in rodents (ATSDR, 1993c).

Chronic Toxicity

IRIS provides an RfD of 1.3×10^{-5} mg/kg-day based on a LEL of 0.0125 mg/kg-day from a 60 week dog feeding study reported in 1958. The critical effect was increased liver-to-body weight ratios in both males and females at the lowest dose tested. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and the use of a LEL rather than a NOEL (IRIS, 1993). No additional uncertainty factors were applied for the use of a less-than-lifetime study. The principal study is of low quality and there is a low confidence in the RfD (IRIS, 1993).

Animal studies have identified the following effects associated with heptachlor (and subsequently heptachlor epoxide via metabolism) or heptachlor epoxide directly: elevated bilirubin and white blood cell count, increased serum creatinine phosphokinase levels suggestive of muscle damage, muscle spasms secondary to CNS stimulation, adrenal gland pathology, and neurological disorders (ATSDR, 1993c).

Significant changes in EEG patterns were found in female adult rats exposed to 1 and 5 mg/kg-day for three generations (ATSDR, 1993c).

A study of reproductive system toxicity with males and females dosed at 0.25 mg/kg-day prior to and during gestation found a significantly decreased pregnancy rate among exposed animals. Based on specific fertility tests it was determined that males were most likely affected and that sperm were probably killed (ATSDR, 1993c). Another reproductive system toxicity study with doses at and above 0.075 mg/kg-day resulted in the failure of animals to reproduce. There were serious deficiencies in this study (ATSDR, 1993c).

Developmental Toxicity

A 1973 two-generation dog reproductive study identified a NOEL of 0.025 mg/kg-day with an LEL of 0.075 mg/kg-day with liver lesions in pups. Other studies with higher LELs based upon a lethality endpoint are listed in the IRIS file. They were not used in this evaluation due to insufficient information. The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1993).

Exposure of adult rats to 6 mg/kg-day caused lens cataracts in 22 percent of the adults, six to eight percent of the F1 generation offspring, and six percent of the F2 generation offspring. A rat study with exposure to 0.25 mg/kg-day occurring 60 days prior to mating and during gestation resulted in severely reduced pup survival (15 percent) at 21 days postpartum (ATSDR, 1993c). This is not a useful LOEL due to the severity of effects observed at the lowest dose tested.

A human study conducted in Hawaii was not considered adequate due to many study design deficiencies (ATSDR, 1993c). In another epidemiological studies of women who had premature deliveries, significantly higher levels of heptachlor epoxide and other organochlorine pesticides were detected in sera (ATSDR, 1993c).

There is limited data on which to base an estimated exposure limit for developmental effects. The NOEL in the two-generation study is not based upon sensitive endpoints and is only a factor of 3 removed from the LEL. The developmental toxicity data base is insufficient for heptachlor epoxide (per the

IRIS file). Consequently, the application of an uncertainty factor for the insufficiency of the data base may be necessary. The dog study, with a NOEL of .025 mg/kg-day, can be used to calculate an exposure limit for developmental effects. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability and a data base factor.

As noted in the pharmacokinetics section above, heptachlor can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

Mixed results have been obtained in mutagenicity assays of heptachlor epoxide.

Carcinogenicity

Heptachlor epoxide is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer potency factor is 9.1 per mg/kg-day. This value is based on the geometric mean of several studies which identified liver carcinomas (IRIS, 1993). Six structurally related compounds have produced tumors in mice and rats: chlordane, aldrin, dieldrin, heptachlor and chlorendic acid (IRIS, 1993).

Statistically significant increases in adenomas and carcinomas of the thyroid were found in female rats. Some researchers discounted the results due to the low incidence and known variability in the control population (ATSDR, 1993c).

Heptachlor (and consequently heptachlor epoxide) exposure have been associated with cerebral gliosarcoma in children exposed prenatally. Multiple chromosomal abnormalities were also identified in the tumor cells. It was not determined whether the effects were caused by environmental or familial factors (ATSDR, 1993c).

Special Susceptibilities

Based on the toxicity data reviewed above, individuals with diseases or disorders of the following systems may be at greater risk than the general population: liver, hematopoietic, musculoskeletal, neurological, and adrenal

gland. ATSDR has noted that pre-adolescent children may be more susceptible due to their greater rate of glutathionine turnover (ATSDR, 1993c). In addition, children exposed prenatally may be at higher risk, based upon the results of developmental toxicity studies.

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5.

Critical Data Gaps

The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1993). The OPP notes the same data gaps (EPA, 1992c). A joint team of scientists from EPA, NTP, and ATSDR have identified the following data gaps: a model to describe the relationship between tissue and blood levels and exposure in humans, chronic oral exposure effects in humans, epidemiological and *in vivo* animal genotoxicity studies, developmental and reproductive toxicity studies and neurotoxicity and immunotoxicity studies in animals, and pharmacokinetic studies (ATSDR, 1993c).

Summary of EPA Risk Values

Chronic Toxicity	1.3×10^{-5} mg/kg-day
Carcinogenicity	9.1 per mg/kg-day

Major Sources: IRIS (1993), ATSDR (1993c)

5.6.8. Hexachlorobenzene

Background

Hexachlorobenzene is a byproduct of manufacturing and has been used as a fungicide seed protectant in the past. It exists as a solid at ambient temperatures, and in aquatic environments is found in higher quantities in sediment than water due to its low solubility (ATSDR, 1990a).

Pharmacokinetics

Hexachlorobenzene is persistent in the body, accumulating preferentially in fat and tissues with a high lipid content, due to its lipophilic nature. It is found in human breast milk (ATSDR, 1990a), which may be a significant route of exposure for young children.

Acute Exposure

Acute exposure studies in animals indicate a relatively low acute toxicity with LD50s between 1700 and 4000 mg/kg (ATSDR, 1990a). Based on animal studies the following systems are adversely affected following acute exposure: liver, kidney, hematological, and dermal (ATSDR, 1990a). See also the discussion of organochlorine pesticides in Section 5.5.

Chronic Toxicity

Hexachlorobenzene exposure of a large number of people in Turkey occurred between 1955 and 1959 due to consumption of contaminated grain. No precise exposure estimates are available for children or adults in this episode; it is likely that exposures occurred over a continuum, with some individuals consuming much higher levels than others. Researchers have estimated relatively low exposure levels occurred over several years as a result of consumption (50 to 200 mg/day). These exposure levels are approximately 0.7 to 2.9 mg/kg-day for a 70 kg individual. ATSDR has emphasized that the exposure estimates are unverified (ATSDR, 1990a).

The following effects have been associated with hexachlorobenzene exposure in individuals exposed chronically via contaminated bread (Turkey)[10]: shortening of the digits due to osteoporosis, painless arthritis, decreased uroporphyrin synthase levels, muscle weakness, rigidity and sensory shading, thyroid enlargement, and histopathological changes in the liver often

[10] Effects are also discussed under reproductive effects below.

accompanied by skin lesions (ATSDR, 1990a). These effects were also observed in numerous animal studies.

The hepatic system appears to be the most sensitive systemic endpoint for hexachlorobenzene exposure, based upon animal studies, with a NOAEL of 0.08 mg/kg-day in a lifetime rat study. This has been converted by ATSDR to an MRL of 8×10^{-4} mg/kg-day using uncertainty factors of 10 each for inter- and intraspecies variability (ATSDR, 1990a). This value is also the IRIS RfD for chronic systemic toxicity (IRIS, 1993). Numerous other studies identified NOAELs in the same numerical range. The IRIS file notes that the sensitive endpoint of porphyria, which is an effect which was noted in exposed human populations, was not evaluated in the critical animal study (IRIS, 1993). It is not possible, based on the current data, to determine whether the RfD will be protective against that effect.

The oral RfD of 8×10^{-4} mg/kg-day developed by IRIS and ATSDR was used to calculate the fish consumption limits listed in Section 3 for chronic exposure toxicity. For a summary of the chronic systemic toxicity data the reader is referred to the *Toxicity Profile for Hexachlorobenzene* (ATSDR, 1990a).

Developmental Toxicity

Lactational exposure to hexachlorobenzene is of significant concern, based on the rapid transfer of the chemical through breast milk, and effects which have been observed in children of exposed mothers. In a study of nursing infants, the infants had blood levels of hexachlorobenzene two to five times that of their mothers, as well as higher tissue levels. A study of monkeys found that the concentration in milk was 17 times higher than that in maternal serum (ATSDR, 1990a). Young children (under one year) of lactating mothers who were exposed via contaminated bread had an extremely high mortality rate. Skin lesions, weakness and convulsions were reported in these infants. Although adults were also adversely affected, children appeared to be at higher risk. The maternal exposure was roughly estimated to be 0.7 to 2.9 mg/kg-day (ATSDR, 1990a).

Among slightly older children (average age of 7) exposure via food resulted in the development of small or atrophied hands and fingers, short stature, pinched faces, osteoporosis in the hands and other arthritic changes. Exposure was estimated to be approximately 0.7 to 2.9 mg/kg-day (ATSDR, 1990a).

It is known that hexachlorobenzene can cross the human placenta; however, no data were available on effects resulting from prenatal exposure in humans. Very limited information is available on experimental animals. Cleft palate and kidney abnormalities were observed in one study in a single litter and fetus at

100 mg/kg-day (ATSDR, 1990a). In another study, the survivability of prenatally exposed rats was significantly reduced at 2 mg/kg-day (estimated from ppm with conversion factor of 0.05 mg/kg per 1 ppm diet for rats). Death was attributed to maternal body burden and cumulative lactational exposure (ATSDR, 1990a). Alterations in immune function levels were reported in pre- and postnatally exposed rats at 4 mg/kg (ATSDR, 1990a).

For purposes of quantitatively estimating an exposure limit, it is of concern that prenatal and lactational exposure of humans at levels roughly estimated to be 0.7 to 2.9 mg/kg-day (maternal) induced serious structural changes in children and increased mortality. Due to the poor quality of data supporting the exposure estimates for the human exposure episode in Turkey, and, more critically, the lack of a no effect level, it would be desirable to obtain a developmental study with a more reliable exposure estimate. However, there do not appear to be such studies currently available. Much higher exposure levels were required to cause structural changes in an experimental animals and the experimental results have not been duplicated. These data suggest that humans may be more susceptible than the animals studied.

In the absence of better data, the human study data from Turkey can be used to calculate an estimated exposure limit for developmental effects. The standard uncertainty factors used in this calculation would typically take into consideration intraspecies variability, the use of a LOAEL rather than a NOAEL, and the overall inadequacy of the data base. An additional modifying factor may be applied for the poor quality of the exposure data and the severity of the effects noted at the LOAEL. Due to the incomplete nature of the data base and the other inadequacies noted above, there would not be a high level of confidence in exposure limits calculated from the current developmental toxicity data base.

As noted above, hexachlorobenzene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

The results of mutagenicity studies on hexachlorobenzene are mixed (IRIS, 1993). Hexachlorobenzene was negative in dominant lethal studies (*in vivo*) at doses from 60 to 221 mg/kg (ATSDR, 1990a).

Carcinogenicity

Carcinogenic assays of hexachlorobenzene in animals have identified an increased incidence of multiple tumor types including hepatomas, hemangioendotheliomas, liver, and thyroid tumors in multiple species. EPA developed a cancer potency of 1.6 mg/kg-day based on liver carcinoma in female rats exposed via diet. In support of this value, cancer potencies were calculated for 14 different data sets; the result were within one order of magnitude. Hexachlorobenzene is classified as a probable human carcinogen (B2) based on the results of animals studies (IRIS, 1993). The IRIS cancer potency of 1.6 per mg/kg-day was used to calculate the fish consumption limits listed in Section 3 for carcinogenic effects.

Human studies have not yet yielded useful results. Follow-up studies of exposure victims in Turkey have not identified cancers in the 25 and 20 to 30 year exposure cohorts; however, ATSDR suggests that the enlarged thyroids noted in members of these groups have not been sufficiently investigated (ATSDR, 1990a). It should also be noted that most cancers have multiple decade latency periods and often occur in the later part of life. Consequently, it will not be possible to assess the carcinogenic impact of exposures in Turkey for some time.

Special Susceptibilities

ATSDR has concluded that young children are susceptible to hexachlorobenzene exposure based upon human poisoning episodes. Exposure led to permanent debilitating effects. Both human and animal data suggest that the risk of exposure to nursing infants may be greater than the risk to their mothers (ATSDR, 1990a).

Based upon the toxicity data reviewed above individuals with liver disease may be at greater risk that the general population.

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

Hexachlorobenzene induces microsomal enzymes. See Section 5.5 for a discussion of associated effects. Pentachlorophenol increases the porphyrinogenic effects of hexachlorobenzene. Hexachlorobenzene potentiated the thymic atrophy and body weight loss caused by 2,3,7,8-TCDD. A 50 percent food deprivation increased liver hypertrophy and microsomal enzyme induction by hexachlorobenzene (ATSDR, 1990a).

Critical Data Gaps

A joint team of scientists from EPA, NTP, and ATSDR have identified the study following data gaps: human carcinogenicity, *in vivo* and *in vitro* genotoxicity, animal reproductive toxicity, animal developmental toxicity, immunotoxicity studies in humans, and pharmacokinetics (ATSDR, 1990a). Information is needed to develop a model which can be used to estimate the relationship between maternal intake, human milk concentration, and adverse effects in infants.

Summary of EPA Risk Values

Chronic Toxicity	8×10^{-4} mg/kg-day
Carcinogenicity	1.6 per mg/kg-day

Major Sources: IRIS (1993), ATSDR (1990a)

5.6.9. Lindane (gamma-hexachlorocyclohexane)

Background

Lindane is an organochlorine pesticide which is comprised of isomers of hexachlorocyclohexane, with the gamma isomer constituting the major (greater than 99 percent) component. There appears to be some difference in toxicity of the various hexachlorocyclohexane isomers (EPA, 1993a). The following data assume that lindane can be defined as the gamma isomer.

Pharmacokinetics

Lindane is readily absorbed by the GI tract following oral exposure. Distribution is primarily to the adipose tissue but also to the brain, kidney, muscle, spleen, adrenal glands, heart, lungs, blood and other organs. It is excreted primarily through urine as chlorophenols. The epoxide metabolite may be responsible for carcinogenic and mutagenic effects (ATSDR, 1992b).

Male exposure to lindane through the environment results in accumulation in testes and semen in addition to the tissues listed above (ATSDR, 1992b). See also a discussion of the accumulation of lindane by pregnant women under developmental effects below.

Acute Toxicity

See the listing of usual effects associated with organochlorine exposure in Section 5.5. The estimated human lethal dose is 125 mg/kg (HSDB,1993). Occupational and accidental exposures in humans have resulted in headaches, vertigo, abnormal EEG patterns, seizures, and convulsions. Death has occurred primarily in children. ATSDR recommends an acute (14 days exposure or less) exposure MRL of 0.003 mg/kg-day based on neurotoxic effects in rats (ATSDR, 1992b).

Chronic Toxicity

IRIS provides an RfD of 3×10^{-4} mg/kg-day based upon a NOAEL of 0.33 mg/kg-day from a subchronic rat study which found liver and kidney toxicity. Uncertainty factors of 10 each for inter- and intraspecies variability and the use of a less-than-lifetime study were applied (IRIS, 1993). A recently completed two year study is under evaluation and may provide additional information regarding toxicity (EPA, 1993k). Liver damage has been observed in animal studies (EPA, 1993k). Immune system effects have been observed in humans exposed via inhalation and in orally dosed animals. A five week study in rabbits found immunosuppression at 1 mg/kg-day (ATSDR, 1992b).

Most observed effects in humans exposed accidentally to lindane are neurological. Behavioral effects have also been noted in many studies on experimental animals, and at relatively high levels seizures were reported. More subtle behavioral effects were noted at an LEL of 2.5 mg/kg-day with 40 days of exposure in rats. No NOEL was reported (ATSDR, 1992b).

Two recent reproductive studies in rats found adverse effects on the male reproductive system. In a seven week study, decreased sperm counts were noted at 50 mg/kg-day and in a 180 day study, seminiferous tubular degeneration was noted at 6 mg/kg-day with a NOEL of 3 mg/kg-day. An older study had identified the same effects at 64.6 mg/kg-day in a three month study. Experimental data indicate that the female reproductive system may also be altered by lindane exposure. A study of rats found uterine, cervical, and vaginal biochemical changes at 20 mg/kg-day in a 30 day study. Antiestrogenic effects were found at 20 mg/kg-day in female rats in a 15 week study with a NOEL of 5 mg/kg-day. This action was also found in two other recent studies (ATSDR, 1992b). Based upon current risk assessment methods, it appears that the current IRIS RfD for chronic effects is protective against reproductive system toxicity. However, the effects in both the male and female reproductive systems have been evaluated only in short-term studies. Evaluation of these effects in a longer-term study, and identification of the underlying mechanisms of toxicity, would provide information needed for a more complete evaluation of toxicity and dose-response dynamics.

It is not clear whether the IRIS RfD is protective against neurotoxic effects because the study of behavioral effects which resulted in an LEL of 2.5 mg/kg-day was a short-term study and no NOEL was identified. Neurotoxic effects have been reported widely in human poisoning incidents and among occupationally exposed individuals. Consequently, it is of significant interest for human toxicity. Additional information is needed to determine whether the current RfD is protective against neurotoxic effects.

Developmental Toxicity

Two developmental toxicity studies in rats and rabbits both identified a NOEL of 10 mg/kg (no effects were described for higher doses). A three-generation rat study found no adverse reproductive effects at 5 mg/kg-day, the highest dose tested (EPA, 1993k). A recent mouse study found increased resorptions at 5 mg/kg-day. Studies in rats and mice have found increased incidence of extra ribs at 5 to 20 mg/kg-day (ATSDR, 1992b). There are multiple studies showing pre and post implantation fetotoxicity and skeletal abnormalities resulting from prenatal exposure at higher doses (HSDB,1993).

Lindane accumulates in the fatty tissue of pregnant (and non-pregnant) women where it can be transferred to the fetus through the placenta and to infants through breast milk. Human milk concentrations are approximately five to seven time greater than maternal blood levels. Concentrations in maternal blood are proportional to the length of time over which exposure occurred, with older women having higher blood levels. During pregnancy the lindane concentration in blood from fetal tissue, uterine muscle, placenta, and amniotic fluid was higher than levels in maternal adipose tissue and blood serum levels increased during delivery (ATSDR, 1992b). There is little information on the effects of exposure during lactation. One study (dose unspecified) in rats indicated that exposure during gestation and lactation did not cause developmental effects; however, this is not consistent with other studies which found effects associated with gestational exposure.

Based upon what is known regarding the transfer of lindane into human milk, nursing infants must be considered at some risk if their mothers have been exposed to significant amounts of lindane (lindane is a lipid seeking chemical). Additional information is needed to characterize the relationship between maternal intake, body burden (blood or adipose levels), milk concentrations, and adverse effects.

Multiple studies have reported that lindane exposure (as measured by body tissue level of lindane) is associated with premature labor and spontaneous abortions. The causal relationship has not been established for this action (ATSDR, 1992b); however, the reproductive system effects discussed under chronic toxicity (biochemical changes in uterine, cervical and vaginal tissues, and antiestrogenic effects) may be involved.

Information was not located on developmental neurotoxicity, which may be an expected effect of lindane based upon the toxicity of other organochlorines. Based on the limited data which is available, the most appropriate studies for use in calculating an estimated exposure limit for developmental effects are the rat and mouse studies which identified the development of extra ribs and fetal resorptions respectively at an LEL of 5 mg/kg-day. Resorptions, which usually arise from early fetal death, are typically the result of toxicity to the fetus. Information on the nature of that toxicity was not available in the data reviewed for this document. In this case, the resorptions could have arisen from systemic toxicity, or there may have been hormonal effects which also jeopardized maintenance of pregnancy, as indicated by the reproductive system toxicity data (See chronic toxicity section above).

In estimating an exposure limit for lindane the uncertainty generated by the potential for lactation exposure must also be considered. It may be advisable to use an additional modifying factor to account for lack of critical information

in the data base regarding the actual dose at which toxic effects occurred (those more sensitive than lethality), the potential for premature labor and spontaneous abortions, and the potential for increased exposure via lactation. For purposes of calculating an exposure limit, if the rat and mouse LEL were used, standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of a LEL rather than a NOEL. A modifying factor may also be applied. (See also the interactive effects and special susceptibilities sections below.)

As noted above, lindane accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

In animals, ingestion of technical grade hexachlorocyclohexane induced dominant lethal mutations in mice. Studies found that lindane binds to mouse liver DNA at a low rate. Based on a review of genotoxicity studies, ATSDR concluded that lindane "has some genotoxic potential, but the evidence for this is not conclusive" (ATSDR, 1992b).

Carcinogenicity

Lindane has been classified as a probable/possible carcinogen (B2/C) based on liver tumors in animals. The cancer potency is 1.3 per mg/kg-day (HEAST, 1992). In addition to tumors identified in experimental animals, human study data indicate that this chemical may cause aplastic anemia (EPA, 1993a). Lindane is currently under review by EPA. Lindane's related isomers, alpha and beta hexachlorocyclohexane, are also classified as probable human carcinogens and have cancer potencies similar to that of lindane. The cancer potency obtained from the HEAST tables was used to calculate the fish consumption limits listed in Section 3 for carcinogenic effects.

Special Susceptibilities

ATSDR has recommended that pregnant and/or lactating women should not be exposed to lindane. The potential for premature labor and spontaneous abortion is noted (ATSDR, 1992b). People with epilepsy, cerebrovascular accidents, or head injuries who have lower thresholds for convulsions may be at greater risk of lindane-induced CNS toxicity and seizures. Also, individuals

with protein deficient diets, liver or kidney disease, or immunodeficiencies may be at greater risk from lindane exposure than the general population (ATSDR, 1992b).

Children may also be at greater risk from lindane exposure due to the immaturity of their immune and nervous systems. ATSDR has cautioned that:

> "Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10 to 12 years of age" (ATSDR, 1990b).

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5.

High and low protein diets and Vitamin A and C deficiencies increased the toxicity of lindane in experimental animals. Vitamin A supplements decreased toxicity. Cadmium inhibited the metabolism of lindane. Combined cadmium and lindane exposure caused significant embryotoxic and teratogenic effects in rats at dosages which caused no effects when administered alone. Exposure to the alpha, beta, and delta hexachlorocyclohexane isomers may reduce the neurotoxic effects of lindane (ATSDR, 1992b).

MIXTOX has reported mixed results for studies of lindane and chlordane, lindane and hexachlorobenzene, lindane and toxaphene, and lindane and mirex interactions, including inhibition, no effect, and potentiation for these combinations in rodents exposed via gavage (MIXTOX, 1992).

Critical Data Gaps

As discussed above, effects on both the male and female reproductive systems have been evaluated in short-term studies. Evaluation of these effects in a longer term study, and identification of the underlying mechanisms of toxicity would provide information needed for a more complete evaluation of toxicity and dose-response dynamics. Additional information is also needed, as noted under developmental effects, on the potential for exposure via lactation and on mechanisms and dose-response for premature labor and spontaneous abortion.

ATSDR has identified data gaps that include chronic duration oral studies, *in vivo* genotoxicity tests, reproductive, developmental immunotoxicity,

neurotoxicity studies, human studies correlating exposure levels with body burdens of lindane and with specific effects, and pharmacokinetic studies. A large group of international studies recently submitted to ATSDR are currently under review and six studies are ongoing in the United States (ATSDR, 1992b).

Summary of EPA Risk Values

Chronic Toxicity	3×10^{-4} mg/kg-day
Carcinogenicity	1.3 per mg/kg-day

Major Sources: IRIS (1993), ATSDR (1992b), HSDB (1993).

5.6.10. Mirex

Background

Mirex is a polymerizing agent and was used as an organochlorine pesticide and fire retardant until 1975 (EPA, 1993a). Mirex has the potential to concentrate many thousand-fold in food chains (Hayes and Laws, 1991).

Pharmacokinetics

Mirex is a lipophilic compound and is readily taken up in fat tissue. The highest residues were found in fat and the liver. Based on a study in cows, it is also found in milk. At 0.01 and 1 ppm dietary exposure for 32 weeks, cows' milk levels were 0.01 to 0.08 ppm (EPA, 1993o).

No clear data on half-life in humans was found; however, studies in primates found that 90 percent of the original dose was retained in fat after 106 days. The researchers predicted that mirex had an extremely long half-life in monkeys. Based upon this, mirex would be expected to have a very long half-life in humans.

Acute Toxicity

See the listing of usual effects associated with organochlorine exposure in Section 5.5. Acute hepatic effects have been observed in experimental animals. These may result from the following cytological effects: disaggregated ribosomes, glycogen depletion, formation of liposomes, and proliferation of smooth endoplasmic reticulum (EPA, 1993o).

Chronic Toxicity

IRIS lists a chronic exposure RfD of 2×10^{-4} mg/kg-day for mirex based upon a NOAEL of 0.07 mg/kg-day from a chronic dietary rat study. The IRIS file notes that the previous RfD was 2×10^{-6} mg/kg-day. The IRIS file states that a dose related increase in hyperplasia of the parathyroid gland was observed in males in the critical study at and above 0.007 mg/kg-day (IRIS, 1993). It is not stated in the file why this value was not used as a LOAEL; although it is noted that the effect was not observed in other studies. Additional effects noted in the study were: nephropathy, renal medullary hyperplasia, multiple types of liver damage, splenic fibrosis, and cystic follicles of the thyroid. The RfD is based on the latter two effects. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and a factor of three was applied for lack of a complete data base (multi-generational data on reproductive effects and cardiovascular toxicity data). The IRIS file also indicates that effects on the

testis (testicular degeneration, hypocellularity and depressed spermatogenesis) which were noted in other studies, may not have been detected in the critical study because of age-related degenerative changes in the study animals (IRIS, 1993).

A subchronic study in rats identified an LEL of 0.01 mg/kg-day with liver lesions and thyroid injury at the lowest dose tested. Another subchronic study in rats noted similar effects with a NOEL of 0.01 in which only females were tested. A 21 month rat feeding study identified a LEL of 0.01 mg/kg-day based upon histological lesions in the liver and thyroid and altered enzyme levels (EPA, 1993o). These results are supported by 28 day feeding studies, which identified LELs at a similar level to the studies listed above. Histopathology of the liver was noted at 0.025 mg/kg-day in two rat studies. No NOELs were identified (EPA, 1993o). Both structural and functional adverse effects on the thyroid have been observed in experimental animals. The effects persisted for more than one year after treatment ceased. Neurobehavioral effects have also been associated with mirex exposure (Hayes and Laws, 1991).

Both the longer term and subchronic study which identified LELs of 0.01 mg/kg-day suggest that toxicity occurs at levels below those identified in the NTP study, which is used as the basis for the IRIS RfD. The lower LELs can be used to calculate an alternative estimated exposure limit. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, and the use of a LEL rather than a NOAEL.

Developmental Toxicity

Numerous developmental toxicity studies have been conducted on mirex. Effects associated with exposure include undescended testes (EPA, 1993o), fetal cataracts, edema, ectopic gonads, hydrocephaly, abnormal kidney enzyme levels, decreased brain and liver weights, scoliosis, runts, cleft palates, heart defects (anatomical), effects on the fetal electrocardiogram, and decreased fertility. Multiple studies have noted increased mortality and cataracts resulting from both pre- and postnatal exposure (IRIS, 1993). Many of the deaths have been due to congestive heart failure. Studies utilizing cross-fostering of litters have found that both cataracts and reduced viability were less pronounced when neonates did not receive their mothers' milk (mothers were dosed with mirex during pregnancy) (Hayes and Laws, 1991).

Mirex is lipophilic and has been found in human breast milk. A small study in the Great Lakes region found levels from 0.1 to 0.6 ppm in human milk (Hayes and Laws, 1991).

Many of the developmental studies noted significant effects at the lowest dose tested (e.g., cardiac function abnormalities occurred at the LOEL of 0.25 mg/kg-day) (IRIS, 1993). Consequently, they do not provide a useful threshold for effects. One study of cardiac effects in the fetus found a dose related increase in first degree heart block; however, the levels which were tested were quite high (5, 6, 7, and 10 mg/kg). A high rate of stillbirth and postnatal mortality, first and second degree heart blocks, respiratory distress, and cataracts were observed in a prenatal exposure study with an LEL of 1 mg/kg-day (EPA, 1993o).

A single dose of 1.25 mg/kg to pregnant rats caused reduced viability and growth, and a high incidence of cataracts in offspring. A developmental study in rats identified an LEL of 0.25 mg/kg-day with an increase in stillborn pups and decreased viability. A one-generation mouse study identified an LEL of 0.075 mg/kg in a single dose causing reduced litter size; no NOEL was identified. A one-generation rat study identified an LEL of 0.125 mg/kg-day with decreased litter size, histopathological changes in the liver and thyroid, and cataracts (EPA, 1993o). Biochemical alterations include significant decreases in plasma protein concentrations and colloid osmotic pressure in fetuses (EPA, 1993o).

Mirex causes serious adverse effects in multiple organ systems in developing animals. Frank teratogenic effects are observed at levels which are much higher than those required to produce other effects. Teratogenic effects have been observed at an LEL of 6.0 mg/kg with an increased incidence of visceral anomalies and deciduomas. A teratogenic NOEL of 3.0 mg/kg was identified (EPA, 1993o).

Due to the absence of a NOEL for many of the effects, there is considerable uncertainty regarding the calculation of an exposure limit for developmental effects. However, the seriousness of the effects argues for inclusion of a developmental risk value to provide some guidance for exposure. Based on the information reviewed, the most sensitive species appears to be the mouse, with effects observed at 0.075 mg/kg in a single dose (LEL). Studies in other species identified multiple effects at exposure levels equal to, or less than, a factor of two-fold greater (0.125 and 0.25 mg/kg-day). If the mouse study results are used to calculate an estimated exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration inter- and intraspecies variability, and the use of an LEL rather than a NOAEL. Due to the multiple and serious effects associated with mirex exposure during development, and the potential for bioaccumulation and exposure through the placenta and via breast milk, an additional modifying factor may be applied.

As noted above, mirex accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

Most genotoxicity tests reported in the tox one-liners are bacterial assays and are negative (EPA, 1993o). A dominant lethal mutagenicity tests in rats (*in vivo*) found a decreased incidence of pregnancy at 6 mg/kg-day with a NOEL of 3 mg/kg-day. Exposure took place over 10 days prior to mating. Additional information is needed on the nature of the toxicity.

Carcinogenicity

Mirex has been classified as a probable human carcinogen (B2) based on liver and adrenal tumors in experimental animals. The cancer potency is 1.8 per mg/kg-day (HEAST, 1992). This chemical is currently under review by EPA.

Special Susceptibilities

Juveniles may be more susceptible than adults based upon the results of animal studies. At 60 ppm (approximately 3 mg/kg-day) adult mice exposed for 15 days experienced only weight loss; this level was lethal for young mice (Hayes and Laws, 1991).

Based upon a review of the toxicity data above, individuals with diseases or disorders of the following organ systems may be at higher risk than the general population: kidney, liver, spleen, thyroid, parathyroid, cardiovascular, and male reproductive. Due to the developmental toxicity observed in experimental animals, prenatal exposure and lactation exposure may pose a risk to children.

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5. No additional data were located.

MIXTOX reports mixed results for interactions between lindane and mirex and for Aroclor 1254 and mirex. Other studies of Aroclor and mirex have not found interactive results (MIXTOX, 1992).

Critical Data Gaps

Additional information is needed on the developmental effects of mirex to identify a NOEL for sensitive developmental toxicity endpoints so that a well-founded exposure limit for developmental effects can be determined. In a related area, the mutagenicity data indicate a potential mutagenic effect based upon *in vivo* studies. A better understanding of the relationship between the results of these types of studies and mutagenic effects in the human population is needed. The chronic exposure toxicity studies do not provide consistent results. Additional clarification of the NOELs for sensitive endpoints in this area is needed.

Summary of EPA Risk Values

Chronic Toxicity	2×10^{-4} mg/kg-day
Carcinogenicity	1.8 per mg/kg-day

Major Sources: IRIS (1993), tox one-liners (EPA, 1993o), Hayes and Laws (1991)

5.6.11. Toxaphene

Background

Toxaphene is an organochlorine pesticide which is comprised of a mixture of 670 chlorinated camphenes. It was banned for most uses in 1982; however, due to its relatively long half-life it persists in the environment. The soil half-life is approximately one to 14 years (HSDB,1993).

Pharmacokinetics

Toxaphene is rapidly degraded via dechlorination, dehydrodechlorination, and oxidation primarily through the action of the mixed function oxidase system and other hepatic microsomal enzymes. Conjugation may occur but is not a major route of metabolism. Each component of toxaphene has its own rate of biotransformation, making the characterization of toxaphene pharmacokinetics complex (ATSDR, 1990b).

Some adverse effects of toxaphene may result from repeated exposure, that do not occur with a single exposure to a lesser dose. Exposures at 0.06 mg/kg-day over five weeks caused adrenal hormone reductions whereas a single dose of 16 mg/kg did not cause effects. This is significant when considering potential risks arising from chronic exposure to toxaphene (ATSDR, 1990b).

Acute Toxicity

Acute high level exposures to toxaphene has resulted in death in adults and children with an estimated minimum lethal dose of 2 to 7 grams which is equivalent to 29 to 100 mg/kg for a male adult. Long-term damage to the central nervous system and liver have also been observed. The kidney and adrenal glands are also target organs (ATSDR, 1990b). A one day NOAEL of 10 mg/kg-day is available from a dog study which used death as the effect of concern. A 14 day LOAEL of 5 mg/kg-day was identified in an eight day study which was used as the basis for an MRL for acute exposure of 0.005 mg/kg-day by ATSDR (ATSDR, 1990b). See the listing of usual effects associated with organochlorine exposure in Section 5.5.

Chronic Toxicity

IRIS does not provide a discussion of chronic effects of exposure to toxaphene or an RfD (IRIS, 1993). The EPA Office of Pesticide Programs provides an RfD of 2.5×10^{-4} mg/kg-day , based on a two year dog feeding study with a NOEL of 0.25 mg/kg-day. The effect noted was liver degeneration. Uncertainty factors totalling 1000 were applied (EPA, 1992h, EPA, 1993b and p).

Chronic exposure to toxaphene may result in damage to the following systems: liver, kidney, adrenal, immunological, and neurological. The use of the liver as the endpoint of concern is supported by a recent subchronic oral rat study which found NOAELs of 0.28 for males and 0.38 for females with liver and kidney effects (ATSDR, 1990b).

Chronic exposure to toxaphene may cause hormonal alterations. A study found increased levels of hepatic metabolism *in vivo* and *in vitro* of estradiol and estrone and a decrease in their uterotropic action. Duration of exposure was not specified in the source reviewed (HSDB,1993). See also notes regarding estrogenic activity under the carcinogenicity section below.

Developmental Toxicity

Adverse developmental effects, including immunosuppressive and behavioral effects, were noted in experimental animals at levels below those required to induce maternal toxicity. Immunosuppression (reduction in macrophage levels, cell-mediated immunity and humoral immunity) was observed in test animals exposed during gestation and nursing with a LOAEL of 1.5 mg/kg-day. Impairment of behavioral maturation (e.g., reflexes) occurred at 0.05 mg/kg-day in a rat study with 47 days of exposure. Delayed ossification (bone development) and alterations in kidney and liver enzymes suggestive of organ-specific toxicity were observed at 15 mg/kg-day. Other adverse effects noted in offspring of maternally exposed individuals included histological changes in the liver, thyroid and kidney (ATSDR, 1990b).

Women exposed to toxaphene through entering a field that had recently been sprayed exhibited a higher incidence of chromosomal aberrations in cultured lymphocytes than was found in unexposed women. Dermal and inhalation exposure were the probable routes of exposure; however, the exposure was not quantified (ATSDR, 1990b). Animal study results suggest that toxaphene does not interfere with fertility in experimental animals at the doses tested (up to 25 mg/kg-day) (ATSDR, 1990b). However, chromosomal aberrations (as observed in women) would lead to decreased fertility due to early fetal loss and may result in heritable birth defects.

Toxaphene is known to be conveyed into milk rapidly after maternal exposure to the chemical. The half-life of toxaphene has been estimated at nine days. It has been found in the milk of cows at all doses tested (20 - 140 ppm). In cows exposed to 20 to 140 ppm in food (mg/kg-day conversion not available) for eight weeks, milk concentrations increased rapidly; they decreased rapidly following cessation of exposure. Information was provided on the relationship between feed and milk concentrations. The exposure range was from 20 ppm feed with milk concentrations reaching 0.36 ppm to 140 ppm feed with a

maximum of 1.89 ppm in milk (ATSDR, 1990b). It may be advisable to use this data to estimate the human dose to nursing infants.

Other aspects of developmental toxicity associated with toxaphene are based on effects observed in adult individuals which are known to pose higher risks to children. The ATSDR has cautioned that:

> "embryos, fetuses, and neonates up to age 2 - 3 months may be at increased risk of adverse effects...because their enzyme detoxification systems are immature"

and

> "Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10 - 12 years of age" (ATSDR, 1990b).

Immunosuppression was noted in multiple subchronic exposure animal studies.

ATSDR also noted that:

> "animal studies suggest that detoxification of the toxaphene mixture may be less efficient in the immature human than the metabolism and detoxification of the single components such as Toxicant A or B."(ATSDR, 1990b).

ATSDR provides an MRL for intermediate exposures (14 to 365 days) of 5 x 10^{-5} mg/kg-day based on an LEL of 0.05 mg/kg-day associated with impaired behavioral development. Uncertainty factors of 10 each for inter- and intraspecies variability and the use of an LEL were applied (ATSDR, 1990b). This value can be used as the estimated exposure limit for developmental effects for use developing fish consumption limits.

As noted above, toxaphene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

There are numerous positive mutagenicity assays of toxaphene: the Ames test, sister chromatid exchange, chromosomal aberrations in toxaphene-exposed humans, and forward mutation assays. The implications of this for human germ cells is not known and one assay designed to assess the effects of dominant lethal effects on implantations in mice yielded negative results. Some data suggest that the polar fraction of toxaphene may be more mutagenic than the nonpolar fraction (ATSDR, 1990b; HSDB,1993).

Changes in human genetic material have been noted in workers exposed to toxaphene (HSDB,1993).

Carcinogenicity

Toxaphene is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The cancer potency is 1.1 per mg/kg-day, based upon liver tumors in experimental animals (IRIS, 1992). This value was used to calculate fish consumption limits listed in Section 3 for carcinogenic effects. No conclusive human epidemiological studies are available for toxaphene (ATSDR, 1990b).

Toxaphene has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto, et al, 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis, et al, 1993). In addition to potential carcinogenic effects, toxaphene may also cause disruption of the endocrine system due to its estrogenic activity (Soto, et al, 1994).

Special Susceptibilities

A protein deficient diet may increase the toxicity of toxaphene approximately three-fold based on an LD50 study in rats (ATSDR, 1990b). Because this information was obtained from an LD50 study it can not be used directly to modify risk values. The Centers for Disease Control has specified that:

"This has important implications with regard to the possible increased susceptibility of humans who ingest a protein-deficient diet and live in areas of potential exposure to toxaphene." (ATSDR, 1990b)

If a population with protein deficient diets is the target group for fish consumption limits, an additional modifying factor of 10 could used in determining the appropriate exposure limit for developmental effects. A factor of 10 rather than three (observed in animal studies) is recommended, because

it is unknown whether human populations exposed under the same conditions will be more or less susceptible than the animals tested, and because the results were obtained from an LD50 study, rather than a study with a more sensitive toxic endpoint.

The nervous system is a primary target of toxaphene toxicity. Individuals with latent or clinical neurological diseases, such as epilepsy or behavioral disorders, may be at higher risk. In addition children may be especially susceptible to toxaphene induced neurotoxicity based on early reports of acute ingestion toxicity (ATSDR, 1990b).

As discussed above under "Developmental Toxicity" ATSDR has identified pregnant women, fetuses, infants and children as populations at greater risk. Other individuals who may be at higher risk are those with diseases of the renal, nervous, cardiac, adrenal, and respiratory systems. Individuals using certain medications are also at potential risk due to the induction of hepatic microsomal enzymes by toxaphene (discussed further in the interactive effects section below).

See also a discussion of susceptibilities associated with pharmaceutical use in Section 5.5.

Interactive Effects

Metabolism of some drugs and alcohol may be affected by toxaphene's induction of hepatic microsomal enzymes. This was observed in a man using warfarin as an anticoagulant while he used toxaphene as an insecticide. The effectiveness of the drug was reduced due to its increased metabolism arising from toxaphene's induction of microsomal enzymes (ATSDR, 1990b).

See a discussion of organochlorine effects related to induction of the mixed function oxidase system in Section 5.5.

Based on acute studies and anecdotal reports of acute exposure in humans, exposure to chemicals which increase microsomal mixed-function oxidase systems (e.g., lindane) are likely to reduce the acute toxicity of other chemicals detoxified by the same system (e.g., toxaphene) because the system is functioning at a higher than normal level. Toxaphene, in turn reduces the acute toxicity of chemicals which require this system for detoxification (ATSDR, 1990b).

In experimental animals toxaphene antagonized the tumorigenic activity of benzo(a)pyrene in the lung. It was theorized that this occurred because

toxaphene inhibited the biotransformation of B(a)P to a reactive metabolite or by promoting its degradation to nonactive forms (ATSDR, 1990b).

MIXTOX has reported synergism between chlordane, toxaphene and malathion in mice exposed via gavage and additive interactions between chlordane and toxaphene. Antagonism was reported between toxaphene and diazinon in rats exposed via gavage. Mixed results have been obtained between lindane and toxaphene (MIXTOX, 1992).

Critical Data Gaps

The following data gaps have been identified by ATSDR, EPA, and the National Toxicology Program: mammalian germ cell genotoxicity, studies which investigate sensitive developmental toxicity endpoints including behavioral effects, epidemiological and animal studies of immunotoxicity, long-term neurotoxicity studies in animals using sensitive functional and neuropathological tests and behavioral effects on prenatally exposed animals, epidemiological studies evaluating multiple organ systems, and pharmacokinetic studies (ATSDR, 1990b).

Summary of EPA Risk Values

Chronic Toxicity	2×10^{-4} mg/kg-day
Carcinogenicity	1.1 per mg/kg-day

Major Sources: IRIS (1993), ATSDR (1990b), HSDB (1993)

ORGANOPHOSPHATE PESTICIDES

In addition to the discussions of individual target analytes, please refer to the discussion of toxicity characteristics of the organochlorine chemical group in Section 5.5.

5.6.12. Carbophenothion (trithion)

Background

Carbophenothion is an organophosphate insecticide which was widely used until very recently when the registration was dropped by the registrant. No IRIS file was located on this chemical (10/93 search).

Pharmacokinetics

Carbophenothion is metabolized to the oxon analog, and both parent and oxon are metabolized to the sulfoxide and sulfone forms (Hayes and Laws, 1991). The major metabolite of carbophenothion is p-chlorobenzenesulfinic acid which is probably derived from the -S-oxide and/or the oxon form of the parent compound (HSDB,1993). Excretion of carbophenothion in experimental animals is rapid; 75 percent of the dose in mice was excreted in 24 hours (Hayes and Laws, 1991).

Acute Toxicity

See the listing of usual effects associated with organophosphate exposure in Section 5.5. The acute oral LD50 in experimental animals ranged from 25 to 217 mg/kg (EPA, 1993d). HSDB lists this chemical as highly toxic with an estimated fatal human oral dose of 8.5 mg/kg (HSDB,1993).

Chronic Toxicity

As noted above, no IRIS file is available for carbophenothion (search 10/93). OPP lists a reference dose of 1.3×10^{-4} mg/kg-day based upon a two year dog study which identified a LEL of 0.125 mg/kg-day with decreased plasma and brain cholinesterase levels at the LEL. Uncertainty factors of 10 each were used for intra and interspecies variability and the use of a LEL rather than a NOEL (EPA, 1992h). Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Section 5.5.2.

A two year dietary study in rats identified a LEL of 4 mg/kg-day with reduction of hemoglobin and increased adrenal weights (Hayes, 1982). A three month

rat feeding study reported tremors and respiratory infection with an NOEL of 1.1 mg/kg-day. This data was obtained from the OPP tox one-liners and, consequently, very little detail was provided. Due to the lack of information on effects other than cholinesterase inhibition for this chemical, and the limited information available to estimate an alternative risk value, it is recommended that the OPP value be used.

Developmental Toxicity

Data currently available regarding developmental toxicity is limited because endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity.

A NOEL of 0.5 mg/kg-day is reported in a 1976 three-generation rat reproduction study which identified decreased pup survival and pup weight at the LEL of 1.5 mg/kg-day. An earlier similar study found a LEL (no NOEL) of 1 mg/kg-day with decreased pup survival and increased stillbirths at the LEL (EPA, 1993d). The reviewed data did not contain any information regarding underlying mechanisms of fetal or neonatal toxicity. Additional uncertainty arises because the study outcomes are gross measures of toxicity and do not provide any indication of the level of exposure at which the organ toxicity which led to death was occurring.

If the 1976 study is used to calculate an estimated exposure limit for developmental effects, the uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, and the inadequacy of the data base. Consideration should also be given to the insensitivity of the toxicity measure. In cases where the available studies provide information on only gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

Mutagenicity

Carbophenothion yielded positive results in a sister chromatid exchange assay in human lymphocytes (HSDB, 1993).

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of carbophenothion.

Special Susceptibilities

No information was found specifically regarding carbophenothion. See also a discussion of susceptibilities associated with organophosphate exposure in Section 5.5.

Interactive Effects

MIXTOX reported additive interaction between carbophenothion and chlordane gavage exposure in rats, with toxaphene antagonism in rats exposed via gavage (MIXTOX, 1992).

Critical Data Gaps

There is very limited information on the chronic systemic toxicity of carbophenothion other than cholinesterase inhibition. Based on the available information, the reader may wish to calculate an alternative exposure limit. However, additional studies are needed to identify toxic mechanisms and sensitive endpoints. This is especially true for the developmental effects because the endpoints in currently available studies are crude measures of toxicity.

OPP lists the following data gaps: a chronic feeding study in rats and developmental toxicity studies in two species (EPA, 1992d).

Summary of EPA Risk Values

Chronic Toxicity	1.3×10^{-4} mg/kg-day (based upon cholinesterase inhibition)
Carcinogenicity	Insufficient data to determine carcinogenic status

Major Sources: HSDB (1993), tox one-liners (EPA, 1993d)

5.6.13. Chlorpyrifos

Background

Chlorpyrifos is an organophosphate insecticide which is applied throughout the United States for various agricultural uses.

Pharmacokinetics

Chlorpyrifos accumulates in fat and has a longer half-life in fatty tissues than in other tissues. It has been detected in cows' milk (HSDB,1993) and would be expected to occur in human milk of exposed mothers. This is of concern because organophosphates may have a higher toxicity for immature individuals than adults (e.g., malathion was more toxic to juveniles in three species tested) (EPA, 1992g). Chlorpyrifos is rapidly metabolized and excreted based upon studies in animals (Hayes and Laws, 1991).

Acute Toxicity

See the listing of usual effects associated with organophosphate exposure in Section 5.5.

Chronic Toxicity

IRIS provides an oral RfD of 0.003 mg/kg-day based on a NOAEL in a 20 day study reported in 1972 which found cholinesterase inhibition in adult male humans after nine days of exposure. There were four subjects per dosed group. An uncertainty factor of 10 was used to calculate the RfD (IRIS, 1993). There are limitations in the use of this study for a chronic toxicity RfD. Although effects were observed at levels lower than the NOAEL, they were discounted due to an inability to achieve statistical significance; however, it is very difficult to achieve statistical significance with four subjects. No uncertainty factor was applied for the acute nature of the study. Most importantly, EPA is reviewing its methods for evaluating cholinesterase inhibitors. Cholinesterase inhibition alone is not necessarily considered an adverse effects, in the absence of other effects. Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Section 5.5.2. The value listed on IRIS was confirmed in 1993 by an Office of Pesticide Programs RfD Peer Review Committee (EPA, 1993e).

Other chronic exposure effects have been observed in study animals. In a 1991 two-generation rat study, adrenal lesions were reported at 1 and 5

mg/kg-day. In a subchronic study at higher doses, the same effects were observed along with increased brain and heart weight (EPA, 1992g).

There are significant uncertainties regarding an appropriate threshold for effects of chlorpyrifos exposure. These include the very limited data on the recently identified adrenal and cardiac effects of chlorpyrifos and the utility of a cholinesterase endpoint. The IRIS value was used to calculate fish consumption limits shown in Section 3 for chronic toxicity. Future improvements in the data base may result in alteration in this recommended value.

Developmental Toxicity

Chlorpyrifos is fetotoxic in numerous species. In a 1987 rat study, a developmental toxicity NOEL of 2.5 mg/kg-day was determined; at the LOEL of 15 mg/kg-day post-implantation losses were observed. In a 1991 rat study, which was rated as "guideline" by OPP, a developmental NOEL of 1 mg/kg-day was obtained, with increased pup mortality at 5 mg/kg-day. No data were available for this document on underlying causes of mortality. Decreased fetal length and increased skeletal variants were noted in mice with a fetotoxic NOEL for the study of 10 mg/kg-day. In a 1987 study on rabbits, increased skeletal variants and an increased incidence of unossified sternebra and xiphisternum were observed at 81 mg/kg-day (EPA, 1992g).

A 1991 rat study yielded the most conservative NOEL at 1 mg/kg-day. Unfortunately, the observed endpoint was mortality. An evaluation of the underlying causes of mortality may yield a more sensitive endpoint. If this study were used to estimate an exposure limit for developmental effects, the standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability and data gaps, based upon the inability of the current studies to identify critical information.

Currently available data regarding developmental toxicity is limited because endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity. In cases such as this, where the available studies provide information only on gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

Mutagenicity

The results of mutagenicity assays of chlorpyrifos are mixed. Chlorpyrifos was weakly positive with and without activation in gene conversion and

recombination assays, and positive for direct damage to DNA in *B. subtilis* (EPA, 1992g). *in vivo* assays of mouse liver DNA and RNA indicated that chlorpyrifos caused more DNA and RNA alkylation than other organophosphates (HSDB,1993). Its toxicity is probably related to formation of its oxon analog (chlorpyrifosoxon) and subsequent enzyme inhibition of cholinesterase activity, carboxylases and mitochondrial oxidative phosphorylases.

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of chlorpyrifos.

Special Susceptibilities

See a discussion of susceptibilities associated with organophosphate exposure in Section 5.5.

Interactive Effects

No data were located.

Critical Data Gaps

IRIS lists the following data gap: chronic feeding/oncogenicity study in rats (IRIS, 1993). Addition data is needed on the non-cholinesterase effects of chronic exposure and on the toxicity which underlies early pup mortality in developmental studies.

Summary of Risk Values

Chronic Toxicity	3×10^{-3} mg/kg-day
Carcinogenicity	Insufficient data to determine carcinogenic status.

Major Sources: IRIS (1993), HSDB (1993), tox one-liners (EPA, 1992g)

5.6.14. Diazinon

Background

Diazinon is an organophosphorus insecticide which has been widely used since its introduction in 1952.

Pharmacokinetics

Very little data were located. Metabolism appears to proceed by similar but somewhat different paths in various mammalian species (HSDB,1993). Human milk may contain trace amounts of diazinon based upon the results of exposure in cows (HSDB,1993).

Acute Toxicity

Diazinon is highly toxic. The estimated adult oral fatal dose is approximately 25 grams (HSDB,1993). See the listing of usual effects associated with organophosphate exposure in Section 5.5.

Chronic Toxicity

IRIS does not currently provide an oral RfD because it is under review within the Agency (IRIS, 1993). OPP provides an RfD of 9×10^{-5} mg/kg-day based upon cholinesterase inhibition observed in a 90 day rat feeding study with a NOEL of .009 mg/kg/day and uncertainty factors totalling 100 (EPA, 1992d). Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Section 5.2.2.

Very little dose-response data are available on chronic systemic toxicity, other than cholinesterase effects. Hematocrit depression was observed in a rat chronic feeding study at 50 mg/kg-day. Gastrointestinal disturbances were noted at 5 mg/kg-day with a NOEL of 0.05 mg/kg-day in a chronic monkey study (EPA, 1993f). If an alternative to cholinesterase inhibition is required, the monkey study can be used with standard uncertainty factors which take into consideration inter- and intraspecies variability.

Developmental Toxicity

The reproductive/teratogenic studies listed in the tox one-liners report no adverse effects at the highest doses tested (EPA, 1993f).

HSDB reported multiple studies indicating diazinon is teratogenic. In a prenatal exposure study (dose not specified) multiple doses of diazinon resulted in a

higher incidence of urinary malformations, hydronephrosis and hydroureter. Diazinon was teratogenic in rats administered a single dose on day 11 of gestation. Decreased fetal body weight was the most sensitive indicator. No dose was specified in the data base (HSDB,1993). In chicks, diazinon exposure led to abnormal vertebral column development including a tortuous and shortened structure with abnormal vertebral bodies. In the neck region, the vertebral bodies had fused neural arches and lacked most intervertebral joints. More severe effects on other elements of the skeleton were observed at higher doses (HSDB,1993 and Hayes, 1982). The dose (1 mg/egg) is not easily convertible to a mammalian dose.

Behavioral effects were observed in mice exposed prenatally at 0.18 and 9 mg/kg-day throughout gestation. The high dose group showed decreased growth, several behavioral effects, and structural pathology of the forebrain. The low dose group did not have brain pathology or growth abnormalities; however, they showed small but measurable defects in behavior and a delay in reaching maturity (Hayes, 1982). This study appears to provide a relatively sensitive endpoint for evaluation of developmental effects associated with exposure to diazinon. If the LOAEL of 0.18 mg/kg-day were used, the uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of a LOAEL rather than a NOAEL. Based on the available information, the current IRIS RfD would be protective against developmental toxicity.

Mutagenicity

Most mutagenicity assays were negative; one positive sister chromatid exchange assay was noted (EPA, 1993f). A study on the effect of diazinon on mitosis in human lymphocytes reported chromosomal aberrations in 74 percent of the cells at 0.5 mg/ml (HSDB, 1993).

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of diazinon.

Special Susceptibilities

See a discussion of susceptibilities associated with organophosphate exposure in Section 5.5.

Interactive Effects

MIXTOX has reported antagonistic effects between diazinon and toxaphene with exposure in rats via gavage (MIXTOX, 1992).

Critical Data Gaps

OPP lists the following data gaps: reproduction study in rats, chronic feeding oncogenicity study in rats and chronic feeding study in dogs (EPA, 1992d). A multigeneration reproductive study which evaluated developmental effects at low doses and defined a NOAEL would be useful in establishing an appropriate RfD.

Summary of EPA Risk Values

Chronic Toxicity	9×10^{-5} mg/kg-day based upon cholinesterase inhibition
Carcinogenicity	insufficient information to determine carcinogenic status

Major Sources: tox one-liners (EPA, 1993f), Hayes (1982), HSDB (1993)

5.6.15. Disulfoton (disyston)

Background

Disulfoton is an organophosphate pesticide with high acute toxicity to all mammals.

Pharmacokinetics

Metabolism of disulfoton involves sequential oxidation of the thioether sulfur and/or oxidative desulfuration, in addition to hydrolytic cleavage. The major metabolites are the sulfoxide acid sulfone analogs of the compound. These are toxic metabolites which are degraded rapidly to water soluble non-toxic metabolites. Their estimated half-life is 30 to 32 hours (EPA, 1993h). Disulfoton is rapidly absorbed through the mucous membrane of the digestive system and conveyed by the blood to body tissues. The kidneys are the main route of elimination (HSDB,1993).

Acute Toxicity

See the listing of usual effects associated with organophosphate exposure in Section 5.5. The acute oral LD50 in animals ranges from 2 to 27.5 mg/kg (EPA, 1993h). Disulfoton is very highly toxic to all mammals by all routes of exposure (HSDB,1993).

Chronic Toxicity

IRIS provides an RfD of 4.0×10^{-5} mg/kg-day based upon a LEL of 0.04 mg/kg-day from a two year rat study that was associated with cholinesterase inhibition and optic nerve degeneration (IRIS, 1993). The IRIS RfD was calculated using a modifying factor of 10 to account for possible findings in the additional recommended optic toxicity studies (EPA, 1992c).[11] Although there is some question regarding the use of cholinesterase inhibition as the basis for establishing an RfD (problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Section 5.5), optic effects also serve as the basis for this RfD (EPA, 1992d).

Numerous other effects of disulfoton have been reported at doses within one order of magnitude of the LEL identified in the critical study. Significant

[11] Standard methods would typically utilize 10 each for inter and intraspecies variability and for the use of a LEL rather than a NOEL. This plus the modifying factor of 10 would yield an RfD of 4×10^{-6} mg/kg/day.

toxicity in multiple organ systems has been observed at 0.1 mg/kg-day (the lowest dose tested) for the following systems: spleen, liver, pituitary, brain, seminal vesicles, and kidneys (IRIS, 1993). In addition, at 0.65 mg/kg-day rats exhibited atrophy of the pancreas, chronic inflammation and hyperplasia in the stomach, and skeletal muscle atrophy (EPA, 1993h). Based upon the chronic exposure information which was reviewed and standard assumptions regarding the use of uncertainty factors, the IRIS RfD appears to be protective against the effects listed above.

Developmental Toxicity

In a rat teratogenicity study, incomplete ossification of the parietals and sternebrae were noted at 1 mg/kg-day with a NOEL of 0.3 mg/kg-day in rats. In a 1966 three-generation reproduction study in rats, male offspring had juvenile hypoplasia in the testes, females had mild nephropathy in the kidneys and both had preliminary stages of liver damage at 0.5 mg/kg-day. No NOEL was obtained and no data were provided on a number of critical parameters including weight, growth rate, and number of stillborn animals. Insufficient histologic data and incomplete necropsy reports were identified by EPA reviewers (IRIS, 1993 and EPA, 1993h). Toxicity was incompletely characterized in this study and additional studies are needed to provide an adequately defined NOEL for developmental effects. Because multiple serious effects were observed at the lowest dose tested, the multigeneration study does not provide an optimal basis for calculation of an exposure limit for developmental effects. However, it does indicate that adverse developmental effects may occur with exposure to disulfoton and provides greater detail on these effects than the other studies which are available.

A more recent two-generation rat study identified a NOEL of 0.04 mg/kg-day with an LEL of 0.12 mg/kg-day based upon decreased litter sizes, pup survival and pup weights at the LEL (EPA, 1993h). This study does not appear to provide the same level of analysis of sensitive endpoints as the three-generation study discussed above. However, it identifies a lower NOEL and LEL than the two older studies. If this study is used to calculate an estimated exposure limit for developmental effects, the uncertainty factors typically used in this calculation would take into consideration inter- and intraspecies variability. A modifying factor could be used for the lack of data on the level at which toxicity occurred which led to death. Additional studies are needed to identify the NOEL for sensitive measures of the testicular, liver and kidney toxicity identified in the multigeneration study.

Mutagenicity

Disulfoton was not mutagenic in most assays; however, it was positive for unscheduled DNA synthesis without activation in human fibroblasts, in a reverse mutation assay in salmonella (EPA, 1993h), and in other *in vitro* assays (HSDB,1993).

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of disulfoton.

Special Susceptibilities

Based upon the organ toxicities observed in animal studies, individuals with diseases or disorders of the following systems may be at greater risk from exposure to disulfoton: pancreas, stomach, spleen, liver, pituitary, brain, seminal vesicles, kidneys, musculoskeletal and ocular. In addition, children who were exposed prenatally to disulfoton may be at risk, depending on the level of exposure. Also see a discussion of susceptibilities associated with organophosphate exposure in Section 5.5.

Interactive Effects

No data were located.

Critical Data Gaps

The IRIS file notes that additional rat reproduction studies and studies to evaluate the ocular effects of disulfoton are needed (IRIS, 1993). HSDB notes that because of data gaps, a full risk assessment cannot be completed. Major relevant data gaps noted under the FIFRA heading in HSDB include chronic toxicity, oncogenicity, and mutagenicity data, animal metabolism, subchronic toxicity, and human dietary and non-dietary exposures (FIFRA, 1987, some data gaps may have been filled, cited in HSDB,1993). As noted above, additional studies are needed to identify the NOEL for sensitive measures of the testicular, liver and kidney toxicity identified in the multigeneration study.

Summary of EPA Risk Values

Chronic Toxicity	4×10^{-5} mg/kg-day
Carcinogenicity	Insufficient data to determine carcinogenic status

Major Sources: IRIS (1993), tox one-liners (EPA, 1993h), HSDB (1993)

5.6.16. Ethion

Background

Ethion is an organophosphate pesticide used primarily on citrus crops (EPA, 1993a).

Pharmacokinetics

No data were located.

Acute Toxicity

See the listing of usual effects associated with organophosphate exposure in Section 5.5.

Chronic Toxicity

A 1970 study of 10 men (six test subjects) with a NOEL of 0.05 mg/kg-day found plasma and brain cholinesterase inhibition (IRIS, 1993). IRIS provides an RfD of 5×10^{-4} mg/kg-day based upon a subchronic study in dogs which found a NOEL of 0.06 and 0.07 mg/kg-day for males and females respectively with the same effects as the human study. Uncertainty factors of 10 each for intraspecies sensitivity and for the effects observed at 0.71 mg/kg-day in the dog study (IRIS, 1993). Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Section 5.5.2.

Developmental Toxicity

A developmental NOEL of 0.6 mg/kg-day was obtained in a rat study which found delayed ossification at an LEL of 2.4 mg/kg-day (IRIS, 1993). A rabbit study by the same laboratory also identified a LEL of 2.4 mg/kg-day with an increased incidence of fused sternal centers and fetal resorptions at that dose level. The NOEL was 0.6 mg/kg-day (EPA, 1993n). A three-generation rat study was also listed in the tox one-liners; however information was only provided on cholinesterase inhibition levels (EPA, 1993n).

The NOEL of 0.6 mg/kg-day from the rat and rabbit studies can be used to calculate an estimated exposure limit for developmental effects. The uncertainty factors would typically take into consideration inter- and intraspecies variability. Teratogenic effects and fetal death often occur at exposure levels considerably higher than levels associated with systemic toxicity. Other organophosphates have shown this gradient of effects (See

diazinon) Consequently, there is concern that the studies available for evaluation may not fully characterize the developmental toxicity of ethion. In cases such as this, where the available studies provide information on only gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

Mutagenicity

The tox one-liners listed no positive study results.

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of ethion.

Special Susceptibilities

See a discussion of susceptibilities associated with organophosphate exposure in Section 5.5.

Interactive Effects

Potentiation between ethion and malathion has been observed. In rats the potentiation was approximately 2.9-fold. In dogs there was very slight, if any potentiation (EPA, 1993n).

Critical Data Gaps

IRIS lists a chronic dog feeding study as a data gap (IRIS, 1993). A multigeneration study and developmental study which evaluate neurobehavioral toxicity are needed to clarify developmental effects.

Summary of EPA Risk Values

Chronic Toxicity	5×10^{-4} mg/kg-day
Carcinogenicity	Insufficient data to determine carcinogenic status

Major Sources: IRIS (1993), tox one-liners (EPA, 1993n)

5.6.17. Terbufos

Background

Terbufos is an organophosphorus insecticide.

Pharmacokinetics

No data were located.

Acute Toxicity

Terbufos has a high acute toxicity to humans. Animal studies yielded the following results: an oral LD50 in rats of 1.3 to 1.6 mg/kg (surveillance index) and an oral LD50 in mice of 1.3 - 6.6 mg/kg (EPA 1992f). See the listing of usual effects associated with organophosphate exposure in Section 5.5.

Chronic Toxicity

Limited information is available on terbufos toxicity and the focus of most toxicity evaluations is on its cholinesterase inhibition properties. IRIS does not provide an RfD for terbufos. HEAST lists an RfD of 2.5×10^{-5} mg/kg-day based on cholinesterase inhibition in a six month dietary dog study with a NOEL of 0.0025 mg/kg-day. Uncertainty factors of 10 each for inter- and intraspecies variation were used. No uncertainty factor was used for the subchronic nature of the study. The HEAST table states that this value is under review (HEAST, 1992).

OPP has recently developed an RfD of 5×10^{-5} mg/kg-day based upon cholinesterase inhibition. This is based upon a 28 day dog study with a NOEL of 0.005 mg/kg-day and a one year dog study with a LOAEL of 0.015 mg/kg-day. Uncertainty factors of 10 each for inter- and intraspecies variability were applied (EPA, 1993p). Problems related to the use of cholinesterase inhibition as a critical endpoint are discussed in Section 5.5.2.

Quantitative chronic toxicity information on cholinesterase inhibition is available which generally supports the OPP RfD. In rats, a 1974 lifetime oral study found a LOEL of 0.0125 mg/kg-day (the lowest dose tested); a 1987 one year oral study found a NOEL of 0.025 mg/kg-day. In dogs, a 1972 six month oral study found a NOEL of 0.0025 mg/kg; 1986 one year study found a LOEL of 0.015 mg/kg-day (the lowest dose tested); a 1987 28 day dog study identified a NOEL of 0.00125 mg/kg-day (EPA, 1992f).

Quantitative data on chronic effects which are not directly related to cholinesterase inhibition are limited, due to the lack of "no effect levels" from many studies, and the need for specific information on some effects. Chronic exposure effects include: corneal cloudiness and opacity, eye rupture, alopecia, disturbances in balance, and exopthalmia noted in multiple studies and multiple species at 0.0125 mg/kg-day and above (EPA, 1992f). Increased liver weight and increased liver extramedullary hematopoiesis at 0.025 mg/kg-day and above, and mesenteric and mandibular lymph node hyperplasia at 0.05 mg/kg-day and above were noted in a subchronic (three month) rat study (animals were not examined for this lesion at lower exposure levels) (EPA, 1992f).

Developmental Toxicity

Data currently available regarding developmental toxicity are limited because the endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity. Results from two developmental studies and one multigeneration study are available: a 1984 rat study found NOEL of 0.1 mg/kg-day with increased fetal resorptions at 0.2 mg/kg-day; a 1988 rabbit study identified a NOEL of 0.25 mg/kg-day with fetal resorptions at 0.5 mg/kg-day. A 1973 multigeneration reproductive study found a NOEL of 0.0125 mg/kg-day in rats, based on an increase in the percentage of deaths in offspring (EPA, 1992f).

The increase in deaths in offspring in the multigeneration study does not provide insight into the causes of death. Fetal resorptions, noted in the developmental studies, often result from gross abnormalities leading to early fetal death or from direct fetotoxicity. A NOEL for adverse effects would be a preferable endpoint, with exploration of the causes underlying fetal loss. A multigeneration study which evaluated sensitive endpoints, including ocular effects, and liver and lymph node toxicity which were observed at low doses in adults animals (See the chronic exposure section above) would provide a better basis for determining a safe developmental exposure level.

Based on the developmental data currently available, the multigeneration study NOEL of 0.0125 appears to be the most sensitive study, (perhaps because exposure occurred over a longer period of time than in the other developmental toxicity studies). However, the developmental toxicity data base embodies considerable uncertainty. Many chronic exposure effects were observed at levels approximating the NOEL obtained from the multigeneration study. Although these effects were not reported in the developmental toxicity studies, it is not known whether effects observed in adult studies, such as liver and lymph node toxicity, were evaluated in the developmental studies. Postnatal

exposure would be expected to be at least as toxic to young individuals as to adults.

If the multigeneration study is used calculate an exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration intra- and interspecies variability and the inadequacy of the data base. In cases such as this, where the available studies provide information on only gross measures of toxicity (i.e., death), it may be advisable to use the RfD for chronic toxicity and consider modifications for application to pregnant women and children.

Mutagenicity

Terbufos was negative in most assays. It was positive in an *in vivo* dominant-lethal assay in rats; at 0.4 mg/kg the numbers of viable implants were reduced (EPA, 1992f).

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of terbufos.

All oncogenicity tests on terbufos have been considered negative by OPP (EPA, 1992f). However, further exploration of mesenteric and mandibular lymph node hyperplasia identified in a three month study (noted above) is warranted because hyperplasia is often a precancerous condition. Evaluation of this endpoint in a lifetime study is necessary to determine the ultimate course of the hyperplasia.

Special Susceptibilities

See a discussion of susceptibilities associated with organophosphate exposure in Section 5.5.

Interactive Effects

No data were located.

Critical Data Gaps

There are inconsistencies in the toxicity data base for terbufos based on a comparison of acute study results and the results obtained in some chronic feeding studies, developmental studies and the LD50s. Some longer term studies reported no effects at exposure levels above the LD50s (EPA, 1992f).

The animal and human studies available on terbufos do not provide a complete and consistent basis for calculation of an alternative exposure limit. The identification of mesenteric and mandibular lymph node hyperplasia is problematic due to its potential oncogenic implications. A NOEL for these effects was not identified and effects were not screened in low dose groups. Other effects, which are not directly related to cholinesterase inhibition, were also noted with terbufos exposure, including optic damage at 0.0125 mg/kg-day in multiple species and studies. In addition, there is uncertainty regarding a safe exposure level to prevent adverse developmental effects, as discussed above. These results warrant further evaluation and may be considered, by some, to justify an additional modifying factor to deal with data gaps and uncertainties in the data base.

Summary of EPA Risk Values

Chronic Toxicity	2.5×10^{-5} mg/kg-day
Carcinogenicity	Insufficient data to determine carcinogenic status

Major Sources: HSDB,1993, tox one-liners (EPA, 1992f)

Chlorophenoxy Herbicides

5.6.18. Oxyfluorfen

Background

Oxyfluorfen is a recently introduced diphenyl ether pesticide in the chlorophenoxy class. Limited data were located on this chemical.

Pharmacokinetics

No data were located.

Acute Toxicity

The acute oral LD50 in rats is greater than 5000 mg/kg (Hayes and Laws, 1991).

Chronic Toxicity

IRIS provides an RfD of 3×10^{-3} mg/kg-day based upon a NOAEL of 0.3 mg/kg-day from a 1977 twenty month mouse feeding study which identified nonneoplastic lesions in the liver and increased absolute liver weight. Uncertainty factors of 10 each for inter- and intraspecies sensitivity were applied (IRIS, 1993).

Developmental Toxicity

A three-generation rat study provided a NOEL of 0.5 mg/kg-day and an LEL of 5 mg/kg-day. A rat teratology study identified a fetotoxic NOEL of 100 mg/kg-day. A rabbit study found fused sternebrae at 30 mg/kg-day and a NOEL of 10 mg/kg-day (IRIS, 1993, EPA, 1993l). A rabbit teratology study data gap is noted in the IRIS file (IRIS, 1993). Nitrofen, a close structural relative of oxyfluorfen has been studied more extensively. Studies of nitrofen identified multiple varied developmental abnormalities associated with prenatal exposure (Hayes, et al., 1991).

The multigeneration study is the most sensitive study of those reviewed; this may be due to the longer period of exposure and follow up than the prenatal exposure studies. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability. Additional information is needed on the nature of effects at the LEL.

Mutagenicity

Results of mutagenicity assays on oxyfluorfen are mixed (EPA, 1993l).

Carcinogenicity

Oxyfluorfen has been classified as a possible human carcinogen (C) based upon liver tumors identified in experimental animals. A cancer potency of 0.13 is provided by OPP (EPA, 1992d).

Interactive Effects

No data were located.

Critical Data Gaps

The IRIS file notes a rabbit teratology study as a data gap.

Summary of EPA Risk Values

Chronic Toxicity	3×10^{-3} mg/kg-day
Carcinogenicity	0.13 per mg/kg-day

Major Sources: IRIS (1993), tox one-liners (EPA, 1993l)

Polychlorinated Biphenyls

5.6.19. PCBs

Background

Polychlorinated biphenyls (PCBs) are a mixture of chlorinated biphenyl chemicals which occur individually as 209 congeners, comprised of various chlorine substitution patterns. Mixtures of PCBs were marketed under the trade name Aroclor, with a numeric designation that indicated their chlorine content. Although production and use were banned in 1979, the chemical group is extremely persistent in the environment and bioaccumulates through the food chain. There is evidence that the most potent, dioxin-like PCB congeners are preferentially accumulated in higher organisms. Consequently, the aggregate toxicity of a PCB mixture may increase as it moves up the food chain (EPA, 1993a). As a result of this, the composition of commercial PCB mixtures may differ significantly from that actually found in fish tissue. Often the mixtures of interest are not those which have been used in studies of laboratory animals to determine toxicity. The preferable studies, under these conditions, are those which utilize human dose-response data from populations who have consumed PCBs via fish. When reliable human data are lacking, animal data may need to be used.

PCB exposure is associated with a wide array of adverse health effects in human and experimental animals (as discussed below). Many effects have only recently been investigated (e.g., hormonal effects), and the implications of newer studies are not fully known. The health effects of PCBs are still under active evaluation and currently there is not sufficient information on the specific congeners to develop congener-specific quantitative estimates of health risk (EPA, 1993a). Due to the lack of congener-specific information, the Office of Water recommends, as an interim measure, that total PCB concentrations reported as the sum of Aroclors. The first volume in this document series, *Sampling and Analysis*, contains a detailed discussion of analysis of this group of chemicals (EPA, 1993a).

Pharmacokinetics

PCBs are absorbed through the GI tract and distributed throughout the body. The highest concentrations are found in adipose tissue. According to ATSDR, human milk may contain a large amount of PCBs due to their high fat content (ATSDR, 1993d). A Canadian study found human milk concentrations more than 10 times higher than whole blood concentrations. The PCB congener composition of milk differs from the exposure composition of PCBs. Offspring can be exposed to PCBs via milk and through transplacental transfer. PCBs

have also been measured in other body fluids including plasma, follicular fluid, and sperm fluid. For a more extensive discussion of this topic see ATSDR (1993d).

The retention of PCBs in fatty tissue is linked to metabolism, with higher chlorinated PCBs persisting for longer periods of time. Pharmacokinetic modeling of PCB disposition indicates that PCB movement in the body is a dynamic process, with exchanges between various tissues that depend on fluctuating exposure levels to specific congeners. The result is clearance of congeners that are more easily metabolized and retention or those which resist metabolism (ATSDR, 1993d). Studies of individual chlorobiphenyl congeners indicate, in general, that PCBs are readily absorbed, with oral absorption efficiency of 75 to greater than 90 percent in rats, mice and monkeys (IRIS, 1994). Indirect evidence of oral absorption in humans is available in studies of PCB-contaminated fish (IRIS, 1994).

Studies indicate that the metabolism of PCBs by monkeys and rats is more similar to humans than other species tested (IRIS, 1994). There are limited data on the half-life of the various PCBs in humans. Under environmental exposure conditions in China, half-lives ranged from four to 21 months and from three to 12 months for two 5-chlorine PCBs. A detailed discussion of PCB pharmacokinetics is available in the ATSDR Toxicological Profile for Selected PCBs (ATSDR, 1993d).

PCBs induce mixed function oxidases and different congeners induce specific forms (isozymes) of the cytochrome P-450 system. Many of the PCB congeners also bind to the Ah receptor, which regulates the synthesis of a variety of proteins. Although there has been much research into the mechanisms of PCB toxicity, there has not been clear definition of the mechanisms for most congeners. The congeners appear to act by a variety of mechanisms (ATSDR, 1993d), and the resulting toxicity will vary depending on the mixture of congeners to which an individual is exposed.

Acute Toxicity

The lethal doses observed in experimental animals do not indicate that PCBs would be acutely toxic to humans (ATSDR, 1993d). Based upon study results obtained for TCDD, it is suggested that exposure to TCDD-like PCBs may result in delayed lethality. Immature animals appear to be more sensitive to acute lethal effects of PCBs than adults (ATSDR, 1993d).

Chronic Toxicity

PCBs have a high chronic exposure toxicity. Dietary doses in animals of 0.1 to 1 mg/kg-day over many months may be lethal (ATSDR, 1993d). Based upon human and animal studies, chronic oral exposure to PCBs affects numerous organ systems including the cardiovascular, GI, hematological, musculoskeletal, hepatic, renal, dermal, immunological, neurological, and reproductive systems (ATSDR, 1993d).

Information has been recently added to IRIS (1994) regarding toxicity of Aroclor 1254. A monkey study found ocular effects and distorted growth of finger and toe nails at the lowest dose tested of 0.005 mg/kg-day. Significant reductions in IgM and IgG in response to injected sheep red blood cells were also seen at the lowest dose tested. On the basis of these effects a LOAEL of 0.005 mg/kg-day was established. Uncertainty factors of 10 for sensitive individuals, 3 for extrapolation from monkeys to humans and 3 for extrapolation from a subchronic exposure to a chronic RfD, and 3 for use of a minimal LOAEL. This yields an RfD of 2×10^{-5} mg/kg-day (IRIS, 1994). This new RfD is lower than the RfD which is available for Aroclor 1016 (discussed below under developmental toxicity) and is, consequently, protective against both chronic systemic toxicity and developmental toxicity. Therefore, the RfD for Aroclor 1254 was used to calculate the consumption limits for non-carcinogenic effects listed in Section 3.

ATSDR has determined that immunological effects are a sensitive endpoint for chronic toxicity and developed a MRL of 2×10^{-5} mg/kg-day based on such effects (ATSDR, 1993d). The studies used as the basis for the MRL are the same as those listed above in the IRIS discussion. Uncertainty factors of 10 each for the use of a LOAEL and for human variability were used. A factor of 3 was used for extrapolation from animals to humans. Decreased IgG and IgM levels were noted. Chronic toxicity in other organ systems (as listed above) was noted at exposure levels higher than the LOAEL of 0.005 mg/kg-day (ATSDR, 1993d).

Developmental Toxicity

All PCB mixtures tested have caused developmental effects in experimental animals (ATSDR, 1993d). Several human studies have also suggested that PCB exposure may cause adverse effects in children and to developing fetuses (EPA, 1993a). As with all epidemiological studies, there are difficulties in these studies with confounding variables. Other problems with the studies include exposure assessment, selection of exposed and control subjects, and the comparability of exposed and control samples (ATSDR. 1993d).

The IRIS RfD for Aroclor 1016 is based upon developmental toxicity observed in a 22 month monkey study (discussed below under longer-term developmental studies), with a NOAEL of 0.007 mg/kg-day. The following uncertainty factors were applied to calculate the RfD: 3 for sensitive individuals (infants exposed transplacentally), 3 for interspecies extrapolation, and 3 due to the limitations of the data base (male reproductive effects are not directly addressed in studies and two-generation reproductive studies are not available). This yields an RfD of 7×10^{-5} mg/kg-day (IRIS, 1994). Readers may elect to use this value to develop alternative consumption limits which are specifically designed for women of reproductive age. However, this approach is not recommended because the developmental toxicity-based RfD was not designed to be protective against the effects discussed under chronic toxicity for Aroclor 1254. Consequently, if the sum of the Aroclors-approach is used in developing fish advisories, the use of the value for Aroclor 1016 may not be protective against adverse effects of all Aroclors.

The following discussion of developmental toxicity contains study information in the following order: human data, short-term, intermediate length, and longer-term studies, and a summary.

A study was conducted of pregnancy outcomes in women who had consumed PCB contaminated fish from Lake Michigan over an average of 16 years (exposure both prior to and during pregnancy). Exposure quantification was not precise; however, it has been estimated that the average exposure was 5×10^{-4} mg/kg-day. Contaminated fish consumption correlated with maternal serum PCB levels. Children whose mothers were exposed had significantly lower birth weights, smaller head circumferences, shorter gestational ages, and poorer neuromuscular maturity; at seven months the children had subnormal visual recognition memory. The exposure estimates in this study were not precise and varied widely; the recall ranged over a number of years with a mean consumption duration (as noted above) of 16 years and the PCB concentrations in different types of fish of 168 ppb to 3012 ppb. The study results were confounded by exposure to other chemicals and the fact that the exposed group, on average, drank more alcohol and caffeine, prior to and during pregnancy, weighed more, and took more cold medications during pregnancy, than the non-exposed group (review in Shubat, 1993a).

A pharmacokinetic approach to estimating safe exposure levels has been taken by the Great Lakes Sport Fish Advisory Task Force using the Michigan study data (Anderson and Amrhein, 1993). This approach utilized relationships between milk PCB concentrations, fish intake and concentrations, and developmental effects. Assumptions were made regarding body weight (60 kg), percentage of body fat (25 percent), and the biological half-life of PCBs in humans (one year) (Anderson and Amrhein, 1993). The pharmacokinetic

approach has the potential for introducing more precision to the process of estimating thresholds and evaluating dose-response relationships. However, it relies on the use of many physiological variables, as well as dose and response values. In the specific case of the Great Lakes approach, there is concern that the assumptions which were made for the "average" women and "average" body fat composition do not take into consideration the 49 percent of women who have above-average values. Although this variability would introduce minimal alterations at values near the average, there could be significant deviation from predicted values at the 75th or 90th percentiles. The approach also assumes that reproduction occurs at 25 years of age with the estimated body burden based upon this assumption (Anderson and Amrhein, 1993). Maternity over the age of 25 would entail greater exposure to the fetus due to the higher maternal body burden associated with a longer accumulation period.

A study of the children of women with background body burdens of PCBs in North Carolina was recently conducted which noted much more moderate effects of PCB exposure, with no changes in birth weight or head circumference. The authors reported that deficits observed through two years of age were not detectable at ages three, four, and five, based on intellectual and motor function assays. Exposure was confounded by the presence of DDE in blood and milk samples from the mothers. This study utilized body burdens, rather than intake as measure of exposure (ATSDR, 1993d).

Studies of women who have spontaneously aborted, miscarried, or delivered prematurely have found an association between these effects and concentrations of PCBs in maternal blood (ATSDR, 1993d).

The results of animal studies generally support the occurrence of neurotoxic effects following prenatal and neonatal childhood exposures to PCBs. Short-term studies in animals exposed prenatally to PCBs have identified the following effects: hydronephrosis in mice with a single dose of 244 mg/kg (Aroclor 1254); no effects in mice with 12 days of dosing up to 12.5 mg/kg-day (Aroclor 1254); fetal weight reduction in rats with nine days of dosing at 5 mg/kg-day with reduced survival at 15 mg/kg-day and a NOEL of 2.5 mg/kg-day (Aroclor 1254); impaired learning in rats at 4 mg/kg-day with 10 days of dosing (Fenclor 42). Decreased survival was observed at higher doses. Based on the results of short-term exposure assays, ATSDR concluded that neurobehavioral endpoints may be the most sensitive for assessing developmental effects.

Intermediate-length exposure studies (e.g., during the prenatal and lactational periods) indicate neurological, thyroid, liver, growth, and hormonal abnormalities in offspring. Reduced litter size was also observed. The lowest NOAEL in this group of studies was observed in rats at 0.13 mg/kg-day, with

increased relative liver weight being the indicator of effects. This effect alone may not indicate toxicity; however, other types of liver toxicity were observed at higher doses. A LOAEL of 0.18 mg/kg-day was observed in mink which found delayed growth and 89 percent neonatal death at this exposure level. Mink and monkeys appear to be more sensitive species for PCB-induced developmental toxicity than rodents (ATSDR, 1993d).

Longer-term developmental toxicity studies have been conducted on the offspring of monkeys exposed over 12 to 22 month periods. Three different studies have identified NOAELs in the range of 0.007 to 0.008 mg/kg-day. In a study which found birth weight reduction at 0.03 mg/kg-day, a NOAEL of 0.007 mg/kg-day was established. In two studies which focused on neurological abnormalities, exposure at 0.03 and 0.08 mg/kg-day was associated with decreased performance in spatial learning and memory tasks. The neurological effects NOAEL for both of these studies was 0.008 mg/kg-day. Dose-related early abortions and low birth weight were associated with prenatal exposures of 0.1 and 0.2 mg/kg-day, along with multiple gross and microscopic organ system abnormalities. At 0.1 mg/kg-day prenatal exposure, multiple studies in monkeys have identified PCB intoxication in offspring (acne, swollen eyelids, loss of eyelashes, and hyperpigmentation of the skin) (ATSDR, 1993d).

In summary, the two sets of human studies carried out in Michigan and North Carolina both indicate a strong association between PCB exposure and adverse reproductive outcomes. However, there are serious deficits in the studies regarding exposure quantification and confounding exposures to other developmental toxics. The primary concern is with the quantification of exposure. Although it is preferable to use dose-response data from human studies, readers may wish to consider the results of the primate studies in developing consumption limits for developmental effects, due to deficits in the human studies. Primates are similar to humans in neurological development and the primate studies focused on a sensitive indicator of developmental toxicity: neurological effects. This was also the organ system of primary concern in children in many human studies. The primate studies evaluated higher cognitive functions rather than more basic neurological effects, such as reflex actions. Effects on higher cognitive function appear to occur at lower levels of exposure than effects on gross motor function or reflexes. The IRIS value for Aroclor 1016 (provided above) is based on a primate toxicity study.

Exposure via lactation is a significant concern for neonates. Animal studies indicate that lactational exposure may be more significant than prenatal exposure. In monkeys, signs of PCB intoxication were observed in lactationally-exposed offspring, but not in offspring exposed only prenatally (ATSDR, 1993d). Consequently, it is recommended that additional research be carried

out to establish a correlation between prenatal and lactational exposure in the human population and the occurrence of neurological effects in children.

Mutagenicity

IRIS reports that the majority of mutagenicity assays of PCBs have been negative (IRIS, 1993 file for Aroclor 1260).

An increase in the percentage of chromosomal aberrations in peripheral lymphocytes was reported in workers manufacturing PCBs for 10 to 25 years. Increased sister-chromatid exchange was also reported. The study was controlled for smoking and drinking; however, concurrent exposure to formaldehyde and benzene occurred (ATSDR, 1993d).

ATSDR reports that most *in vitro* assays and *in vivo* animal assays yielded negative results, although both positive and negative results were reported. Positive study results include an increase in unscheduled DNA synthesis (ATSDR, 1993d). See also Interactive Effects below.

Carcinogenicity

PCBs are classified by EPA as probable human carcinogens (Group B2). The carcinogenic potency of the individual PCBs vary with their structure. A cancer potency of 7.7 per mg/kg-day, derived from studies of Aroclor 1260, is listed in IRIS, and was used to calculate fish consumption limits (IRIS, 1993). It is suggested that this value be applied to the sum of the Aroclors (EPA, 1993a).

Human epidemiological studies of PCBs have not yielded conclusive results. As with all epidemiological studies, it is very difficult to obtain clear unequivocal results due to the long latency period required for cancer induction and the multiple confounders arising from concurrent exposures, lifestyle differences, and other factors.

A recent study of PCBs and pesticides in human breast lipids has found an association between elevated levels of these chemicals and breast cancer (Falck, et al, 1992).

Special Susceptibilities

ATSDR has indicated that embryos, fetuses, and neonates are unusually susceptible to PCBs, due to their underdeveloped enzymatic systems which may cause delayed elimination and, therefore, accumulation of PCBs in the body. Breast-fed infants are at particular risk because a steroid secreted in

human milk, but not cows' milk, inhibits glucuronyl transferase activity, which is critical to PCB metabolism and excretion (ATSDR, 1993d).

Other individuals at potentially greater risk include those with syndromes associated with incompletely developed glucuronide conjugation mechanisms, those with hepatic infections, compromised liver functions, or acute intermittent porphyria (ATSDR, 1993d).

Due to effects noted on the cardiovascular, GI, hematological, musculoskeletal, hepatic, renal, dermal, immunological, neurological, and reproductive systems, individuals with diseases or disorders of these systems may be at greater risk. In addition, PCBs cause induction of the mixed function oxidase system. Individuals exposed to chemicals (including pharmaceuticals) which rely on the mixed function oxidase system for activation or detoxification may experience altered effectiveness of the chemicals. This is discussed in Section 5.5 under "Organochlorines."

Interactive Effects

PCBs induce microsomal enzymes. See Section 5.5 under "Organochlorines" for potential interactions arising from this characteristic.

ATSDR reports that:

> "it is well established that the addition of liver microsomal preparations from PCB-treated animals to *in vitro* genotoxicity assays potentiates the genotoxic activity of numerous carcinogens by activation to reactive intermediates and proximate carcinogens" (ATSDR, 1993d).

Mixtox reports potentiation between PCBS and Mirex in a rat dietary study. Other studies of this combination have not found interactive results (MIXTOX).

Critical Data Gaps

A joint team of scientists from EPA, ATSDR, and NTP have identified the following data gaps: human epidemiological studies; genotoxicity studies of various mixtures of PCBs including cytogenetic analysis of human populations exposed to PCBs; reproduction studies in humans and animals including fertility studies in males of a sensitive species; developmental studies including histological examination of developing neurological tissues in experimental animals, neurodevelopmental studies designed to identify NOAELs, and immunological studies in developing animals; immunotoxicity studies in humans and animals; neurotoxicity studies in humans with high PCB body burdens and

in animals; chronic studies to determine the most sensitive animal target organ and species; human studies on PCBs and hypertension and liver toxicity; pharmacokinetic studies; and studies to elucidate the differing toxicities of the various congeners comprising PCB mixtures (ATSDR, 1993d).

Summary of EPA Risk Values

Chronic Toxicity	7×10^{-5} mg/kg-day based upon Aroclor 1254
Carcinogenicity	7.7 per mg/kg-day based upon Aroclor 1260

Major Sources: IRIS for Aroclor 1254, 1260, and 1016 (1993 and 1994), ATSDR (1993d), HSDB (1993)

Dioxins

5.6.20. Dioxin

Background

Dioxin is undergoing extensive review within EPA. Consequently, only a brief summary, taken from the **Sampling and Analysis Guidance**, is provided below. It is anticipated that EPA will provide the results of a detailed evaluation of dioxin toxicity in the very near future.

Dioxin is a generic term which is used, in this case, to specify 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It is recommended that the seventeen 2,3,7,8- substituted tetra- through octa-chlorinated dibenzo-p-dioxins and dibenzofurans be considered together as a simplifying and interim approach until further guidance is available on this chemical. Alternatively, the reader may consult guidance on the use of a toxicity equivalency approach to refine the toxicity estimate and fish consumption limit calculations (Barnes and Bellin, 1989, U.S. EPA, 1991c).

Dioxin is extremely toxic to humans and animals and affects multiple organ systems. Adverse effects observed in animal studies include teratogenicity, fetotoxicity, reproductive dysfunction, carcinogenicity, and immunotoxicity (EPA, 1993a). Dioxin has the highest cancer potency in animals of the chemicals evaluated by EPA. A cancer risk based health advisory can be calculated using the existing cancer potency value of $1.56 \times 10^{+5}$ per mg/kg-day (EPA, 1993a).

Summary of Risk Values

Carcinogenicity	$1.56 \times 10^{+5}$ per mg/kg-day

Major Source: EPA (1993a)

Metals

5.6.21. Cadmium

Background

Cadmium is a heavy metal which is released through a wide variety of industrial and agricultural activities. It accumulates in human and other biological tissue and has been evaluated in both epidemiological and toxicological studies. ATSDR has determined that exposure conditions of most concern are long-term exposures to elevated levels in the diet (ATSDR, 1993a).

The FDA has estimated that cadmium exposure among smokers is approximately 10 μg/day (0.01 mg/day). Passive exposure of non-smokers may also be a source of exposure (U.S.FDA, 1993). This should be considered in evaluating the total exposure and risks associated with cadmium.

Pharmacokinetics

Cadmium is not readily absorbed when exposure occurs via ingestion. Most ingested cadmium passes through the GI tract without being absorbed. Studies in humans indicate that approximately 25 percent of cadmium consumed with food was retained in health adults after three to five days; this value fell to six percent after 20 days. Absorption may be much higher in iron deficient individuals. Evaluations of the impact of cadmium complexation indicate that cadmium absorption from food is not dependent upon chemical complexation. However, some populations with high dietary cadmium intakes have elevated blood cadmium levels, and this may be due to the particular forms of cadmium in their food (ATSDR, 1993a).

Cadmium absorption studies in animals indicate that the proportion of an oral dose which is absorbed is lower in animals than in humans. Absorption is elevated during pregnancy, with whole-body retention in mice of 0.2 percent in those that had undergone pregnancy and lactation and 0.08 percent in those that had not. In rats absorption decreased dramatically over the early lifetime ranging from 12 percent at two hours to 0.5 percent at six weeks after birth. The placenta may act as a partial barrier to fetal exposure, with cord blood concentrations being approximately half those of maternal blood. The human data on placental concentrations are conflicting. Cadmium levels in human milk is approximately five to 10 percent of those found in blood (ATSDR, 1993a).

Cadmium absorption appears to involve sequestering by metallothionein, and plasma cadmium is found primarily bound to this protein. This binding appears

to protect the kidney from otherwise toxic effects of cadmium. It has been suggested that kidney damage by cadmium occurs primarily due to unbound cadmium (ATSDR, 1993a). Once cadmium is absorbed, it is eliminated slowly; the biological half-life has been estimated at 10 to 30 years (U.S. FDA, 1993).

Body stores of iron, zinc and calcium may affect absorption and retention, although the retention may not be in readily available tissues (e.g., intestinal wall versus blood). The greatest concentrations of cadmium are typically found in the liver and kidney. Cadmium is not directly metabolized, although the cadmium ion binds to anionic groups in proteins, especially albumin and metallothionein (ATSDR, 1993a).

Acute Toxicity

Effects of acute oral exposure to cadmium include GI irritation, nausea, vomiting, abdominal pain, cramps, salivation, and diarrhea. In humans lethal doses caused massive fluid loss, edema and widespread organ destruction. The ingested doses were 25 mg/kg and 1500 mg/kg (ATSDR, 1993a).

Chronic Toxicity

Kidney toxicity is a significant concern with cadmium exposure. Increased death rates from renal disease have been observed in exposed human populations in Belgium, England, and Japan (ATSDR, 1993a). There are also extensive animal data indicating that the kidney is a target organ. IRIS contains an RfD of 0.001 mg/kg-day in food based upon a NOAEL of 0.005 mg/kg-day in multiple human studies of waterborne cadmium. The critical effect was significant proteinuria (an indicator of kidney toxicity). To calculate the RfD, it was assumed that 2.5 percent of cadmium in food was absorbed and approximately five percent in water was absorbed. Using an uncertainty factor of 10 to account for intrahuman variability in cadmium sensitivity, the RfD for cadmium in food was calculated to be 0.001 mg/kg-day. The RfD was calculated using a toxicokinetic model to determine the highest level of cadmium in the human renal cortex not associated with significant proteinuria (IRIS, 1993).

The FDA has calculated a tolerable daily intake of 55 μg/person/day, which is approximately equal to 0.78 μg/kg/day (7.8×10^{-4} mg/kg-day) in a 70 kg person and 5.5 μg/kg/day (0.005 mg/kg-day) in a 10 kg child (their example uses 2+ years of age). The FDA value is based upon a pharmacokinetic approach which utilized the critical body burden associated with kidney toxicity. See FDA (1993) for more details.

ATSDR has also recently calculated a risk value for oral exposure based upon kidney toxicity in humans. They developed a chronic MRL of 7×10^{-4} mg/kg-day based upon a NOAEL of 0.0021 mg/kg-day in a large human cohort. The critical endpoint was an elevation of urinary beta-(2)-microglobulin. A toxicity threshold was estimated using a kinetic model of cadmium metabolism which predicted that approximately five percent of non-smokers will reach or the dose required to cause an effect at the NOAEL. To calculate the MRL, ATSDR used an addition uncertainty factor of 3 to account for sensitive members of the population. However, the critical study used a large population which included the elderly, who are considered a sensitive subpopulation (ATSDR, 1993a). The MRL developed by ATSDR is within one order of magnitude of the RfD developed by IRIS.

Cadmium causes many other types of toxic effects in addition to nephrotoxicity. In humans some studies have suggested an association between neurotoxicity and cadmium exposure, at levels below those which cause kidney toxicity (no additional details available). Cadmium exposure reduces the GI uptake of iron which may cause anemia if iron intakes are low. Bone disorders including osteomalacia, osteoporosis and spontaneous bone fracture have been observed in some chronically exposed individuals. Increased calcium excretion associated with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in post-menopausal women, many of whom are already at risk of osteoporosis. Cardiovascular toxicity and elevated blood pressure has been suggested in some human studies; however, the results are conflicting (ATSDR. 1993a).

Animal studies indicate that cadmium causes a wide variety of alterations in the function of the immune system. Some aspects of the systems were enhanced and others were impaired (e.g., susceptibility to virally-induced leukemia). In short-term studies serious effects occurred at levels as low as 1.9 mg/kg-day and less serious effects (induction of anti-nuclear antibodies) at 0.57 mg/kg-day in a ten week study in mice (ATSDR, 1993a). No longer term studies were located for this work. An alternative exposure could be calculated for immunological effects based upon the above study. The standard uncertainty factors used in this calculation would typically take into consideration inter- and intraspecies variability, use of a less than lifetime study, and the use of a LOAEL rather than a NOAEL. Immunological effects require further investigation to determine whether this is an effect which occurs in humans. It appears to be a sensitive endpoint for chronic exposure toxicity.

Developmental Toxicity

Developmental toxicity has been associated with cadmium exposure both in short and long term studies. In ten day prenatal dosing studies in rats at 18.4

mg/kg, malformations including split palate and dysplasia of the facial bones were observed with a NOAEL of 6.1 mg/kg-day. A similar study in rats found delayed ossification at 2 mg/kg-day. Other studies have found gross abnormalities and reduced weight in the range of 2 to 20 mg/kg-day (ATSDR, 1993a). Oral cadmium exposure of young mice depresses their humoral immune responses; the study did not find the same effect in adult mice (ATSDR, 1993a).

More sensitive measures of effects for cadmium have identified effects at much lower doses. ATSDR has determined that:

> "the most sensitive indicator of development toxicity of cadmium in animals appears to be neurobehavioral development, which was impaired in offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg-day prior to and during gestation..." (ATSDR, 1993a).

Reduced locomotor activity and impaired balance were noted at a LOEL of 0.04 mg/kg-day with 11 weeks of exposure occurring prior to and during gestation. The effects were also observed at 0.7 mg/kg-day with exposure occurring only during gestation. Neurobehavioral effects were observed in other developmental studies and in chronic studies of effects in adult animals. Two studies yielding similar results were conducted with maternal exposures of 4.3 to 17.2 μg/ml of water (See numerous citations in Baranski,et al., 1983).

Studies of developmental toxicity in human populations have been conducted on women exposed via inhalation in the workplace. Decreased birth weight has been reported in two studies, one with statistically significant results and the other lacking statistical significance. Inhalation studies in animals have found structural and neurobehavioral abnormalities similar to those found in the oral dosing studies (ATSDR, 1993a).

Based on the mutagenicity data results (discussed below), heritable defects may result from exposure to cadmium. However, mutagenicity assays do not provide dose-response data suitable for use for the calculation of a risk value. Calcium deficiency has been shown to increase the fetotoxicity of cadmium, and lindane exposure increased developmental toxicity in animal studies (ATSDR, 1993a).

Based on the reviewed information, neurobehavioral effects appear to be a critical endpoint for developmental effects as indicated by the LOEL of 0.04 mg/kg-day. The standard uncertainty factors used in the calculation of an exposure limit would typically take into consideration inter- and intraspecies variability, and the use of a LOEL rather than a NOAEL.

Estimating an exposure limit for cadmium based on developmental toxicity is problematic because the average daily dose is approximately 0.03 mg/day (ATSDR, 1993a) which is equivalent to 4×10^{-4} per mg/kg-day in a 70 kg individual. The exposure for developmental effects which would be calculated using the neurobehavioral LOEL noted above (approximately 4×10^{-5} mg/kg-day) is one tenth of the average background consumption rate. Due to the margin of safety introduced by these factors, the estimated exposure limit should be viewed in the context of the overall exposure of population groups from all sources, as well as the benefits of fish consumption. Balancing risks and benefits is discussed in Volume 3 in this series, *Risk Management.*

Mutagenicity

Results of bacteria, yeast, and human lymphyocyte assays have been mixed. Positive results were observed in chromosomal aberration studies on human lymphocytes treated both *in vitro* and obtained from exposed workers. Mouse and hamster germ cell studies indicate that cadmium may interfere with spindle formation resulting in aneuploidy. Positive results have also been obtained in Chinese hamster ovary and mouse lymphoma cell assays (IRIS, 1993).

Carcinogenicity.

No animal or human oral exposure studies suggest that cadmium is carcinogenic via the oral exposure route. Animal studies conducted at relatively low exposure levels (up to 4.4 mg/kg-day) have yielded negative results. Studies have been conducted on population groups in high cadmium exposure areas and organ-specific cancer rates have been examined (kidney, prostate, and urinary tract). Most studies yielded negative results. A study in Canada found that elevated rates of prostate cancer paralleled the elevated cadmium exposure of the populations studied. ATSDR concluded that there was little evidence of an association between cadmium exposure and increased cancer risk in humans but that the statistical power of the studies to detect an effect was not high. They determined that neither the human or animal studies provided sufficient evidence to determine the carcinogenic status of cadmium (ATSDR, 1993a).

Cadmium is classified as a probable human carcinogen (B1) by EPA based on **inhalation** studies in humans. The airborne cancer potency is 1.8×10^{-3} per μg/cubic meter (IRIS, 1993).

Special Susceptibilities

Populations with genetically-determined lower ability to induce metallothionein are less able to sequester cadmium. Populations with depleted stores of dietary

components such as calcium and iron due to multiple pregnancies and/or dietary deficiencies may have increased cadmium absorption from the GI tract. As stated above, increased calcium excretion associated with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in post-menopausal women. The relationship between cadmium toxicity and iron levels is not well established; however, in some studies it appears that iron deficient individuals may be at greater risk. Individuals with kidney disease, diabetes, and age-related decreased kidney function may be at greater risk of cadmium-induced kidney toxicity (ATSDR, 1993a).

Immunological effects may be of concern for children because it appears, based upon animal studies, that young individuals may be at greater risk than adults. In addition, the immune system is not fully developed in humans until approximately 12 years of age. Immunological effects have also been observed in multiple animal studies of adults. These pose special risks for individuals with compromised immune systems (e.g., those with AIDS).

A variety of types of developmental effects have been associated with cadmium exposure (See discussion above). These all pose special risks for infants and children, as well as women having or planning to have children.

Interactive Effects

Dietary deficiencies of calcium, protein, zinc, copper, iron, and vitamin D may cause increased susceptibility to adverse skeletal effects. Animal studies have found an association between lindane and increase developmental toxicity and between calcium deficiency and increased fetotoxicity. Ethanol increased liver toxicity and garlic decreased kidney toxicity. Lead increased neurotoxicity and selenium decreased the clastogenic effect of cadmium on bone marrow. Exposure to chemicals that induce metallothionein (e.g., metals) reduced toxicity with parenteral cadmium exposure (ATSDR, 1993a).

MIXTOX reports a number of interactive studies on cadmium and selenium compounds. The studies have yielded mixed results with reports of inhibition, potentiation, additive effects and no effects (MIXTOX, 1992).

Critical Data Gaps

A joint team of scientists from ATSDR, NTP, and EPA have identified the following data gaps: immunotoxicity, neurotoxicity, and developmental toxicity in human populations, quantitative data on acute and intermediate toxicity in humans, and chronic exposure studies in humans using sensitive indicators of kidney toxicity, animal and human studies of carcinogenic effects, human

genotoxicity, animal reproductive, immunotoxicity, and pharmacokinetic studies (ATSDR, 1993a).

Summary of EPA Risk Values

Chronic Toxicity	1×10^{-3} mg/kg-day
Carcinogenicity	Probable inhalation carcinogen (B1). Insufficient data to determine carcinogenic status via oral exposure route.

Major Sources: IRIS (1993), ATSDR (1993a), HSDB (1993), U.S. FDA (1993)

5.6.22. Methylmercury[12]

Background

Mercury is widely distributed in the environment due to both natural and industrial processes. Mercury is transformed through biological processes; in fish it is found primarily in the form of methylmercury (EPA, 1993a). The data regarding methylmercury toxicity are undergoing review within EPA. An IRIS RfD is discussed below and was used to develop the consumption limits for the general population. In addition, an interim dose-response value developed by the Office of Water was used in this document to calculate the fish consumption limits for women of reproductive age and for children (See discussion under developmental toxicity below). Methylmercury has also been the subject of evaluation by numerous states. Detailed analyses have been conducted in some areas, which included evaluations of data regarding blood and hair mercury levels, toxic effects, and biological half-life to estimate safe consumption levels of contaminated fish (Shubat, 1991 and 1993a; Stern, 1993).

As discussed in previous sections, a total exposure assessment is beyond the scope of this document. Readers may wish to consult other sources to obtain information regarding background levels of methylmercury in the environment. Additional information on dietary sources of mercury may be found in the FDA Adult Total Diet Study, conducted from October 1977 through September 1978, which contains information on total mercury content (not restricted to methymercury) in a number of foods (Podrebarac, 1984). Average airborne exposure has been estimated for total mercury (elemental and methylmercury) at 0.14 ug/day based upon an average ambient concentration of 7 ng/cubic meter (Bennett, 1986); however, recent studies indicate that the levels may be increasing (Slemr and Langer, 1992).

[12] Methylmercury is an organic form of mercury which has similar toxicological properties to other organic mercury forms. There are significant differences in the toxicity of metallic, inorganic and organic mercury (ATSDR, 1992a). Based on a review of the toxicity of various forms of mercury, it is assumed in this document that data on inorganic mercury and mercury in its pure metallic form are less relevant to fish contamination than organic mercury, and they are not used in evaluating health effects.

Pharmacokinetics

Organic mercury compounds are rapidly and nearly completely absorbed (95 percent) following oral exposure (ATSDR, 1992a).[13] The World Health Organization (WHO) has similarly estimated an absorption of 90 to 100 percent for methylmercury (WHO, 1990). Methylmercury is lipophilic, allowing it to pass through lipid membranes of cells and facilitating its distribution to all tissues, following absorption from the GI tract. Methylmercury also binds readily to proteins.[14] The highest methylmercury levels in humans are generally found in the kidney. Methylmercury and other organic mercury compounds are transformed via the oxidation reduction cycle into an inorganic form in most tissues, most significantly in the liver, kidney and brain. The location of methylmercury in the brain shifts following exposure; this is probably related to biotransformation (ATSDR, 1992a). Methylmercury causes disruption of several enzyme systems, primarily sulfhydryl enzymes (HSDB, 1993). It also destroys microtubules which are critical to various physiological and developmental functions (additional information is provided under developmental toxicity below) (Clarkson, et al., 1987).

Methylmercury has been reported to occur in breast milk in women exposed to methylmercury in fish and bread in Iraq. The concentration measured in breast milk was approximately 5 percent of the methylmercury level in the blood of the mother (WHO, 1976). In experimental animals, females eliminated mercury more slowly than males, and young animals more slowly than adults. Neonatal excretion is slowed by the immaturity of the transport system. Methylmercury readily transverses the placental barrier. Often higher concentrations are found in fetal organs than in maternal organs. Methylmercury is secreted during lactation and is eliminated primarily via the biliary system. The estimated half-life of organic mercury is 70 to 79 days. (ATSDR, 1992a).

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[13] The ATSDR document cited in this work (ATSDR, 1992a) refers to methylmercury under the broader heading of organic mercury. Consequently, when cited information is taken from the ATSDR document, mercury is referred to as "organic" mercury.

[14] Methylmercury is found throughout fish tissue and a substantial portion of the mercury in fish can be found in a trimmed fillet. Because of this, methylmercury exposure is not significantly reduced by trimming fat and skin from fish.

Acute Toxicity

Acute high-level exposures to methylmercury may result in kidney damage and failure, gastrointestinal damage, cardiovascular collapse, shock, and death. The estimated lethal dose is 10 to 60 mg/kg (ATSDR, 1992a). An acute exposure MRL calculated by ATSDR using a prenatal exposure study is discussed below under developmental effects.

Chronic Toxicity

There have been numerous studies of human poisonings in various populations around the globe exposed via contaminated grain and fish. Significant population exposures to methylmercury have occurred in Minimata and Niigata, Japan in the 1950s and in Iraq in 1971-1972. More recently, exposures in New Zealand have been studied (WHO, 1976 and 1990; Stern, 1993). Summaries of human and animal data are available (WHO, 1976 and 1990; ATSDR, 1992a; Stern, 1993). The human exposure studies are often complex, due in part to the difficulty in quantifying exposure and evaluating neurological effects. In human poisoning incidents, exposure has resulted in serious neurological effects in both adults and children (children are discussed under developmental toxicity below). Readers is urged to review the data for a comprehensive understanding of the toxicity of methylmercury.

The central nervous system (CNS) is a major target organ for methylmercury-induced toxicity. Adverse effects in humans and experimental animals include a wide variety of central and peripheral nervous system disorders including neuronal degeneration, structural changes in the brain, motor incoordination, blindness, tremor, weakness, and decreased performance on behavioral tests (ATSDR, 1992a). Tilson and Sparber (1987) also provide detailed descriptions and discussions, contributed by numerous specialists in neurobiology and clinical neurology, of human, animal, and *in vitro* studies of developmental and adult neurotoxicity due to methymercury exposure.

In addition to CNS effects, numerous other systems are affected by organic mercury exposure. A study in rats found a persistent increase in systolic blood pressure following three to four weeks of exposure at 0.4 mg/kg-day. At higher exposure levels animal studies indicate that organic mercury may act on the endocrine system. Results include altered hormone levels (decreased testosterone and corticosterone levels), resulting in stress intolerance and decreased sexual activity (ATSDR, 1992a). Reproductive system functional abnormalities have been associated with methylmercury exposure. A subchronic (20 week) study in monkeys studies found decreased sperm motility and structural defects in the sperm with methylmercury exposure at 0.025 mg/kg/day. Numerous other animal studies have observed decreased fertility

with organic mercury exposure. Organic mercury exposure caused increased early abortions and stillbirths in pregnant monkeys and guinea pigs and decreased litter size in many rodent studies (ATSDR, 1992a).

The kidneys are also a major target organ for methylmercury toxicity. Kidney damage has been associated with methylmercury exposure in humans; however, exposures were not well quantified. Multiple animal studies have also noted kidney damage yielding sufficient information to estimate a kidney toxicity-based exposure limit. However, kidney toxicity does not appear to be as sensitive an endpoint as neurotoxicity based on currently available data. Although the kidney studies are of short duration, one study was identified which was of adequate duration (12 weeks) and used a sensitive endpoint (ultrastructural changes in the kidney proximal tubules). This rat feeding study identified a NOAEL of 0.08 mg/kg-day (ATSDR, 1992a). If the NOAEL from this study were used to calculate an alternative estimated exposure limit, standard uncertainty factors would typically take into consideration inter- and intraspecies variability, and the use of a less-than-lifetime study.

IRIS provides an RfD of 3×10^{-4} mg/kg-day based upon a LOAEL of 0.003 mg/kg-day in environmentally-exposed humans reporting paresthesias. An uncertainty factor of 10 was applied to adjust for the use of a LOAEL. However, it was determined that no additional uncertainty factor was required for intraspecies variability because a sensitive human population was used. The LOAEL is based upon a review of several studies and utilizes an evaluation of the levels of methylmercury in the blood in relation to toxicity. The LOAEL of 0.003 mg/kg-day is assumed to be equivalent to a mercury level of 200 ng mercury/ml of blood (IRIS, 1993). The IRIS RfD was used to calculate the consumption limits for the general adult population provided in Section 3.

ATSDR declined to estimate a chronic exposure MRL because in the study data they reviewed "serious neurological effects were observed at the lowest doses tested" (ATSDR, 1992a). This statement is based on their review of monkey and cat studies with doses of 0.05 and 0.074 mg/kg-day respectively. These studies found degeneration of the dorsal root ganglia, decreased fine motor performance, diminished pain sensitivity, reflex impairment, and spatial visual impairment associated with chronic exposure at the LOELs (ATSDR, 1992a). These studies include evaluations of behavioral and complex sensory data, which appear to be more sensitive endpoints for toxicity evaluation than those serving as the basis for the IRIS value (ataxia and paresthesias), although they are still considered too severe by ATSDR to form the basis for an MRL (ATSDR, 1992a). If the LOEL of 0.05 mg/kg-day from the monkey study were used to calculate an alternative exposure limit, standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use

of a LOEL. In addition, a modifying factor to account for the severity of effects at the LOEL could be employed.

Developmental Toxicity

As discussed under chronic toxicity above, there have been numerous studies of human poisonings in various populations around the globe via contaminated grain and fish. Summaries of the human and animal data are available (WHO, 1976 and 1990; ATSDR, 1992a; Choi, 1989 (primarily a developmental toxicity review); Burbacher et al, 1990 (primarily a developmental toxicity review); Clarkson and Fitzgerald, 1991; Clarkson, 1990; Stern, 1993); readers are urged to review the data for a comprehensive understanding of the toxicity of methylmercury.

Prenatal and childhood exposure to methylmercury has caused severe nervous system damage including retardation and a variety of nervous system disorders. Central nervous system effects include mental retardation, inability to move, paresthesias, seizures, blindness, neuromuscular weakness, and inability to speak. Less severe effects including delayed development, subtle neurologic abnormalities, irritability, and incoordination have also been reported. An underlying mechanism for CNS disturbances has been hypothesized, based upon anatomical evaluations of infants, to be the development of "abnormal cytoarchitecture of the brain (e.g., incomplete or abnormal migration of neurons to cerebellar and cerebral cortices and deranged cortical organization of cerebrum)" (ATSDR, 1992a). A detailed description of the nature of the structural and functional developmental changes seen in human populations is provided in Tilson and Sparber (1987). Although some aspects of adult methylmercury poisoning are reversible, most developmental effects of exposure appear not to be reversible because they arise from permanent structural changes in the brain.

Animal study results support the observations made in human studies. Although they are limited in that interspecies extrapolation is required to use animal studies as the basis for exposures limits for humans, they have the advantage of having more precisely quantified exposures. In addition, some animal studies have been carried out on sensitive neurological endpoints. Animal studies may be consulted to support the human studies or to estimate an independent exposure limit. A variety of CNS effects have been observed in experimental animals, analogous to effects observed in children. In addition to CNS effects, animal studies have found immunotoxicity, liver toxicity, abnormal immune system function, incomplete ossification and calcification of bones, and kidney damage associated with prenatal and lactational exposure (ATSDR, 1992a).

It has been hypothesized that the reason the developing nervous system is particularly susceptible to methylmercury poisoning is that microtubules are destroyed by this form of mercury. This action causes inhibition of cell division and cell migration, which are processes occurring primarily during development and which are necessary to normal development (Clarkson, et al., 1987). This is supported by autopsy data on prenatally-exposed children from Japan and Iraq, who had significant disruption in cerebellar and cerebral cytoarchitecture and a lack of regional specificity. This was in marked contrast to observations of adults who had been exposed to methylmercury; considerable anatomic selectivity in damage was seen with adult exposure (Chang, 1987). Reuhl has suggested "that animals with longer gestational periods and more extended "bursts" of neuronal development would be more likely than rodents to display migratory disturbances, since neuronal commitment and migration in these species occur over a longer period of time. He goes on to suggest that cats, dogs, and non-human primates would be preferable to rodents as study subjects for evaluating the developmental toxicity of methylmercury (Reuhl, 1987).

A critical question in evaluating the developmental toxicity of methylmercury or other developmental toxics is the effect of the timing of exposure on toxicity. It is difficult to determine the precise timing and duration of exposure which is most damaging to developing individuals. Animal studies have shown that exposure during early gestation results in embryo death with effects resembling the embryocidal effects of ionizing radiation. Postnatal behavioral effects (which also resemble the effects of ionizing radiation) are most pronounced when fetuses are exposed late in gestation (Norton, 1987). Readers may wish to consult Norton (1987) to obtain more specific information.

EPA is currently conducting an extensive review of methylmercury toxicity. It is anticipated that the IRIS value may change in the future. In the interim, the Office of Water has recommended a dose-response value of 6×10^{-5} mg/kg-day, which is listed in Volume 1 in this series (EPA, 1993a). The value is based upon an evaluation of the human and animal toxicity data, and is derived primarily from the human studies on exposed populations in Iraq. In Volume 1, a discussion of the rationale for utilizing the lower value is presented. It is based upon a concern that the fetus and possibly pregnant women are at increased risk of adverse neurological effects from exposure to methylmercury. Study findings suggest that fetal sensitivity may be five-fold greater than adult sensitivity. Consequently, an additional uncertainty factor of 5 was applied to

the current IRIS RfD for methylmercury.[15] This approach is an interim measure until the reevaluation of the methylmercury RfD is complete (EPA, 1993a). The Office of Water value of 6×10^{-5} mg/kg-day was used in the calculation of fish consumption limits listed in Section 3 for women of reproductive age and children.

ATSDR provides an **acute** developmental MRL of 4×10^{-5} mg/kg-day based upon a NOAEL of 0.004 mg/kg-day in rats from an acute exposure study (the LOAEL was 0.008 mg/kg-day). A significant reduction in operant behavioral performance was observed in four month old offspring (ATSDR, 1992a). Longer term animal studies have not identified NOAELs as low as that found in the acute study noted above. In a longer-term study of monkeys exposed pre- and postnatally to methylmercury, a LOAEL of 0.01 mg/kg-day was identified with impaired spatial visual function at and above the LOAEL. Dosing in this study continued through four years of age (ATSDR, 1992a). This study yielded the lowest LOAEL of the animal studies reviewed for this work and has a relatively sensitive health endpoint. In addition, the study was carried out on a species which is more similar to humans than the rodents used in most other toxicity studies of methylmercury (See Reuhl's recommendation above (1987)).

Methylmercury accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result of this, it is necessary to reduce exposure to girls and women with childbearing potential, to reduce overall body burden. If exposure is reduced during pregnancy, but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Mutagenicity

Mutagenicity assays of methylmercury have yielded mixed results. Studies in animals suggest species and often strain specificity in response. Data suggest that mercury compounds may be clastogenic for mammalian germ cell lines but less damaging to somatic cells. ATSDR concluded on the basis of *in vitro* and animal studies that organic mercury compounds have some genotoxic potential (ATSDR, 1992a).

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[15] The human data support consideration of the fetus as being more sensitive than adults. Both structural data (Clarkson, 1987 and Chang, 1987 referred to above) and functional studies of mother-child pairs indicate a greater fetal sensitivity (Clarkson, et al, 1987; Clarkson, et al, 1989; Clarkson, 1990; Clarkson and Fitzgerald, 1990; WHO, 1990).

In a group of 23 humans exposed to methylmercury in fish, a correlation was found between blood mercury levels and structural and numerical chromosome aberrations in lymphocytes. Another study found a correlation between consumption of contaminated seal meat and an increased incidence of sister chromatid exchange. There were multiple confounders in these studies and exposure was not quantified (ATSDR, 1992a).

There are not sufficient dose-response data on the mutagenicity of mercury to calculate an exposure limit based upon mutagenicity. However, available scientific data suggest that mercury may be mutagenic. This should be considered in determining appropriate consumption advisories for mercury contaminated fish.

Carcinogenicity

Insufficient information is available to determine the carcinogenic status of oral exposure to methylmercury.

Special Susceptibilities

Developing individuals are at significant risk from methylmercury exposure due primarily to toxic effects on the developing nervous system. This is addressed under developmental effects above. Additional risk may also result from the apparently decreased ability of young individuals to eliminate mercury (See pharmacokinetics above).

In addition, ATSDR has listed the following groups as particularly susceptible: the elderly, people with impaired organ function (especially kidney, CNS, and liver), the ill or malnourished (due to the absence of protective essential minerals), and those who are exposed to other synergistic toxicants (ATSDR, 1992a).

Interactive Effects

Potassium dichromate and ethanol may increase the toxicity of mercury, although these effects have been noted with metallic and inorganic mercury. Atrazine increases the toxicity of methylmercury in experimental animals. Vitamin D and E, thiol compounds, selenium, copper, and possibly zinc are antagonistic to the toxic effects of mercury (ATSDR, 1992a). There is insufficient information to recommend quantitative changes in risk estimations based upon interactive effects.

Critical Data Gaps

Additional data are needed regarding the exposure level at which humans experience adverse neurological effects. Human and primate studies suggest that neurotoxicity is a sensitive measure of methylmercury toxicity; consequently, a well-founded NOAEL for this type of toxicity should be obtained. Kidney toxicity is also a sensitive measure of toxicity; however, no chronic exposure studies were available for this effect. A lifetime study using sensitive endpoints and including various organ toxicities not fully explored in other studies (e.g., reproductive system toxicity, blood pressure changes, hormonal effects) is needed to more accurately estimate an exposure limit.

Although there are numerous developmental toxicity studies available, the dose-response results are not consistent due, in part, to the variety of endpoints which have been evaluated. Additional studies are needed to identify a NOAEL based upon sensitive developmental toxicity endpoints.

Summary of EPA Risk Values

Developmental Toxicity	6×10^{-5} mg/kg-day for women of reproductive age and children (EPA, Office of Water)
Chronic Toxicity	3×10^{-4} mg/kg-day for adults excluding women of reproductive age (IRIS, 1993)
Carcinogenicity	Insufficient data to determine carcinogenic status

Major Sources: ATSDR (1992a), IRIS (1993), EPA (1993a), Stern (1993), Shubat (1993a)

5.6.23. Selenium

Background

Selenium occurs naturally in many areas and is produced through industrial processes. It is an essential nutrient with a Recommended Dietary Allowance (RDA) of 55 μg/day (0.055 mg) for non-lactating women and 20 additional μg/day during lactation. ATSDR has identified daily intake at non-toxic levels of approximately 0.05 to 0.15 mg/day (ATSDR, 1989 and HSDB,1993). This is approximately equivalent to 7×10^{-4} to 2×10^{-3} mg/kg-day in a 70 kg individual. The RDA for adult males is 70 μg/day (NRC, 1989). Selenium plays a critical role in the antioxidant enzyme glutationine peroxidase. Selenium deficiency has been associated with muscle degeneration in humans. A serious form of this, congestive cardiomyopathy (Keshan disease) has been studied in areas of China with low naturally occurring levels of selenium. It has also been shown to have a protective effect against chemically induced cancers in laboratory animals (Robbins et al, 1989). Although selenium is an essential nutrient, it is toxic at high exposure levels and is mutagenic in some test systems (ATSDR, 1989).

Definitive information regarding the chemical forms of selenium which are found in fish is not available (EPA, 1993a). Due to the lack of information on chemical forms, the toxicity of a variety of selenium forms are included in the discussion below. In some parts of the United States, particularly in western states, soil concentrations lead to selenium levels in plants that can cause human exposure at potentially toxic levels (ATSDR, 1989). This exposure should be considered in evaluating the overall exposure to selenium and in development of fish consumption advisories.

Pharmacokinetics

Selenium contained in food is generally associated with proteins as organic selenium compounds. It is easily absorbed by the body and accumulates primarily in the liver and kidneys. It accumulates to a lesser extent in the blood, lungs, heart, testes and hair (ATSDR, 1989) Detailed information on metabolism of selenium can be found in the *Toxicological Profile for Selenium.* This document also contains an extensive discussion of the selenium concentrations in human tissues and fluids correlated with specific health effects (ATSDR, 1989).

Acute Toxicity

Signs of acute selenium poisoning include difficulty in walking, labored breathing, cyanosis of the mucous membranes, congestion of the liver,

endocarditis and myocarditis, degeneration of the smooth musculature of the GI tract, gallbladder and bladder, and erosion of the long bones (IRIS, 1993). Subacute selenosis (prolonged exposure at relatively high doses) causes impaired vision, ataxia, disorientation and respiratory distress (IRIS, 1993). Tachycardia has been reported in humans exposed to high doses; myocardial disorders have also been associated with selenium deficiencies. Acute exposure dog studies at high doses have found multiple alterations in blood chemistry (ATSDR, 1989).

Chronic Toxicity

IRIS provides an RfD of 0.005 mg/kg-day for selenium and selenium compounds based upon a NOAEL of 0.015 mg/kg-day from a 1989 human epidemiological study which found clinical selenosis at the LOAEL of 0.023 mg/kg-day. The NOAEL was calculated from regression analysis of blood selenium levels and selenium intake. An uncertainty factor of 3 rather than 10 was used for intraspecies variability (IRIS, 1993). Note that the NOAEL and LOAEL for selenium in the 1989 human study are only slightly higher than the average daily intake and the RDA (See above).

High levels of selenium exposure has caused the following effects: lowered hemoglobin levels, mottled teeth, skin lesions, CNS abnormalities, fatigue, anorexia, enlarged spleen, thickened and brittle nails, hair and nail loss, decreased blood clotting ability, liver dysfunction, and muscle twitching (IRIS, 1993). Humans exposed to high dietary levels have reported GI disturbances (dose unspecified). Cows with high naturally occurring dietary exposures were found to have ulcers in the upper GI tract (ATSDR, 1989).

Lifetime exposure of mice to sodium selenate or sodium selenite at 0.31 mg/kg-day caused amyloidosis of the lung, liver, kidney, and heart. Mice appear to be more sensitive to selenium with regard to lung toxicity than rats. Rats may be more sensitive to the cardiotoxic effects, with an LEL of 0.1 mg/kg-day in a chronic study (the study had some deficits in study design) (ATSDR, 1989).

Hematological effects have been observed in multiple acute and chronic animal studies. No human studies were located for this report or by ATSDR in their literature review. Rats subchronically exposed to wheat containing selenium at a dose of 0.68 mg/kg-day for six weeks had a reduction of blood hemoglobin. At 0.75 mg/kg-day in a similar study red cell hemolysis was observed (ATSDR, 1989).

Bone softening in livestock has been noted with an LEL of 0.2 mg/kg-day with exposure over several months (less than 100 days). Adverse effects on the liver have been observed in multiple animal studies with LELs of 0.8 mg/kg-day

and above. Kidney damage has also been noted with an LEL of 0.31 mg/kg-day. Dermal effects have been observed at doses as low as 0.053 mg/kg-day in humans with dietary exposure (ATSDR, 1989). This observation served as a partial basis for the calculation of an MRL by ATSDR (See below). Depression of the immune system was observed in rats exposed subchronically to sodium selenite at 0.75 mg/kg-day. At lower doses (0.075 mg/kg-day and 0.28 mg/kg-day) mixed results were obtained, with a stimulation of some components of the immune system and depression of others. No NOEL was identified in the study (ATSDR, 1989).

Chronic exposure studies in animals have identified multiple adverse effects on the reproductive ability of animals and on offspring viability. Effects include: reduced rates of conception at 0.41 mg in pigs exposed from eight weeks of age (other offspring effects are listed under developmental effects), abnormal length estrus cycles in rats exposed subchronically to 0.34 mg/kg-day, increased fetal resorption and decreased conception rate in livestock exposed at a LEL of approximately 0.5 mg/kg-day, failure to breed in a three-generation study of mice exposed at 0.42 mg/kg-day, no effects in a two-generation study of mice at 0.21 mg/kg-day, and a 50 percent reduction in the number of young successfully reared with maternal exposure to 0.35 mg/kg-day for one year. Male fertility did not appear to be affected in the results reported, although the testes are a storage site for selenium (ATSDR, 1989).

Neurological symptoms have been reported in human and animal studies. A family exposed to approximately 0.26 mg/kg-day via drinking water reported various symptoms of selenosis including listlessness and a lack of mental alertness. Effects ceased when the water use was discontinued. More severe effects have been observed in high-selenium areas of China. Peripheral anesthesia and pain in the limbs were reported, although no associated estimate of exposure was provided. Exaggerated tendon reflexes, convulsions, paralysis and hemiplegia were estimated to occur at a minimum chronic exposure of 0.053 and an average of 0.083 mg/kg-day. A NOAEL of 0.025 was estimated. This information was used by ATSDR to calculate a chronic exposure MRL of 0.003 mg/kg-day (ATSDR, 1989).

Neurological effects identified in animal studies include: drowsiness, lethargy, ataxia, paralysis, bilateral lesions in the spinal cord, impaired vision, aimless wandering behavior, and neuronal degeneration of the cerebral and cerebellar cortices. Many of these were observed at relatively high doses; however, the neuronal degeneration was observed at a LEL of 0.6 mg/kg-day dosing with sodium selenite mixed in food (ATSDR, 1989).

The IRIS RfD and ATSDR MRL are within one order of magnitude of each other. The IRIS value was used to calculate fish consumption limits shown in Section

3 for chronic exposure toxicity. Please see the note at the end of the developmental toxicity section for cautions regarding this use of these values.

Developmental Toxicity

Limited information is available on the developmental toxicity of selenium in humans. One anecdotal report indicated that selenium exposure may be associated with spontaneous abortion and skeletal abnormalities (ATSDR, 1989); however, the anecdotal nature of the report makes it inappropriate for drawing conclusions regarding causality.

In animals selenium has caused growth retardation, decreased fertility, embryotoxicity, fetotoxicity, and teratogenic effects. One researcher noted that in a high selenium area teratogenic effects were not seen in humans, but they were observed in chickens (IRIS, 1993).

A multigeneration study in mice dosed with selenate at 0.39 mg/kg-day identified a significant increase in young deaths in the F1 generation, and increased runts in the F1 through F3 generations. Because only one dose was used, only a LOEL can be obtained from this study. A one-generation mouse study found a NOEL of 0.39 mg/kg-day. An early five-generation study identified a NOEL of 0.075 mg/kg-day and a LOEL of 0.125 mg/kg-day with a 50 percent reduction in the number of young reared at that dose. There are multiple possible reasons for the reduction, including decreased fertility; consequently it is not appropriate for use in calculating an exposure limit for developmental effects. A recent study in primates identified no developmental effects up to 0.3 mg/kg-day. However, the study utilized dosing over a portion of the pregnancy, and unlike the multigenerational studies, it did not include dosing prior to and during all of the pregnancy or dosing of the neonates (IRIS, 1993).

Multiple studies have determined that exposure of livestock (e.g., sheep, pigs, cattle) to naturally seleniferous diets resulted in fetal malformations and interference with normal fetal development. Malformations were associated with other manifestations of toxicity. The specific selenium compounds associated with these effects have not been identified (ATSDR, 1989). At 0.41 mg pigs exposed from eight weeks of age had offspring with significantly reduced birth weight and weaning weights (ATSDR, 1989).

ATSDR has reported studies on experimental animals that have yielded the following results: prenatal exposure at 0.34 mg/kg-day caused reduced fetal growth with a NOAEL of 0.17 mg/kg-day; mice exposed to 0.42 mg/kg-day for three generations had an increased incidence in fetal deaths and a high proportion of runts among survivors; macaques exposed prenatally at levels up

to 0.3 mg/kg-day exhibited no adverse effects. It was noted that exposure to inorganic selenium compounds at levels that are not maternally toxic have not produced teratogenic effects (ATSDR, 1989).[16]

Based on the reviewed information, the multigeneration mouse study cited in IRIS with a LOEL of 0.39 mg/kg-day appears to be the most appropriate value for calculating an estimated exposure limit for developmental effects because there are no other appropriate studies which provide data on long term maternal and offspring exposure effects. There is concern regarding the use of these results because severe effects were seen at the LOEL and because severe effects have been observed in other studies at approximately the same exposure level. The standard uncertainty factors used to calculate an estimated exposure limit would typically take into consideration inter- and intraspecies variability and the use of a LOEL rather than a NOEL. A modifying factors for the severity of effects at the LOEL could also be applied. The resulting value is within one order of magnitude of an exposure limit which could be calculated from the NOEL of 0.17 mg/kg-day for reduced fetal growth (as reported by ATSDR). Due to the longer term nature of the dosing, the multigeneration study cited in IRIS may be more appropriate.

NOTE: Decisions regarding thresholds for adverse effects of selenium are complex because selenium is an essential nutrient. Consequently, the application of uncertainty factors in the standard manner may not be appropriate. Some exposure to selenium is necessary, as indicated by the RDA. There appears to be a relatively small margin between the effective/necessary dose and the toxic dose for this chemical. Additionally, the need for selenium and the toxicity of selenium is expected to vary among individuals. Consequently, it is necessary to evaluate the overall exposure to selenium in order to evaluate potential risks and make well-informed decisions regarding exposure limits. Decisions regarding the contribution to total selenium exposure which can come from fish without generating toxicity will depend on the cumulative exposures from other sources. This is expected to vary considerably depending on the part of the country in which a person resides, their dietary habits, and other factors.[17] Readers should carefully review the

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[16] EPA's guidelines on developmental toxicity specify that dosing should include doses which cause some level of maternal toxicity; therefore, this is not cause for dismissing the study results.

[17] If these factors were not a consideration for selenium exposure, an additional modifying factor would be recommended when estimating exposure limits for developmental effects due to the serious nature of effects observed in multiple species at or near the LEL of .39.

toxicity data regarding selenium and determine the appropriate exposure limit for developmental effects, based upon the exposures anticipated in their states and their interpretation of the toxicological and epidemiological literature. See also Abernathy, et al (1993) for additional guidance on this topic.

It will be necessary to obtain a NOEL from a multigeneration study and to further explore the mechanisms of fetal and neonatal lethality associated with selenium exposure to adequately determine the appropriate exposure limit for developmental effects. A well designed human epidemiological study of prenatally exposed individuals from high naturally occurring selenium areas is needed to provide insight into human effects of selenium exposure.

Mutagenicity

There are many positive mutagenicity assays on selenium compounds including unscheduled DNA synthesis, increased chromosomal aberrations in human lymphocytes and in the bone marrow of rats, and an increase in sister chromatid exchanges in human whole-blood cultures. There are also assays with negative results (IRIS, 1993).

Inorganic selenium compounds appear to have genotoxic effects at relatively high doses and antigenotoxic effects at lower doses. For example, a study of mice exposed to mutagens and given doses of 0.05 to 0.125 mg/kg-day of selenium indicates that selenium may inhibit the mutagenic effects of chemical agents (ATSDR, 1989). For a summary of study results see the *Toxicological Profile for Selenium* (ATSDR, 1989).

Carcinogenicity

EPA has determined that there is insufficient data to assess the carcinogenic potency of selenium. EPA has classified selenium sulfide as a probable human carcinogen (B2), based on liver and lung tumors in oral exposure studies in multiple species (IRIS, 1993).

Some human studies indicated that combined Vitamin E and selenium **deficiencies** may lead to higher cancer risks (ATSDR, 1989).

Special Susceptibilities

ATSDR has listed the following groups as potentially having greater susceptibility: pregnant women and their fetuses, persons exposed to high fluoride levels in drinking water (evidence equivocal), those with vitamin E deficiencies, and populations with elevated exposures arising from exposure via food produced in high selenium areas (ATSDR, 1989).

Based on the occurrence of adverse effects reported in human and animal studies, individuals with diseases or disorders of the following organ systems may be at greater risk from selenium exposure than the general population: hematopoietic, dermal, nervous, liver, kidney, cardiac and immune systems.

HSDB listed individuals with the following conditions as requiring additional protection: chronic indigestion or a history of peptic ulceration, skin, lung, kidney or liver disease, dermatitis, chronic bronchitis, skin allergy or respiratory tract infection, jaundice, or albuminuria (HSDB,1993). Their cautions are based upon all routes of selenium exposure.

Interactive Effects

Selenium alters the toxicity of many chemicals. It reduces the toxicity of mercury, cadmium, lead, silver and copper; some forms reduce arsenic toxicity. Detailed information on specific interactions can be found in the *Toxicological Profile for Selenium* (ATSDR, 1989). Selenium also interacts with vitamins, sulfur-containing amino acids, xenobiotics, and essential and non-essential elements. ATSDR notes that most interactions are beneficial (ATSDR, 1989).

Critical Data Gaps

ATSDR has reported the following data gaps: human epidemiological data for all relevant effects, relationship between selenium dietary exposure levels and cancer, mechanisms of genotoxicity, reproductive, developmental studies regarding cataract formation, immunotoxicity, neurotoxicity, especially behavioral and histopathological CNS effects, pharmacokinetic, and bioaccumulation and bioavailability from environmental media (ATSDR, 1989). A multigeneration study which utilizes sensitive endpoints for toxicity is needed to develop a more adequately based exposure limit for developmental effects.

Summary of EPA Risk Values

Chronic Toxicity	5×10^{-3} mg/kg-day
Carcinogenicity	Insufficient data to assess carcinogenicity. Note that selenium sulfide is classified as a Group B2 carcinogen

Major Sources: IRIS (1993), ATSDR (1989), HSDB (1993)

SECTION 6.

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[1] The addresses from which to obtain state documents are listed in Appendix B, Sources of Additional Information.

[2] Article titles were not usually available for citations obtained from HSDB; consequently, page number were included for those citations (only).

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APPENDIX A

MUTAGENICITY AND GENOTOXICITY

EPA has developed and published *Guidelines for Mutagenicity Risk Assessment* (EPA, 1986c). The information in this appendix was primarily taken from that document. Quantitative assessment of mutagenicity requires two steps: 1) determining the heritable effect per unit of exposure (dose-response) and the relationship between mutation rate and disease incidence, and 2) combining dose-response information with anticipated levels and patterns of human exposure in order to derive a quantitative assessment of risk (EPA, 1986c). Current EPA guidance on mutagenicity risk assessment specifies that:

> "Dose-response assessments can presently only be performed using data from *in vivo*, heritable mammalian germ-cell tests, until such time as other approaches can be demonstrated to have equivalent predictability." (EPA, 1986c).

The relationship between *in vitro* assay results and effects in mammalian systems is not sufficiently characterized to be able to use *in vitro* assays as the basis for developing a dose-response assessment.

An example of the type of study which could be used for mutagenicity risk assessment is an assay that directly detects heritable health effects in the first generation offspring. Human risk estimates are obtained by extrapolating the induced mutation frequency or observed phenotypic effect downward to the anticipated level of human exposure (EPA, 1986c). No one extrapolation model has been identified as the most appropriate. The Agency notes that departures from linearity at low exposure and exposure rates has been observed for at least one chemical. According to EPA, "[t]he Agency will consider all relevant models for gene and chromosomal mutations in performing low-dose extrapolations and will choose the most appropriate model. This choice will be consistent both with the experimental data available and with current knowledge of relevant mutational mechanisms" (EPA, 1986c).

The factors which should be considered in evaluating chemicals for mutagenic activity include:

- Genetic endpoints,
- Sensitivity and predictive value of the test systems for various classes of chemical compounds,
- Number of different test systems used for detecting each genetic endpoint,
- Consistency of the results obtained in different test systems and different species,
- Aspects of the dose-response relationship, and
- Whether the tests are conducted in accordance with appropriate test protocols agreed upon by experts in the field (EPA, 1986c).

Although there are often no *in vivo* data available on a chemical, there are *in vitro* assay results for most common chemicals. This data may be used qualitatively to evaluate the mutagenicity of chemicals. They are often used as supporting evidence in carcinogenicity, developmental toxicity and reproductive toxicity evaluations.

Various types of test results may be obtained regarding mutagenicity. In evaluating interactions in the mammalian gonad, two possible types of evidence have been specified. Evidence for chemical interactions in the mammalian gonad may be considered sufficient if it is demonstrated that "an agent interacts with germ-cell DNA or other chromatin constituents, or that it induces such endpoints as unscheduled DNA synthesis, sister-chromatid exchange, or chromosomal aberrations in germinal cells" (EPA, 1986c). Suggestive evidence of interaction in the mammalian gonad "includes effects such as sperm abnormalities following acute, subchronic or chronic toxicity testing, or finding of adverse reproductive effects such as decreased fertility, which are consistent with the chemical's interaction with germ cells" (EPA, 1986c).

In practice, the outcomes of developmental and reproductivity toxicity testing often do not indicate the type of toxicity which lead to effects such as decreased fertility. The causes of decreased fertility range from mutagenicity leading to early fetal death or failure to implant; to maternal, paternal, or fetal toxicity. Positive significant mutagenicity studies along with fetal toxicity or reduced fertility may be suggestive that mutagenic action was a causal action. Developmental toxicity has been studied in most chemicals (other than frank teratogens) only relatively recently. The use of the data from these studies with other types of data such as mutagenic, pharmacokinetic and reproductive system studies is developing; however, there is not currently clear guidance on these types of evaluations.

EPA has addressed the issue of weight-of-evidence for mutagenicity by providing a classification scheme with categories presented in decreasing order of strength of evidence:

1. Positive data derived from human germ-cell mutagenicity studies;
2. Valid positive results from studies on heritable mutational events in mammalian germ cells;
3. Valid positive results from mammalian germ-cell chromosome aberrations studies that do not include an intergenerational test;
4. Sufficient evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity test results from two assay systems, at least one of which is mammalian (*in vitro* or *in vivo*). The positive results from the two assays may be both for gene mutations or both for chromosome aberrations; if one is for gene mutations and the other for chromosome aberrations, both must be from mammalian systems;
5. Suggestive evidence for a chemical's interaction with mammalian germ cells, together with valid positive mutagenicity evidence from two assay systems, as described under 4 above. Alternatively, positive mutagenicity evidence of less strength than defined under 4 above, when combined with sufficient evidence for a chemical's interaction with mammalian germ cells;
6. Positive mutagenicity test results of less strength than defined under 4., combined with suggestive evidence for a chemical's interaction with mammalian germ cells;
7. Although definitive proof of non-mutagenicity is not possible, a chemical could be classified operationally as a non-mutagen for human germ cells, if it gives valid negative test results for all end points of concern;
8. Inadequate evidence bearing on either mutagenicity or chemical interaction with mammalian germ cells.

Certain responses in tests that do not measure direct mutagenicity endpoints (e.g., sister chromatid exchange) may provide the basis for raising the weight of evidence from one category to the next (EPA, 1986c).

EPA noted that it was not possible to illustrate all potential combinations of evidence and suggests that judgment must be exercised in reaching conclusions. In addition, the test results often do not provide a consistent picture of the mutagenicity of a chemical. For example, most target analytes discussed in Section 5 had both positive and negative mutagenicity data. Although the use of mutagenicity data in risk assessment has been limited in the past, a recent EPA Scientific Advisory Board (SAB) report, which addressed the methodology for developing ambient water quality criteria, has

recommended that it be used more extensively in cancer risk assessment in the future (EPA, 1993r). The SAB report states that:

> "Data on genetic activity of chemicals in short and long term tests *in vitro* and even *in vivo* should be given greater weight in the future. However, the incorporation of this information in risk assessment should emphasize the relationships between specific mutation sites, the resulting alterations in specific proteins, and the development of cancer. The simple identification of the ability of a given compound to produce mutations in various test systems has limited utility in risk assessment, beyond the ability of classifying compounds as putative mutagens or non-mutagens. Studies that give insight into the normal and abnormal behavior of human cells and tissues should be used to help bridge the gap between studies in animals and effects in human beings" (EPA, 1993r).

As information becomes available on this topic, updates will be provided.

APPENDIX B

SOURCES OF ADDITIONAL INFORMATION

The sources listed below were consulted in the development of this document and may be useful to readers who wish to obtain more in-depth information on specific topics. A listing of the state documents and addresses begins on page B-9.

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The documents are listed in alphabetical order by state. The address, which follows the first document listed for each state, is the location of the office(s) which have participated in this project.

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Office of Environmental Health Assessment
Pesticide and Environmental Toxicology Section
601 N. 7th Street, P. O. Box 942732
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Toxicology and Hazard Assessment
1317 Winewood Blvd.
Tallahassee, FL 32399-0700

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New Orleans, Louisiana
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MI Dept. of Public Health
Division of Health Risk Assessment
3423 N. Martin Luther King Blvd.
Lansing, MI 48909

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MN Dept. of Health
Div. of Environ. Health
Section of Health Risk Assessment
925 S.E. Delaware Street, P.O. Box 59040
Minneapolis, MN 55459-0040

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1730 E.Elm St.
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NJ DEPE
Division of Science & Research
CN 409
401 E. State St., 41E
Trenton, NJ 08625

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New York State Department of Environmental Conservation
50 Wolf Rd.
Albany, N.Y.
12233

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ND Dept. of Health and Consolidated Laboratories
Environmental Health Section
1200 Missouri Avenue
P.O. Box 5520
Bismarck, ND 58502-5520

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